

**Division of Antiviral Drug Products (DAVDP)  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
Food and Drug Administration**

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**TELEFACSIMILE TRANSMISSION RECORD**

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To: Barbara Taylor, Ph.D., Program Director, Drug  
Regulatory Affairs

Fax Number: (973) 562-3700

Date: September 19, 2000

Company: Hoffmann-La Roche Inc.

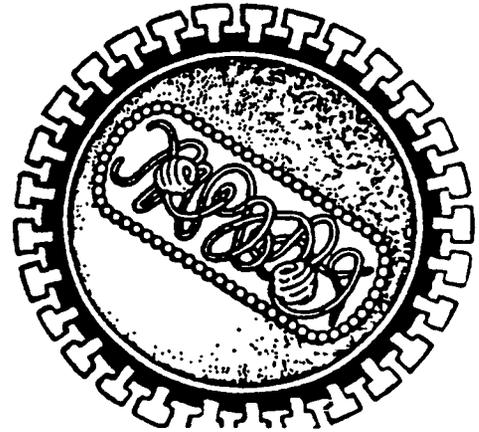
No. of pages (excluding cover): 2

Message: Comments for NDA 21-246 and IND 53,093

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From: Grace N. Carrouze, Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

**Mail:**  
Division of Antiviral Drug Products  
5600 Fishers Lane (HFD-530)  
Rockville, Maryland 20857

**Courier:**  
Division of Antiviral Drug Products  
HFD-530  
Document Control Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** September 19, 2000

**To:** Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

**Address:** Hoffman-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

**From:** Grace N. Carmouze, Regulatory Project Manager, HFD-530

**Through:** Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530  
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530  
Jenny Zheng, Ph.D., Pharmacokinetics Reviewer, HFD-530

**NDA:** 21-246

**Subject:** Clinical Pharmacology and Biopharmaceutics Comment

LSI  
LSI  
LSI

This comment is being conveyed on behalf of Dr. Jenny Zheng, Pharmacokinetics Reviewer, and is directed towards your NDA submission dated June 15, 2000.

1. The adult pharmacokinetic data from studies NP15717 and WP15525 were used to compare with data from studies NP15826 and WV15758 in children. Please provide a rationale for using the data derived from the influenza challenge study in adults (NP15717) and pk study in healthy adults (WP 15525) instead of using the data from a larger database from the phase III clinical trials in adults.

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

LSI  
Grace N. Carmouze /  
Regulatory Project Manager  
Division of Antiviral Drug Products

**Concurrence**

HFD-530/MOTL/Murray  
HFD-530/BiopharmTL/Reynoldsk  
HFD-530/Biopharm/Zheng  
HFD-530/RPM/Carmouze-19-Sep-00

LS  
LS

**cc:**

Original NDA 21-246  
Division File  
HFD-530/MO/Lewis  
HFD-530/BiopharmTL/Reynoldsk  
HFD-530/Biopharm/Zheng  
HFD-530/RPM/Carmouze

**Facsimile**

Location: V:\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\000919fx2.doc

JS 9/20/00

Division of Antiviral Drug Products (DAVDP)  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
Food and Drug Administration

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TELEFACSIMILE TRANSMISSION RECORD

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To: Barbara Taylor, Ph.D., Program Director, Drug  
Regulatory Affairs

Fax Number: (973) 562-3700

Date: September 19, 2000

Company: Hoffmann-La Roche Inc.

