

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021246Orig1s045 and 021087Orig1s062

OTHER REVIEW(S)

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Applications: 21087/S-062
21246/S-045

Name of Drug: TAMIFLU (oseltamivir phosphate) 30, 45, and 75 mg capsules
TAMIFLU (oseltamivir phosphate) 6 mg/mL oral suspension

Applicant: Hoffmann-La Roche, Inc.

Labeling Reviewed

Submission Date: June 21, 2012

Receipt Date: June 21, 2012

Amendment Date (labeling): December 21, 2012

Note: Last approved labeling for Tamiflu was NDA 21087/S-059 and NDA 21246/S-042 dated February 28, 2012 and approved August 16, 2012.

Background and Summary Description:

On June 21, 2012, Roche submitted supplemental NDAs to expand the patient population and support the dosing recommendation of Tamiflu for the treatment of influenza in infants less than one year of age who have been symptomatic for no more than 2 days.

Two clinical studies served as the foundation for the sNDA clinical and label review: CASG 114 (WP20749) entitled "A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu) for the Treatment of Children Less Than 24 Months of Age with Confirmed Influenza Infection" and WP22849 entitled "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."

Review

GENERAL

1. Throughout the full prescribing information, clarification was made regarding the use of "subjects" versus "patients".
2. In Section 6.1, "≥" or "<" symbols were revised to read "greater or less than"

1

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/s/

ELIZABETH G THOMPSON

12/21/2012

Chief agreement on review on Dec 20. Notified could sign off on Dec 21 without secondary signature.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 19, 2012

To: Elizabeth Thompson, MS, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Jessica Fox, PharmD, Regulatory Review Officer
Sheila Ryan, PharmD, Group Leader
Division of Professional Drug Promotion (DPDP)

Subject: NDA 021087/S-062; NDA 021246/S-045
TAMIFLU (oseltamivir phosphate) capsules, for oral use
TAMIFLU (oseltamivir phosphate) for oral suspension

As requested in DAVP's consult dated [REDACTED] (b) (4), DPDP has reviewed a proposed [REDACTED] (b) (4) for TAMIFLU, sent via email by DAVP on December 13, 2012.

DPDP's comments are provided directly below in the proposed [REDACTED] (b) (4)

Thank you for the opportunity to provide comments. If you have any questions, please contact Jessica Fox at 301-796-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
12/19/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 12, 2012

To: Elizabeth Thompson, MS, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Kemi Asante, PharmD, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: NDA 021087/S-62; NDA 021246/S-45
TAMIFLU (oseltamivir phosphate) capsules, for oral use
TAMIFLU (oseltamivir phosphate) for oral suspension

As requested in DAVP's consult dated July 12, 2012, DCDP has reviewed the TAMIFLU substantially complete prescribing information (PI) sent via email by DAVP on November 29, 2012 and DMPP's version of the patient package insert (PPI) sent via email on December, 11, 2012.

DCDP's comments on the prescribing information are provided directly below in DMPP's version of the PPI.

Thank you for your consult. If you have any questions on the PPI, please contact Kemi Asante at 6-7425 or at Kemi.Asante@fda.hhs.gov.

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/s/

OLUWASEUN A ASANTE
12/12/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 10, 2012

To: Debra B. Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Latonia Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI) and Instructions for Use (IFU)

Drug Name (established name): TAMIFLU (oseltamivir phosphate)

Dosage Form and Route, Application Type/Number/
Supplement Number: capsules, NDA 21087/S-062
for oral suspension, NDA 21246/S-045

Applicant: Hoffmann-La Roche, Inc.

1 INTRODUCTION

On June 21, 2012, Hoffmann-La Roche, Inc. submitted Supplemental New Drug Applications (sNDA) 21087/S-062 for TAMIFLU (oseltamivir phosphate) capsules and (sNDA) 21246/S-045 for TAMIFLU (oseltamivir phosphate) for oral suspension. The Supplements provide proposed changes to the Prescribing Information and Patient Package Insert for the treatment of influenza in infants with a post conceptual age of at least ^(b)₍₄₎ weeks to 1 year of age who have been symptomatic for no more than 2 days.

TAMIFLU (oseltamivir phosphate) capsules were originally approved October 27, 1999 for the treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than 2 days. TAMIFLU (oseltamivir phosphate) for oral suspension was originally approved on December 14, 2000 for the treatment of uncomplicated acute illness due to influenza in patients older than one year of age who have been symptomatic for no more than 2 days.

On July 12, 2012, the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TAMIFLU (oseltamivir phosphate) capsules and TAMIFLU (oseltamivir phosphate) for oral suspension.

This review is written in response to a request by DAVP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TAMIFLU (oseltamivir phosphate) capsules and TAMIFLU (oseltamivir phosphate) for oral suspension.

2 MATERIAL REVIEWED

- Draft TAMIFLU (oseltamivir phosphate) capsules and TAMIFLU (oseltamivir phosphate) for oral suspension PPI received on June 21, 2012, and received by DMPP on November 28, 2012.
- Draft TAMIFLU (oseltamivir phosphate) capsules and TAMIFLU (oseltamivir phosphate) for oral suspension IFU received on June 21, 2012, and received by DMPP on November 28, 2012.
- Draft TAMIFLU (oseltamivir phosphate) capsules and TAMIFLU (oseltamivir phosphate) for oral suspension Prescribing Information (PI) received June 21, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on November 28, 2012

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFU appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
12/10/2012

BARBARA A FULLER
12/10/2012

LASHAWN M GRIFFITHS
12/10/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 7, 2012

To: Elizabeth Thompson, MS, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Jessica Fox, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: NDA 021087/S-062; NDA 021246/S-045
TAMIFLU (oseltamivir phosphate) capsules, for oral use
TAMIFLU (oseltamivir phosphate) for oral suspension

As requested in DAVP's consult dated July 12, 2012, DPDP has reviewed the TAMIFLU substantially complete prescribing information, sent via email by DAVP on November 29, 2012.

DPDP's comments on the prescribing information are provided directly below in the proposed labeling.

Thank you for your consult. If you have any questions, please contact Jessica Fox at 301-796-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
12/07/2012

MEMORANDUM

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

DATE: November 27, 2012

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

FROM: Xikui Chen, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
Michael F. Skelly, Ph.D.
Pharmacologist, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations
and
William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDAs 21-246/S-45 and
21-087/S-62, Oseltamivir Phosphate, Sponsored by
Hoffman-LaRoche, Inc.

At the request of DAVP, the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections for the following pharmacokinetic studies:

Study Number: WP22849
Study Title: "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"

Study Number: WP20749
Study Title: "A pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu®) for the treatment of children less than 24 months of age with confirmed influenza infection (CASG 114)"

The audits included thorough examinations of study records, facilities, and equipment, and interviews and discussions with the firms' management and staff.

Clinical Sites: Pablo J. Sanchez, M.D. (Centers 140 and 166 in Study WP20749)
University of Texas Southwestern Medical Center at Dallas
Children's Medical Center
Parkland Health and Hospitals Systems
Dallas, TX

Barbara Rath, M.D. (Center 204725 in Study WP22849)
Charité Universitätsmedizin Berlin, Klinik für Pädiatrie mit Schwerpunkt, Pneumologie und Immunologie
Berlin, Germany

David W. Kimberlin, M.D. (Center 001 in Study WP20749)
The Children's Hospital of Alabama
The University of Alabama Hospital
Birmingham, AL 35249

Clinical portions of the study were audited at the offices of Dr. Sanchez (by ORA Investigators [REDACTED] (b) (4); Form FDA 483 was issued), the offices of Dr. Rath (by ORA Investigator [REDACTED] (b) (4) no Form FDA 483 was issued), and the offices of Dr. Kimberlin (by ORA Investigator [REDACTED] (b) (4) no Form FDA 483 was issued). Dr. Sanchez's response to the observations was received at OSI on [REDACTED] (b) (4) [See separate document uploaded into DARRTS.] The observations, Dr. Sanchez's response, and OSI/DBGC's evaluations follow.

- 1) Failure to assure that an IRB was responsible for the initial and continuing review and approval of a clinical study. Specifically, Manual of Procedures

Version 1.0 dated December 19, 2006 and Version 2.0 dated November 11, 2009 was not approved by the IRB. The Manual of Procedures was observed to be an extension of the protocol and includes steps to be completed in the conduct of the clinical investigation.

Dr. Sanchez responded that because the instructions in the Manual of Procedures did not involve or affect protection of subject safety, review by the IRB was not required. The OSI/DBGC reviewers accept Dr. Sanchez's response as adequate.

- 2) An investigation was not conducted in accordance with the investigational plan. Specifically,
 - 1 Protocol section 8.2.3 *Specimen Preparation, Handling, and Shipping* states, Specific instruction on specimen preparation, handling and shipping will be provided in the Manual of Procedures (MOP) for this study. MOP section 6.1.2 *PK Sample Preparation, Labeling and Shipment* state "Plasma must be separated by centrifugation (e.g. 1500g for 10 minutes at 4 degrees Celsius) within 60 minutes of sample collection ... Plasma samples would be immediately stored in an upright position at or below -70 degrees C until ready to ship. The temperature of the freezer must be maintained and monitored."
 - a. For 13 out of 25 subjects, there was inadequate documentation regarding the time Pharmacokinetic (PK) samples were placed at -70°C and the freezer used to store PK samples. At least two freezers were used to store samples at -70°C or below throughout the study. According to the Laboratory Research Coordinator, from (b) (4) [REDACTED], two separate freezers were used simultaneously to store samples. These freezers were only identified by probe numbers; however, you failed to document the freezer each probe was monitoring. For these subjects, you failed to document the freezer used to store each sample at any given time and you failed to document the time each sample went into and was removed from the freezer.

Five PK blood samples were acquired on Day 3 of the study for each subject. There were a total of 48 protocol deviations submitted for temperature excursions above -70°.

- b. For six (6) out of 25 subjects there were no records demonstrating the conditions of processing for the PK samples, including the centrifugation spin time and temperature.
- 2 Not all concomitant medications were recorded for five (5) of 26 subjects. Protocol Section 6.4 *Concomitant Medications* states, "Concomitant medications will be recorded on the specified CRF at Study Visit Days 1, 3, 5±1, and 10±2."
- a. For Subject #222, Ferrous Sulfate was prescribed on study Day 3, 2/3/2007, but the Concomitant Medications Case Report Form (CRF) for this visit does not list Ferrous Sulfate. Ferrous Sulfate, with a start date of 2/14/2007, was found in a Concomitant Medications CRF that was completed 3/2/2007.
 - b. For Subject #226, Palivizumab (Synagis[®]) was given 2/23/2007 (Day One), and was not included in the CRF for Concomitant Medications.
 - c. For Subject #402, Oxacillin was being given intravenously from 8/6/2009 until 8/8/2009. The subject's Day One was 8/7/2009 and Oxacillin was not included in the CRF for Concomitant Medications.
 - d. For Subject #642, Palivizumab (Synagis[®]) was given 10/2/2009 (Day One) of the study, and was not included in the CRF for Concomitant Medications.
 - e. For Subject #643, Palivizumab (Synagis[®]) was given 10/5/2009 (Day One) of the study, and was not included in the CRF for Concomitant Medications.