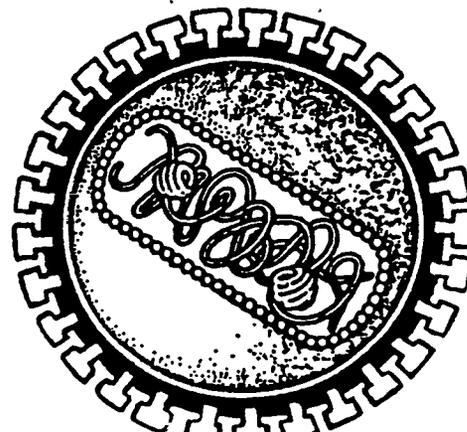
No. of pages (excluding cover): 1

Message: PK Comments for NDA 21-246

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From: Grace N. Carmouze, Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

Mail:  
Division of Antiviral Drug Products  
5600 Fishers Lane (HFD-530)  
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9201 Corporate Blvd.  
Rockville, Maryland 20850

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** September 19, 2000

**To:** Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

**Address:** Hoffman-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

**From:** Grace N. Carmouze, Regulatory Project Manager, HFD-530

**Through:** James Farelly, Ph.D., Pharmacology/Toxicology Team Leader, HFD-530  
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, HFD-530

**NDA:** 21-246

**Subject:** Request for Information

This comment is being conveyed on behalf of Dr. Ita Yuen, Pharmacology/Toxicology Reviewer, and is directed towards your NDA submission dated June 15, 2000.

1. Please submit the results from your Toxicology study SAR 703 that contains information on the degradant ~~\_\_\_\_\_~~ Although, it was mentioned that some testicular pathology was observed in SAR 703, this study was not included in the NDA package.

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

151  
Grace N. Carmouze  
Regulatory Project Manager  
Division of Antiviral Drug Products

Concurrence  
HFD-530/PharmToxTL/Farrelly  
HFD-530/PharmTox/Yuen  
HFD-530/RPM/Carmouze-19-Sep-00

cc:  
Original NDA 21-246  
Division File  
HFD-530/PharmTox/Yuen  
HFD-530/RPM/Carmouze

**Facsimile**

Location: \\CDS030\ODEIV\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\000919fx.doc

*DJS 9/19/00*

Division of Antiviral Drug Products (DAVDP)  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
Food and Drug Administration

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TELEFACSIMILE TRANSMISSION RECORD

---

To: Barbara Taylor, Ph.D., Program Director, Drug  
Regulatory Affairs

Fax Number: (973) 562-3700

Date: September 18, 2000

Company: Hoffmann-La Roche Inc.

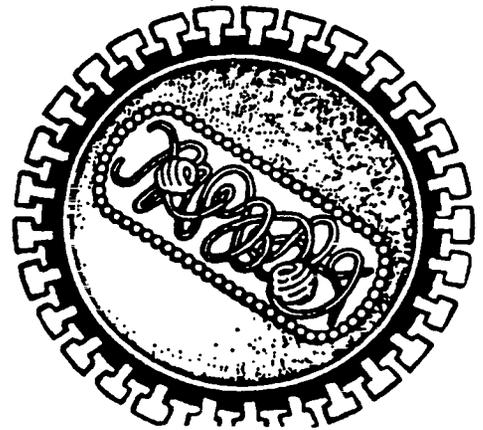
No. of pages (excluding cover): 1

Message: Biopharm comment

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From: Grace N. Carmouze, Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

**Mail:**

Division of Antiviral Drug Products  
5600 Fishers Lane (HFD-530)  
Rockville, Maryland 20857

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9201 Corporate Blvd.  
Rockville, Maryland 20850

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** September 18, 2000

**To:** Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

**Address:** Hoffman-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

**From:** Grace N. Carmouze, Regulatory Project Manager, HFD-530

**Through:** Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530  
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530  
Jenny Zheng, Ph.D., Pharmacokinetics Reviewer, HFD-530

**NDA:** 21-246

**Subject:** Clinical Pharmacology and Biopharmaceutics Comment

This comment is being conveyed on behalf of Dr. Jenny Zheng, Pharmacokinetics Reviewer, and is directed towards your NDA submission dated June 15, 2000.

1. For study WV15758, it is unacceptable to use one plasma concentration to adjust the plasma concentration vs. time profiles. Please re-calculate all PK parameters based on unadjusted concentrations and provide all related information (i.e., plots and simulations).

**MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

LSI  
\_\_\_\_\_  
Grace N. Carmouze  
Regulatory Project Manager  
Division of Antiviral Drug Products

Concurrence

HFD-530/MOTL/Murray

HFD-530/BiopharmTL/Reynoldsk

HFD-530/Biopharm/Zheng

HFD-530/RPM/Carmouze-18-Sep-00

LSI

LSI

cc:

Original NDA 21-246

Division File

HFD-530/MO/Lewis

HFD-530/BiopharmTL/Reynoldsk

HFD-530/Biopharm/Zheng

HFD-530/RPM/Carmouze

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D.S. 9/18/00

7

**Division of Antiviral Drug Products (DAVDP)  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
Food and Drug Administration**

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**TELEFACSIMILE TRANSMISSION RECORD**

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To: Barbara Taylor, Ph.D., Program Director, Drug  
Regulatory Affairs

Fax Number: (973) 562-3700

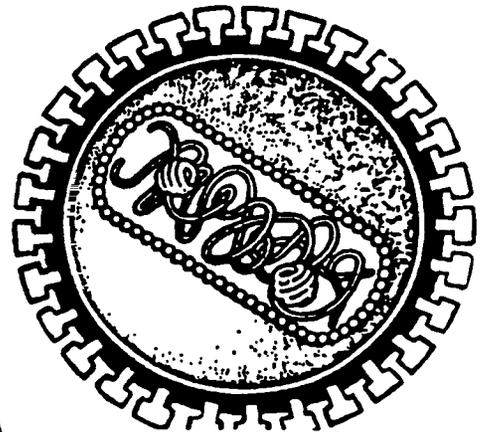
Date: August 29, 2000

Company: Hoffmann-La Roche Inc.

No. of pages (excluding cover): 2

Message: Request for Information

*Handwritten note:*  
Signed (10/24/00)



From: Grace N. Carmouze, Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

**Mail:**

Division of Antiviral Drug Products  
5600 Fishers Lane (HFD-530)  
Rockville, Maryland 20857

**Courier:**

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9201 Corporate Blvd.  
Rockville, Maryland 20850

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Carmouze

Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** August 29, 2000

**To:** Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

**Address:** Hoffman-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

**From:** Grace N. Carmouze, Regulatory Project Manager, HFD-530

**Through:** Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530 *LS*  
Linda Lewis, M.D., Medical Officer, HFD-530 *LS*

**NDA:** 21-246

**Subject:** Request for Information

This comment is being conveyed on behalf of Dr. Linda Lewis, Medical Officer, and is directed towards your NDA submission dated June 15, 2000.

- For each of the patients who were analyzed as having "acute otitis media" please provide the rationale for this determination. Please also include hard copies of the relevant parts of the case report form that were used to come to this conclusion (e.g., for patients diagnosed based on clinical signs/symptoms and supportive tympanometry data, please provide the pages of the case report form that document these).

**MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

*LS*  
Grace N. Carmouze  
Regulatory Project Manager  
Division of Antiviral Drug Products

**Concurrence:**

HFD-530/MOTL/Murray

HFD-530/MO/Lewis

HFD-530/RPM/Carmouze-29-Aug-00

cc:

Original NDA 21-246

Division File

HFD-530/MO/Lewis

HFD-520/MO/Smith

HFD-530/RPM/Carmouze

**Facsimile**

Location: V:\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\000829fx.doc

DJS 8/30/00



Carmouze

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** August 16, 2000

**To:** Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

**Address:** Hoffman-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

**From:** Grace N. Carmouze, Regulatory Project Manager, HFD-530 *LS1*

**Through:** Stephen Miller., Chemistry Team Leader, HFD-530 *LS1*  
Daniel Boring, Ph.D., Chemistry Reviewer, HFD-530  
Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530 *LS1*