Dr. Sanchez responded to observation 2)1a. that the temperature recording probes uniquely identified individual freezers. In addition, he provided a statement from Roche Laboratories that the short temperature excursions were within the documented range under which oseltamivir is stable. The OSI/DBGC reviewers accept Dr. Sanchez's response as adequate.

Dr. Sanchez responded to observation 2)1b. that during the study, upon recognition of the importance of documenting centrifugation conditions, the staff began to record them. The OSI/DBGC reviewers recommend that the deviations in recording are unlikely to have affected the study outcomes for the six subjects significantly.

Dr. Sanchez responded to observation 2)2 that a delay in filling the prescription for ferrous sulfate resulted in the child's parents not beginning its administration until 2/14/2007, and not reporting it to Dr. Sanchez until the visit on 3/2/2007, when he entered it into the concomitant medications records. He notes that the palivizumab doses were given before the first oseltamivir dose, and that the protocol did not require them to be listed as concomitant medications. He acknowledges that oxacillin should have been listed as a concomitant medication. The OSI/DBGC reviewers accept Dr. Sanchez's responses as adequate to address questions of protocol compliance, and recommend that the clinical pharmacology reviewer evaluate the possible impact of ferrous sulfate, palivizumab, and oxacillin on pharmacokinetics of oseltamivir and its metabolite.

- 3) Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically,**
- 1. Subject #236 was given the commercial drug oseltamivir on 9/15/09 at 16:15, after consent and after randomization. This subject was consented on 9/15/09 at 15:39. Randomization for the subjects occurred on 9/15/09 at 16:11. The commercial drug oseltamivir was not observed on the concomitant medications source documentation. This dose was also not listed on the Study Medication Dosing Record for this subject.**
 - 2. For six (6) out of 26 subjects enrolled in the study, there was no record of the time the informed consent form was signed in order to verify that study procedures did not occur before consent.**
 - 3. For four (4) out of 26 subjects, you failed to write the date you signed source documents that pertain to study procedures, including Progress Records and Physical Examination Source worksheets.**
 - 4. Subject #232 has a history of a brain cyst under neurologic evaluation; however, this was not listed on the Medical and Surgical History source documentation. Subject #232 was consented on 05/18/09.**

Dr. Sanchez responds that subject #236 was treated with oseltamivir by a primary physician at 04:15 on 9/15/09, before entering the study, and as such the oseltamivir was not required by the protocol to be listed on the Study Medication Dosing Record. However, he acknowledges that it should have been listed as a concomitant medication. The OSI/DBGC reviewers

accept Dr. Sanchez's response as adequate, and recommend that the clinical pharmacology reviewer consider the pre-study dose of oseltamivir when evaluating pharmacokinetic data for this subject.

Dr. Sanchez responds that the actual times and dates of events in the study are supported by external documents and records, such as electronic medical records and separate date records on the documents. Since the time of the study, institutional procedures have been amended to require detailed time and date records.

Dr. Sanchez responds that the feature seen in the ultrasound image in the coronal profile for subject #232 was not confirmed by ultrasound in the sagittal profile, nor in a computed tomography scan. Therefore, he regarded the questionable cyst as likely absent. The OSI/DBGC reviewers accept Dr. Sanchez's response as adequate.

Analytical Sites:

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
Study WP22849

Analytical portions of the studies were audited at (b) (4) (b) (4) (b) (4) by ORA Investigator (b) (4) and OSI/DBGC (b) (4) and (b) (4) (b) (4) (conducted (b) (4) by ORA Investigator (b) (4) and OSI/DBGC Scientist (b) (4)). Following the inspection at (b) (4), Form FDA 483 was not issued. Following the inspection at (b) (4), Form FDA 483 was issued. (b) (4) response to the observation was received on (b) (4). The observation, (b) (4) response, and OSI/DBGC's evaluations follow.

- 1) The calibration failures associated with Pipettor 79, used during testing of run 13 of Sponsor Study Number WP20749, and Pipettor 9, used during testing of run 40 of Sponsor Study Number WP20749, were not evaluated to determine the calibration failure's adverse effects to the accuracy, sensitivity and precision of the analytical results reported for these runs.

The OSI/DBGC reviewers note that the calibrators and QC samples handled during runs 13 and 40 passed all run acceptance and system suitability criteria. Therefore, the pipette calibration failures had no consequences on data quality in these runs.

Conclusions:

Following the above inspections, the DBGC reviewers recommend the following:

- The clinical pharmacology reviewer should evaluate the possible impact of ferrous sulfate, palivizumab, and oxacillin on pharmacokinetics of oseltamivir and its metabolite, for subjects #222, 226, 402, 642, and 643.
- The clinical pharmacology review should consider the pre-study dose of oseltamivir when evaluating pharmacokinetic data for subject #236.
- All other data from these studies are acceptable for review.