**NDA:** 21-246

**Subject:** Response to Proposed Change in Fill Weight

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These comments are being conveyed on behalf of Dr. Boring, Chemistry Reviewer, and are directed towards the e-mail transmission dated August 14, 2000

There are no CMC concerns about your proposal to place an additional \_\_\_\_\_ of product in the Tamiflu for oral suspension. However, DAVDP requests that you conduct the same reconstitution studies on the \_\_\_\_\_ bottle as was done on the \_\_\_\_\_ bottle and submit the results to the pending NDA. Because this product is packaged in a glass container, and you have comparative data that indicates that stability is not a function of fill volume, DAVDP feels that release data plus a commitment to place the \_\_\_\_\_ batches of the \_\_\_\_\_ size on stability would be sufficient.

We would like to emphasize that your proposed fill size is at risk since the bioequivalence data has not been reviewed. If DAVDP does not agree with your assessment for dosing, then you may have chosen the incorrect fill weight and will have to propose another fill weight.

Additionally, DAVDP requests that you provide estimates of the usage patterns that you expect to see in the marketplace as a function of patient age. We are concerned that a single market presentation that captures the extreme of dosing may result in many patients throwing away a large portion of unused medication. In fact, you may want to consider at \_\_\_\_\_ to efficiently provide medication over the large weight variation seen in the intended patient population.

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151

Grace N. Carmouze  
Regulatory Project Manager  
Division of Antiviral Drug Products

**Concurrence:**

HFD-530/ChemTL/Miller  
HFD-530/Chem/Boring  
HFD-530/MOTL/Murray  
HFD-530/RPM/Carmouze-

cc:

Original NDA 21-246  
Division File  
HFD-530/ChemTL/Miller  
HFD-530/Chem/Boring  
HFD-530/MO/Lewis  
HFD-530/RPM/Carmouze

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Location: V:\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\0008076<sup>14</sup>fx.DOC

*DFS* 8/16/00  
v

**Division of Antiviral Drug Products (DAVDP)  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
Food and Drug Administration**

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**TELEFACSIMILE TRANSMISSION RECORD**

---

To: Barbara Taylor, Ph.D., Program Director, Drug  
Regulatory Affairs

Fax Number: (973) 562-3700

Date: August 8, 2000

Company: Hoffmann-La Roche Inc.

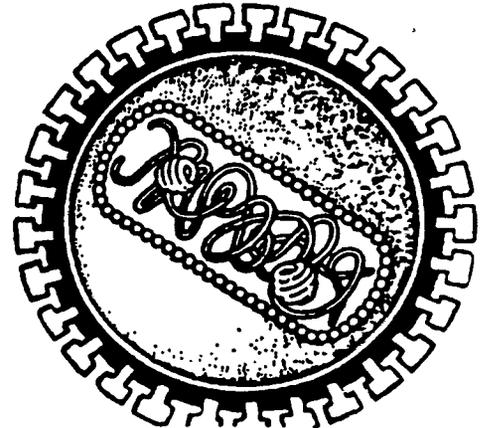
No. of pages (excluding cover): 1

Message: Pharmacokinetics comments

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From: Grace N. Carmouze, Project Manager

Telephone: (301) 827- 2335

Fax Number: (301) 827-2471

**Mail:**  
Division of Antiviral Drug Products  
5600 Fishers Lane (HFD-530)  
Rockville, Maryland 20857

**Courier:**  
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9201 Corporate Blvd.  
Rockville, Maryland 20850

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Carmouze

Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**Date:** August 2, 2000

**To:** Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

**Address:** Hoffman-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

**From:** Grace N. Carmouze, Regulatory Project Manager, HFD-530

**Through:** Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530  
Jenny Zheng, Ph.D., Pharmacokinetics Reviewer, HFD-503  
Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530

**NDA:** 21-246

**Subject:** Pharmacokinetics Comments

LSI  
LSI  
LSI

These comments are being conveyed on behalf of Dr. Zheng, Pharmacokinetics Reviewer, and are directed towards the July 15, 2000 NDA submission.

1. Please investigate whether homogeneity issues were observed with the clinical trial formulation of oseltamivir. Based on the homogeneity issues observed with the previous market formulation, as well as the steady-state  $C_{min}$  difference between patients with extensive PK evaluation and patients with limited PK data in study WV15758, we believe that an investigation is necessary.
2. Please submit all available PK data, including data from study WV15731.

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

LSI  
Grace N. Carmouze  
Regulatory Project Manager  
Division of Antiviral Drug Products

Concurrence:

HFD-530/BiopharmTL/Reynolds

HFD-530/Biopharm/Zheng

HFD-530/MOTL/Murray

HFD-530/MO/Lewis

HFD-530/RPM/Carmouze-

cc:

Original NDA 21-246

Division File

HFD-530/BiopharmTL/Reynolds

HFD-530/Biopharm/Zheng

HFD-530/MO/Lewis

HFD-530/RPM/Carmouze

LS

LS

Facsimile

Location: V:\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\000807fx.DOC

DJS 8/9/00

# DIVISION OF ANTIVIRAL DRUG PRODUCTS

Center for Drug Evaluation and Research  
Food and Drug Administration  
9201 Corporate Boulevard, HFD-530  
Rockville, MD 20850

## FACSIMILE TRANSMISSION COVER SHEET

Date: 07/27/00 Number of Pages (including cover sheet): 3

To: Barb Taylor

Company: HLR

Fax Number: 973-562-3700

Message: NDA 21-246

From: **Marsha S. Holloman, BS Pharm, JD**

Title: **Regulatory Project Manager HFD-530**

Telephone: **(301) 827-2335**

Fax: **(301) 827-2471**

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** July 27, 2000

**To:** Barbara Taylor, Ph.D., Program Director, Drug Regulatory Affairs

**Address:** Hoffman-La Roche Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

**From:** Grace N. Carmouze, Regulatory Project Manager, HFD-530

**Through:** Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530  
Jenny Zheng, Ph.D., Pharmacokinetics Reviewer, HFD-530  
Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530

**NDA:** 21-246

**Subject:** Pharmacokinetics comments

BSI  
- BSI  
LSI

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These comments are being conveyed on behalf of Dr. Jenny Zheng, Pharmacokinetics Reviewer, and are directed towards your submission dated June 15, 2000.

1. Without reviewing the pivotal bioequivalence study, it is not possible for us to assess the proposed pediatric dosing regimens and dosing syringe markings.
2. During the February 18, 2000 pre-NDA meeting, DAVDP recommended that you conduct a regression analysis to obtain an exposure closer to the approved 75 mg twice daily dosing. However, this analysis is not included in the NDA submission. Please explain.
3. Please provide SAS transport files of the pharmacokinetic/pharmacodynamic data for Section 6 of the NDA.

**MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

51

~~Grace N. Carmouze~~  
Regulatory Project Manager  
Division of Antiviral Drug Products

Concurrence:

HFD-530/BiopharmTL/Reynolds  
HFD-530/Biopharm/Zheng  
HFD-530/MOTL/Murray  
HFD-530/RPM/Carmouze-27-Jul-00

LS  
LS

cc:

Original NDA 21-246  
Division File  
HFD-530/BiopharmTL/Reynolds  
HFD-530/Biopharm/Zheng  
HFD-530/MO/Lewis  
HFD-530/RPM/Carmouze

Facsimile

Location: \\CDS030\ODEIV\DAVDP\CSO\CARMOUZE\NDA\21246\FAXES\000727fx.doc

DJS 7/28/00



**MEMORANDUM OF INDUSTRY MEETING**

**Date of Meeting:** March 20, 2000      **Time:** 10:00 A.M.  
**IND:** 53,093  
**Drug:** Osetamivir phosphate (Ro 64-0796)  
**Indication:** Treatment of Influenza  
**Sponsor:** Hoffmann-La Roche, Inc.  
**Type of Meeting:** Chemistry, Manufacturing and Controls Pre-NDA Meeting  
**Meeting Chair:** Daniel Boring, Ph.D.      **Sponsor Chair:** Duane Voss  
**Project Manager:** Grace Carmouze