Final Classifications:

NAI: Barbara Rath, M.D. (Center 204725 in Study WP22840)
Charité Universitätsmedizin Berlin, Klinik für
Pädiatrie mit Schwerpunkt, Pneumologie und Immunologie
Berlin, Germany
FEI 3001919105

VAI: Pablo J. Sanchez, M.D. (Centers 140 and 166 in Study
WP20749)
University of Texas Southwestern Medical Center at
Dallas; Children's Medical Center; Parkland Health and
Hospitals Systems; Dallas, TX
FEI 3006996981

NAI: David W. Kimberlin, M.D. (Center 001 in Study WP20749)
The Children's Hospital of Alabama; The University of
Alabama Hospital; Birmingham, AL

VAI: [REDACTED] (b) (4)
[REDACTED] (now closed)
FEI [REDACTED] (b) (4)

NAI: [REDACTED] (b) (4)
[REDACTED]
FEI [REDACTED] (b) (4)

CC:

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OSI/DBGLPC/Taylor/Haidar/Dejernet/XChen/Skelly/CF

DAVP/Birnkrant/Thompson

OCP/DCPIV/Zheng

[REDACTED] (b) (4)

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/s/

MICHAEL F SKELLY

11/27/2012

See separate file for the response to Form FDA 483 by Dr. Sanchez.

XIKUI CHEN

11/27/2012

SAM H HAIDAR

11/28/2012

WILLIAM H TAYLOR

11/28/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: November 15, 2012

Reviewer: Morgan Walker, Pharm.D., M.B.A.
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Tamiflu (Oseltamivir Phosphate)
Capsules: 30 mg, 45 mg, 75 mg
Powder for Oral Suspension: 6 mg/mL

Application Type/Number: NDA 021087/S-062 and 021246/S-045

Applicant: Hoffmann-La Roche, Inc.

OSE RCM #: 2012-1565

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed package insert labeling for Tamiflu (Oseltamivir Phosphate) Capsules (NDA 021087/S-062) and Oral Suspension (NDA 021246/S-045) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

This efficacy supplement, NDA 021087/S-062 and 021246/S-045, provides for the dosing recommendation for the treatment of influenza in infants with a post conceptual age of at least ^(b)₍₄₎ weeks to 1 year of age who have been symptomatic for no more than 2 days. It should be noted that both Tamiflu products share the same package insert labeling.

1.2 REGULATORY HISTORY

Tamiflu (Oseltamivir Phosphate) is currently marketed in the United States. Tamiflu Capsules were approved by the FDA on October 27, 1999 under NDA 021087. Tamiflu Oral Suspension was approved on December 14, 2000 under the NDA 021246.

1.3 PRODUCT INFORMATION

The following product information is provided in the June 21, 2012 submission.

- Active Ingredient: Oseltamivir Phosphate
- Indication of Use: For the treatment of influenza in patients 1 year and older who have been symptomatic for no more than 2 days, and for the prophylaxis of influenza in patients 1 year and older
- Route of Administration: Oral
- Dosage Form: Capsules and Oral Suspension
- Strength: Capsules: 30 mg, 45 mg, and 75 mg; Oral suspension: 6 mg/mL
- Dose and Frequency:
 - Treatment of influenza
 - Adults and adolescents (13 years and older): 75 mg twice daily for 5 days
 - Pediatric patients (1 year to 12 years of age): Based on weight twice daily for 5 days
 - Renally impaired patients (creatinine clearance 10-30 mL/min): Reduce to 75 mg once daily for 5 days
 - Prophylaxis of influenza
 - Adults and adolescents (13 years and older): 75 mg once daily for at least 10 days
 - Community outbreak: 75 mg once daily for up to 6 weeks
 - Pediatric patients (1 year and older): Based on weight once daily for 10 days

- Community outbreak: Based on weight once daily for up to 6 weeks
- Renally impaired patients (creatinine clearance 10-30 mL/min):
Reduce to 75 mg once every other day or 30 mg once daily

Table 1: Treatment and Prophylaxis Dosing of Oral TAMIFLU for Influenza for Patients 1 Year of Age and Older Based on Body Weight

Weight (kg)	Weight (lbs)	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days	Volume of Oral Suspension (6 mg/mL) for each Dose*	Number of Bottles of Oral Suspension to Dispense	Number of Capsules and Strength to Dispense
15 kg or less	33 lbs or less	30 mg twice daily	30 mg once daily	5 mL	1 bottle	10 Capsules 30 mg
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg twice daily	45 mg once daily	7.5 mL	2 bottles	10 Capsules 45 mg
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg twice daily	60 mg once daily	10 mL	2 bottles	20 Capsules 30 mg
41 kg or more	89 lbs or more	75 mg twice daily	75 mg once daily	12.5 mL	3 bottles	10 Capsules 75 mg

- How Supplied: Capsules: 30-mg capsules, 45-mg capsules, and 75-mg capsules;
Oral Suspension: 6 mg/mL
- Storage: Store the capsules at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Store dry powder at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Store constituted suspension under refrigeration for up to 17 days at 2° to 8°C (36° to 46°F). Do not freeze. Alternatively, store constituted suspension for up to 10 days at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Tamiflu medication error reports. We also reviewed the proposed Tamiflu insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1. Since the last label revision occurred on March 21, 2011, our AERS search was initiated using this date to present date.