**DAVDP Attendees:**

Stephen Miller, Ph.D., Chemistry Team Leader  
Daniel Boring, Ph.D., Chemistry Reviewer  
Jeffrey Murray, M.D., M.P.H., Medical Team Leader  
Linda Lewis, M.D., Medical Reviewer  
Prabhu Rajagopalan, Ph.D., Pharmacokinetics Reviewer  
Grace Carmouze, Regulatory Project Manager

**Division of New Drug Chemistry III Attendees:**

Chi-Wan Chen, Ph.D., Director

**External Constituents:**

**Hoffmann-La Roche, Inc:**

Joanna McNamara, Program Director, Regulatory Affairs  
Barbara Taylor, Ph.D., Program Director, Regulatory Affairs  
Duane Voss, Program Director, Regulatory Affairs  
Rudolf Hausmann, Ph.D., Technical Project Manager  
Mathias Usteri, Ph.D., Technical Drug Regulatory Affairs  
Hans-Guenter Kaestle, Ph.D., Pharmaceutical Development  
Ulrich Fritz, Ph.D., Galenical Development-Analytics  
arah Orris, Pharmaceutical Development  
Peter Collum, Package Design and Development

**Background:** In a facsimile, dated February 2, 2000 (serial no. 196), the sponsor requested a type-B face to face meeting to discuss their filing strategy for the oral suspension formulation of oseltamivir phosphate NDA. In the briefing package, dated March 1, 2000 (serial no. 206), the sponsor indicated that they plan to submit the NDA on [redacted]. The purpose of the meeting was to discuss the CMC comments conveyed to the sponsor on February 24, 2000, via facsimile, and the questions and proposals outlined in the briefing package.

**Discussion:**

{The proceeding text, in bold font, was sent to the sponsor on February 24, 2000, via facsimile transmission.}

1. For both the [redacted] and glass container closure systems, please indicated whether you will be providing the following:
  - A. Moisture permeation data for the container/closure systems used in the supportive stability lots (V36 lots 152, 154 & 159);
  - B. Comparative data on moisture permeation for the container/closure in the primary (HM17, HM18 and HM19) and commercial (C17, C18 and C19) lots. Please also indicate whether the moisture permeation rates between different materials and bottle sizes will investigated.

The sponsor indicated that the original closure is no longer available and a new closure was necessary. It was discussed that [redacted] systems were tested to compare the moisture permeation rates between each system. DAVDP requested that the sponsor provide the following: 1) linkage between the various bottle sizes used in the trials and old closure systems to the proposed market the bottle size and closure system; 2) an analysis of the moisture uptake (i.e. difference in permeation rates) in the NDA; and 3) a written rationale for utilizing the newer closure in the NDA. The sponsor was also informed that the material must be certified for food use.

2. Please provide the proposed drug product specifications.

It was discussed that although the product appears as a suspension, the active drug [redacted] [redacted] are the excipients. Due to this unique characteristic, the sponsor proposed to delete homogeneity, redispersibility, and dissolution tests for the drug product's specifications.

It was discussed that the [redacted] which is an in-process control, would be acceptable as a surrogate for uniformity.

The sponsor was asked why the rate of dissolution did not appear in the bioequivalence study. The sponsor indicated that a rationale would be included in the NDA.

DAVDP expressed concerns that caking may affect the drug product's dissolution and requested to investigate the effects.

The sponsor was requested to conduct a repeat homogeneity test using representative stored batches. In addition, the sponsor was requested to provide a description of the redispersibility studies.

Additionally, DAVDP indicated that moisture content should be a release and stability test, since the drug is [redacted]. In response to a question regarding [redacted] DAVDP stated that as long as there were no changes in stability, the [redacted] is acceptable as an in-process control.

**3. Please verify whether there are changes to the drug substance section of the existing NDA.**

The sponsor indicated that there would no changes to the drug substance section.

**4. Provide the timing schedule for the stability update(s) for the primary batches.**

The sponsor indicated that they will establish the necessary statistical analyses for stability by summer 2000 in preparation for a final analysis in fall 2000. Additionally, the sponsor will submit a revised stability update timeline to DAVDP shortly.

**5. Please provide the sizes of the primary stability and NDA batches. Please also provide the projected scale of commercial manufacture.**

DAVDP stated that the amount of data on the batches sizes for [redacted] and [redacted] stability would be acceptable to establish an expiry. The sponsor indicated that the scale of commercial manufacture was [redacted] which would also be acceptable to DAVDP.

**6. Please indicate whether a dosing device be provided with packaged product.**

The sponsor indicated that a dosing syringe would be included with the package product. The sponsor proposed that the syringe will have three [redacted] markings: 30 mg, [redacted], and 60 mg. It was noted that the [redacted] marking is an option under the sponsor's internal review. This dose would be for those [redacted]

The sponsor indicated that a [redacted] was required to prepare the syringes for marketing. DAVDP informed the sponsor that the proposed markings would require review shortly after the NDA is submitted.

**7. Please indicate whether direct analytical evidence is available to support the complete solution of the drug substance in the reconstituted product.**

It was discussed that homogeneity and dissolution tests were conducted, however, it is unclear whether they demonstrate complete solution.

It was noted that if the product were judged to be a suspension, dissolution tests would need to be conducted on a lot by lot basis.

**8. Please confirm whether complete dissolution occurs quickly.**

When asked about direct evidence for complete solution, the sponsor indicated that the highly viscous suspension was difficult to filter and assay for complete solution. Therefore, unambiguous demonstration of complete solution was difficult. However, the sponsor is going to investigate further. The sponsor was informed that dissolution studies of aged samples should also be conducted.

**9. Please verify whether data are available regarding time to reconstitution for the suspension.**

The recommended testing methodology is not feasible due to the product's high viscosity.

**10. Given the physical and chemical instability of this product in \_\_\_\_\_ container and the apparent need for a separate storage condition for the product contained in \_\_\_\_\_ (vs. glass), please provide a rationale for why for you want to market the product in an \_\_\_\_\_ presentation.**

The sponsor indicated that glass representation is preferred, however, \_\_\_\_\_ they may proceed with the \_\_\_\_\_ presentation. Currently, they are conducting an internal analysis to determine which presentation to market.

**11. Please explain your ability to market a product with an expiration dating period based upon your achievable stability updates. In the absence of quantitative links between the \_\_\_\_\_ and \_\_\_\_\_ batches (moisture permeation, statistical analysis of stability trends, time to reconstitution, etc.), the expiration dating period may be limited to the real-time data available on the primary stability batches**

It was noted that data from the \_\_\_\_\_ batches are significant and can be used in conjunction with the \_\_\_\_\_ stability batch data to estimate a valid expiration dating period. However, the shelf life will be based upon the real-time data on the \_\_\_\_\_ stability batches and must be accompanied by a statistical analysis of the primary data to support the proposed extrapolation.

{The sponsor provided the proceeding text, in bold font, in the briefing package.}

**1. We propose to file the NDA with \_\_\_\_\_ of stability data on Tamiflu Powder for Oral Suspension batches that are strongly supportive, and \_\_\_\_\_ of data on primary stability batches. We acknowledge that the Agency prefers to receive a complete data package at the time of submission and understand that the amount of data (as described above) is limited to support a practical shelf life.**

Additional data ( \_\_\_\_\_ ), however will become available during the review to support at least a \_\_\_\_\_ shelf life.