Table 1: AERS Search Strategy	
Date	March 21, 2011 - present
Drug Names	Oseltamivir (active ingredient) Tamiflu (trade name) Osletamiv% (verbatim term) Tamifl% (verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search identified 91 reports. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². After individual review, 83 reports were not included in the final analysis for the following reasons:

- Foreign cases involving:
 - Adverse drug reaction unrelated to medication error
 - Accidental ingestion
 - Overdoses (causes not reported, outcomes include rash, increased body temperature, laughing improperly, urticaria, fatigue, malaise, filmy vision, nausea and diarrhea)
 - Expired drug use (causes and outcomes not reported)
 - Wrong patient (causes and outcomes not reported)
 - Wrong technique (causes included not adding water to the powder; outcomes not reported)
- U.S. cases involving:
 - Accidental overdose
 - Expired drug use (causes and outcomes not reported)

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

- Dose omissions (causes and outcomes not reported)
- No medication error reported
- Product quality issues from consumers complaining of the bitter taste of the reconstituted suspension resulting in patients vomiting

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted June 21, 2012

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed the proprietary name (OSE RCM # 00-0248, dated December 7, 2000), the labels and labeling (OSE RCM # 2010-2272, dated March 10, 2011), completed a postmarketing safety review (OSE RCM # 06-0158, dated September 1, 2006), attended a Type A Meeting (OSE RCM # 2008-1447, dated September 22, 2008), completed a Usability Study Protocol Review (OSE RCM # 2011-3176, dated November 2, 2011), and a Protocol Review (OSE RCM # 2011-3280, dated October 4, 2011). Thus, we reviewed them to ensure all of our recommendations were implemented. Our evaluation found that all of our recommendations were implemented.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the Tamiflu product design as well as the associated labels and labeling.

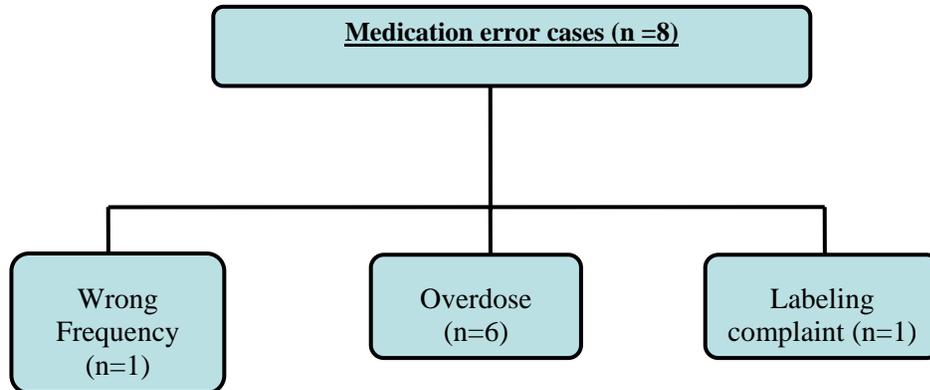
3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, eight Tamiflu medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of cases included in the review by type of error.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Figure 1: Tamiflu medication errors (n = 8) categorized by type of error



Wrong Frequency:

- ISR # 7363894 (March 21, 2011): Patient received therapy with oral Tamiflu at a dose of 2 mL twice daily. The reported stated that the pharmacy had dispensed the medication and labeled it with the instructions to be administered four times a day instead of two times a day as prescribed. The patient had only taken two doses. Outcomes were not reported.

Overdose:

- ISR # 7377866 (March 28, 2011): A patient was prescribed Tamiflu 75 mg oral capsules twice daily for five days. However the patient took 2 capsules, equaling 150 mg twice daily for 2 days. Cause and outcomes were not reported.
- ISR # 7386600 (March 31, 2011): A patient started therapy with Tamiflu Oral Suspension with a dose of 120 mg twice daily. The pharmacist stated that the patient was receiving twice the dose prescribed. The patient was supposed to take 60 mg twice a day and instead, the patient took 120 mg twice a day. The reporter stated the cause of the error was pharmacist error. Outcomes were not reported.
- ISR # 7402740 (April 8, 2011): A patient started treatment with Tamiflu “15/mL” twice daily. The mother reported that on the same day that the patient received the drug, the pharmacy made a mistake on the amount her son was supposed to receive. Her son received 3 doses of Tamiflu at twice the recommended amount. The patient experienced diarrhea.
- ISR # 7568266 (June 23, 2011): A patient was prescribed Tamiflu 12 mg/mL Oral Suspension at a dose of 3.75 mL twice a day. The prescription was filled in error as Tamiflu 12 mg/mL suspension teaspoonfuls twice a day. The patient

received one 3.75 teaspoonful dose on the first day of therapy and then two 3.75 teaspoonful doses the next day. The patient experienced nausea and vomiting

- ISR # 8038013 (January 11, 2012): A physician prescribed Tamiflu 45 mg/day for a patient and the pharmacy filled the prescription from an older Tamiflu suspension with a concentration of 12 mg/mL. The patient was given oral Tamiflu 89 mg per 1.5 teaspoonfuls twice a day for 2 days. The pharmacist stated this was overdose because she received more than the typical adult dose and was referred to the poison center for further assistance. Outcomes were not reported.
- ISR # 8238122 (March 27, 2012): A patient was prescribed Tamiflu and the physician originally wrote the order for the 12 mg/mL concentration. When he got to the pharmacy he was told that it was the old formulation and that they would convert it to the new formulation. However the pharmacist did not call the physician to verify dosing. The pharmacy dispensed 4 bottles of Tamiflu and the label read as 6 mg/mL to be given 20 mL twice daily. This meant the total daily dose was 40ml. On the same day, the child took her first dose. The next day, she vomited and continued to vomit for two days. On the third day, the patient's fever got worse and went up to 104.0 degrees. It was reported that the Tamiflu was not working. She was given Acetaminophen and Ibuprofen staggered every 2 hours and her fever came down to 99.0 degrees. The fever eventually resolved.

Labeling Complaint:

- ISR # 7671529 (August 9, 2011): The reporter stated that the Tamiflu package insert is confusing. In the table titled, "Table 1: Treatment and Prophylaxis Dosing of Oral Tamiflu for Influenza for Patients 1 Year of Age and Older Based on Body Weight", the table presents a weight-based dosing chart from 15 kg to 41 kg. Further in the package insert, it states standard dosing for patients 13 years of age or older is 75 mg once daily for prophylaxis and twice daily for treatment. It is unclear what correct dosing should be for patients who are 13 years or older and weigh under 41 kg. The reporter spoke with a Genetech representative and was told that any patient over the age of 13 should receive adult dosing. The reporter stated that the title of Table 1 should read "For patients age 1 to 12".

After review of the proposed insert labeling, we find that the Applicant has made revisions to the Dosage and Administration section that may mitigate the above mentioned medication errors, such as revising the title of Table 1. However, we have further recommendations that may help eliminate the risk of the above mentioned medication errors from occurring.

3.2 INSERT LABELING RISK ASSESSMENT

A review of the insert labeling identified the following inconsistencies within the package insert labeling:

- Table 1 of the Dosage and Administration section
 - In the title, the word "of" in (5 day of dosing) does not seem to be grammatically correct.

- The table has weight represented in terms of both kilograms and pounds. The preferred practice in medicine is to use the metric system to express weight, volume, and units. There are exceptions to this practice, such as over-the-counter (OTC) product labeling. Having both kilograms and pounds for a prescription drug product can be confusing to prescribers. A practitioner could misread the weight columns and select the wrong dose for a patient. Removing all references to dosing in pounds will help alleviate confusion with associating a weight to a dose.
- The Treatment and Prophylaxis dosing columns do not have the frequency in the title. Incorporating a frequency into the title or header can help to further differentiate the treatment and prophylaxis dosing. This may help prevent prescribing errors.

4 CONCLUSIONS

DMEPA concludes that the proposed insert labeling is unacceptable due to inconsistencies in Table 1 of the Dosage and Administration section.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

A. Insert Labeling

- Table 1 of the Dosage and Administration section
 - In the title of Table 1, remove the word (b) (4) after (5 day) to make it grammatically correct.
 - The table has weight represented in terms of both kilograms and (b) (4). The preferred practice in medicine is to use the metric system to express weight, volume, and units. There are exceptions to this practice, such as over-the-counter (OTC) product labeling. Having both kilograms and (b) (4) for a prescription drug product can be confusing to prescribers. (b) (4)
 - Insert the phrase “(Twice Daily Dosing)” under the title “Treatment Dosing for 5 days” and the phrase “(Once Daily Dosing)” under the title “Prophylaxis Dosing for 10 days” to help further distinguish between the two regimens.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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

/s/

MORGAN A WALKER
11/15/2012

JAMIE C WILKINS PARKER
11/16/2012

SCOTT M DALLAS
11/16/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 21087 NDA # 21246 BLA#	NDA Supplement #: S- 062 NDA Supplement #: S-045 BLA Supplement #	Efficacy Supplement Type SE-5 and pediatric
Proprietary Name: TAMIFLU Established/Proper Name: oseltamivir phosphate Dosage Form: capsules; oral suspension Strengths: 30, 45 and 75 mg capsules; 6 mg/mL (powder for oral suspension)		
Applicant: Hoffmann-La Roche, Inc. Agent for Applicant (if applicable): Genentech, Inc.		
Date of Application: June 21, 2012 Date of Receipt: June 21, 2012 (NDA 21-087/S-062 received June 22, 2012) Date clock started after UN: N/A		
PDUFA Goal Date: December 21, 2012	Action Goal Date (if different):	
Filing Date: August 20, 2012	Date of Filing Meeting: July 31, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): expanded patient population to include treatment for under one year of age		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 53093				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1444 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p>PREA</p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			consult sent 7-12-12
MedGuide, PPI, IFU (plus PI) consulted to Patient Labeling Team? (<i>send WORD version if available</i>)	X			consult sent 7-12-12
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			consult sent 7-12-12
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 31, 2012

NDA/Supp #: 21087/S-062 and 21246/S-045

PROPRIETARY NAME: TAMIFLU

ESTABLISHED/PROPER NAME: oseltamivir phosphate

DOSAGE FORM/STRENGTH: 30, 45, 75 mg capsules and 6mg/mL powder for oral suspension

APPLICANT: Hoffmann-La Roche, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Expands the patient population for the treatment of influenza in infants with a post conceptual age of ^(b)₍₄₎ weeks to one year of age

BACKGROUND: Tamiflu is currently approved under NDA 21087 (capsules) and NDA 21246 (powder for oral suspension). Tamiflu is indicated for (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 and (2) prophylaxis of influenza in patients 1 year and older.

These supplements provide two pivotal pediatric studies for review (1) CASG114 entitled “A Pharmacokinetic/Pharmacodynamic and Safety Evaluation of Oseltamivir (Tamiflu®) for the Treatment of Children Less than 24 Months of Age with Confirmed Influenza Infection” and (2) WP22849 entitled “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.”

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Thompson	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Linda Lewis		Y
Clinical	Reviewer:	Tafadzwa Vargas-Kasambira	Y
	TL:	Linda Lewis	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	

	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Damon Deming	Y
	TL:	Jules O'Rear	Y
Clinical Pharmacology	Reviewer:	Jenny Zheng	Y (phone)
	TL:	Shirley Seo	Y (phone)
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ita Yuen	N
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Steve Miller	N
	TL:	Tom Oliver	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:	N/A	

OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	DMPP Reviewer: Latonia Ford DMPP TL: Barbara Fuller DMEPA Reviewer: Morgan Walker DMEPA TL: Jamie Wilkins-Parker DDTCP Reviewer: Kemi Asante DPP Reviewer: Jessica Fox DDTCP/DPP TL: Olga Salis	Y (phone) N Y N N N N	
Other attendees	Jee Eun Lee, Pharmacometrics Reviewer Yaning Wang, Pharmacometrics TL		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: No comments</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<p>Comments: To be included in filing letter</p>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? 	<input type="checkbox"/> YES

<p>If no, explain:</p>	<input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments: No comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: No comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: No changes proposed</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Debbie Birnkrant, M.D.</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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
08/28/2012

KAREN D WINESTOCK
08/28/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 21087/S-062 and NDA 21246/S-045

Application Type: Efficacy Supplement (**Expand patient population to include patients with a post conceptual age of at least (b)(4) weeks to less than 1 year of age**)

Name of Drug: TAMIFLU (oseltamivir phosphate) 30, 45, 75 mg capsules and 6 mg/mL powder for oral suspension

Applicant: Hoffmann-La Roche, Inc.

Submission Date: June 21, 2012

Receipt Date: June 21, 2012 (NDA 21246) and June 22, 2012 (NDA 21087)

1.0 Regulatory History and Applicant's Main Proposals

These supplements propose an expanded patient population for the treatment of influenza in infants with a post conceptual age of at least (b)(4) weeks to 1 year of age.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A** 12. All text must be **bolded**.
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- YES** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- YES** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

YES

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

Comment:

N/A

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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
08/28/2012

KAREN D WINESTOCK
08/28/2012

MEMORANDUM

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

DATE: August 24, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

Director, Investigations Branch

(b) (4)

Director, Investigations Branch

(b) (4)

Director, Investigations Branch

(b) (4)

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA, Pre-Approval Data
Validation Inspection** Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 21246/S-45 and NDA 21-087/S-62
DRUG: Tamiflu (Oseltamivir Phosphate)
SPONSOR: Hoffmann-La Roche, Inc.

Please note this is an Amendment to the inspection assignment.
The analytical site for Study WP20749 has closed, and records
have been moved to the (b) (4)

This memo requests that you arrange inspections of the clinical and analytical portions of the following pharmacokinetic and safety studies. **A DBGLPC scientist with specialized knowledge may participate in the inspections of the analytical sites to provide scientific and technical expertise. Please contact the DBGLPC point of contact (POC) upon receipt of this assignment to arrange scheduling of the analytical inspection. All of these inspections should be completed before [REDACTED] (b) (4)** Following identification of the FDA investigators, background material will be forwarded directly. Please contact the POC for background materials

Please do not identify the application type or number, the studies to be inspected, the drug name, or the names of the study investigators prior to the start of inspection.

Study Number: WP22849
Study Title: "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"

Clinical Site# 1: Charité Universitätsmedizin Berlin
Klinik für Pädiatrie mit Schwerpunkt
Pneumologie und Immunologie
Augustenburger Platz 1
D-13353 Berlin, Germany
TEL: +49 30 450-50
FAX: Not available
Investigator: Barbara Rath, M.D.
TEL: +49 30 450-566-182
Email: Barbara.Rath@gmail.com

Study Number: WP20749 (CASG 114)
Study Title: "A pharmacokinetic/pharmacodynamic and safety evaluation of Oseltamivir (Tamiflu®) for the treatment of children less than 24 months of age with confirmed influenza infection (CASG 114)"

Clinical Site# 1: University of Texas Southwestern Medical
Center at Dallas
5323 Harry Hines Blvd.
Dallas, TX 75390
TEL: (214)648-3753
FAX: (214)648-2481

Clinical Site# 2: Children's Medical Center
1935 Medical District Drive
Dallas, TX 75235
TEL: (214)456-7000

Clinical Site# 3: Parkland Health and Hospitals Systems
5201 Harry Hines Blvd.
Dallas, TX 75235
TEL: (214)590-8000

Investigator: **Pablo J. Sanchez, M.D.**
(same for sites 1, 2, and 3 in TX)

Contact Info: **TEL: (214)648-3753**
FAX: (214)648-2481
Email: pablo.sanchez@utsouthwestern.edu

Clinical Site# 4: The Children's Hospital of Alabama
1600 7th Avenue South
Birmingham, AL 35233
TEL: (205)996-6097, (205)638-9100
FAX: (205)975-9972

Clinical Site# 5: The University of Alabama Hospital,
619 19th Street
Birmingham, AL 35249
TEL: (205)934-4011

Investigator: **David Winston Kimberlin, M.D.**
(same for sites 4 and 5 in AL)

Contact Info: **TEL: (205)996-6097; (205)934-2424**
FAX: (205)975-9972
Email: dkimberlin@peds.uab.edu

Please assure the following during the inspection:

- Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the site.
- Please verify the protocol and actual study conduct, IRB approval, inclusion/exclusion criteria, adverse events, concomitant medication, drug accountability, as well as the source documents and case report forms for dosing.
- Please scrutinize the SOPs for study related procedures.
- Please check the dosing logs to confirm that correct drug products were administered to the subjects.
- Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and

dated consent forms, and comment on this informed consent check in the EIR.

- In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report.
- Please collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

ANALYTICAL:

Study Number: WP22849

Analytical Site: [REDACTED] (b) (4)
[REDACTED]
[REDACTED] (b) (4)
[REDACTED] (b) (4)

Investigator:

Contact Person: [REDACTED] (b) (4)
[REDACTED]

Methodology: LC-MS/MS
Method code: PBRL-RD-1018

Study Number: WP20749 (CASG 114)

Analytical Site: [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] (b) (4)

Investigator:

Methodology: LC-MS/MS
Method code: [REDACTED] (b) (4) SAP.055

Please confirm the following during the inspection:

- All pertinent items related to the analytical method used for the measurement of Oseltamivir and Oseltamivir carboxylate concentrations in human plasma should be examined.
- The accuracy of the analytical data provided in the NDA submission by the applicant should be compared with the original documents at the site.

- **The method validation and the actual assay of the subject plasma samples, the variability between and within runs, QC, demonstration of accuracy and precision in matrix using standards and QCs prepared from separate stocks, stability of subject samples covered by validated stability period.**
- **Scrutinize the number of repeat assays of the subject plasma samples, and the reason for such repetitions, the SOP(s) for repeat assays and other study specific procedures.**
- In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

In addition to the compliance program elements, additional study specific instructions, if any, may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC/OSI reviewer or POC be contacted for any further follow-up instructions before the inspection regarding any data anomalies or questions noted during review of study report. The ORA investigator should contact the DBGLPC POC for inspection related questions or clarifications.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive to Sam Haidar and POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC Point of Contact: Foreign Sites
Arindam Dasgupta, Ph.D.
(301)796-3326
arindam.dasgupta@fda.hhs.gov

Domestic Sites
Jyoti B. Patel, Ph.D.
(301)796-4617
jyoti.patel@fda.hhs.gov

CC:

CDER OSI PM TRACK

OSI/DBGC/Taylor/Haidar/Skelly/Patel/Dasgupta/Biswas/Dejernett/CF
HFC-130/ORA HQ DFFI IOB BIMO

OND/OAP/DAVP/Thompson

OTS/OCP/DCP4/Zheng

Page 6 - BIMO Assignment, NDA 21246/S-45 and NDA 21-087/S-62,
Tamiflu (Oseltamivir Phosphate)

HFR-SW150/Turcovski (DIB)/

HFR-SW1540/Martinez (BIMO)/HFR-SW1515/Alanna Bias (BIMO)

HFR-SE350/Clarida (DIB)/HFR-SE450/Abel/Blakely (BIMO)

HFR-CE750/Jasukaitis (DIB)/Bellamy (BIMO)

Draft: JBP 8/21/2012

Edit: GB 8/22/2012, MFS/8/22/2012

Amend: JBP 8/24/2012, MFS 8/24/2012

OSI File #6368; O:\BE\assigns\amendbio21246.doc

FACTS: 1434272

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

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

/s/

JYOTI B PATEL
08/24/2012

MICHAEL F SKELLY
08/24/2012
Skelly signing on behalf of Dr. Haidar

MEMORANDUM

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

DATE: August 22, 2012

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

Director, Investigations Branch

(b) (4)

Director, Investigations Branch

(b) (4)

From: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA, Pre-Approval Data Validation Inspection** Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21246/S-45 and NDA 21-087/S-62
DRUG: Tamiflu (Oseltamivir Phosphate)
SPONSOR: Hoffmann-La Roche, Inc.

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Klinik für Pädiatrie mit Schwerpunkt
Pneumologie und Immunologie
Augustenburger Platz 1
D-13353 Berlin, Germany
TEL: +49 30 450-50
FAX: Not available

Investigator: Barbara Rath, M.D.
TEL: +49 30 450-566-182
Email: Barbara.Rath@gmail.com

Study Number: WP20749
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Dallas, TX 75390
TEL: (214)648-3753
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ANALYTICAL:

Study Number: WP22849

Analytical Site:

(b) (4)

(b) (4)

Investigator:

Contact Person:

(b) (4)

Methodology:

LC-MS/MS
Method code: PBRL-RD-1018

Study Number: WP20749

Analytical Site:

(b) (4)

(b) (4)

Investigator:

Contact Person:

(b) (4)

Methodology:

LC-MS/MS
Method code: (b) (4) SAP.055

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DBGLPC Point of Contact: Foreign Sites
Arindam Dasgupta, Ph.D.
(301)796-3326
arindam.dasgupta@fda.hhs.gov

Domestic Sites
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(301)796-4617
jyoti.patel@fda.hhs.gov

CC:

CDER OSI PM TRACK
OSI/DBGC/Taylor/Haidar/Skelly/Patel/Dasgupta/Biswas/Dejernett/CF
HFC-130/ORA HQ DFFI IOB BIMO
OND/OAP/DAVP/Thompson
OTS/OCP/DCP4/Zheng
HFR-SW150/Turcovski (DIB)/
HFR-SW1540/Martinez (BIMO)/HFR-SW1515/Alanna Bias (BIMO)
HFR-SE350/Clarida (DIB)/HFR-SE450/Abel/Blakely (BIMO)
Draft: JBP 8/21/2012
Edit: GB 8/22/2012, MFS/8/22/2012

Page 6 - BIMO Assignment, NDA 21246/S-45 and NDA 21-087/S-62,
Tamiflu (Oseltamivir Phosphate)

OSI File #6368; O:\BE\assigns\bio21246.doc

FACTS: 1434272

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

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/s/

JYOTI B PATEL
08/22/2012

MICHAEL F SKELLY
08/23/2012
Skelly signing on behalf of Dr. Haidar

WILLIAM H TAYLOR
08/23/2012