**Does the Agency concur with this proposal and agree to accept this additional stability data during the review in order to facilitate approval for the flu season.**

This is a review issue.

- 2. We believe that our proposed controls are appropriate for the drug product and will assure consistent quality. Because of drug substance is highly soluble in aqueous medium and the suspension shows a very fast dissolution, we propose that some tests usually required of suspension products are not needed routinely for Tamiflu Suspension: Homogeneity, Redispersibility, and Dissolution. In addition, evaluation of in-process control (IPC) data of the bottle filling process is considered sufficient to control the uniformity of the batch. Does the Agency agree?**

This is a review issue, however, DAVDP indicated that it was premature to delete homogeneity redispersibility, and dissolution at this time.

- 3. The closure supplier is discontinuing the production of the closure used in stability studies with the glass bottle. Since the new trade closure will offer identical contact materials, we propose that moisture vapor transmission testing is sufficient to qualify the container-closure system intended for commercial use. Does the Agency agree?**

This is a review issue; however, in addition to moisture transmission, oxygen transmission, food certification, and equipment operating comparability will be evaluated.

#### MISCELLANEOUS

1. DAVDP requested that the sponsor submit the toxicology study data conducted for the new impurities with the NDA
2. The sponsor indicated that they would provide an electronic version of the NDA as a desk copy only, as it is not compliant with CDER guidelines.
3. The sponsor was requested to submit all labels, including physician's samples with the NDA. The sponsor was also requested to submit data on both the deliverable volume and calibration content of the dosing device.
4. The sponsor will submit the oral suspension NDA along with the pediatric indication.

Signature, Minutes Preparer:

LSI

Date: 6/2/00

Concurrence, Meeting Chair:

LSI

Date: 6/2/00

LSI

Concurrence:

HFD-530/CHEMTL/Miller

HFD-530/CHEM/Boring

HFD-830/DivDir/Chen

HFD-530/MOTL/Murray

HFD-530/MO/Lewis

HFD-530/Biopharm/Rajagopalan

HFD-530/RPM/Carmouze

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LSI

cc:

HFD-530/IND 53,093

HFD-530/Division File

HFD-530/MOTL/Murray

HFD-530/MO/Wu

HFD-530/MO/Lewis

HFD-530/Boring

HFD-530/Micro/Battula

HFD-530/PharmTox/Yuen

HFD-530/Stats/Hammerstrom

HFD-530/Biopharm/Rajagopalan

HFD-530/Biopharm/Reynolds

HFD-530/RPM/Carmouze

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MEETING MINUTES

**Addendum**

It has been noted that while, uniformity of mass was thought to be acceptable during the March 20, 2000 Pre-NDA meeting, recent information discussed during the May 2, 2000 teleconference between the sponsor and DAVDP has lead to a revision of the Division's position on the subject. For further details, please see minutes from May 2, 2000 teleconference.

Concurrence:

HFD-530/CHEMTL/Miller

LSI

HFD-530/CHEM/Boring

LSI

HFD-530/RPM/Carmouze

LSI

**Record of Teleconference****IND:** 53,093**Date:** June 8, 2000**Drug:** Oseltamivir phosphate oral capsules**Sponsor:** Hoffmann-La Roche Pharmaceuticals**BETWEEN: Representatives of Hoffmann-La Roche Pharmaceuticals**

Duane Voss, CMC Regulatory Affairs  
Joanna McNamara, Regulatory Affairs Leader  
Barbara Taylor, Ph.D., Program Director, Regulatory Affairs  
Penelope Ward, M.D., Clinical Scientific Leader  
Daniel O'Day, Program Leader  
Rudolf Hausmann, Ph.D., Technical Project Manager  
Mathias Usteri, Ph.D., Technical Registration  
Peter Collum, Package Development  
David Eichler, Ph.D., Toxicology  
Anita Maurhofer, Ph.D., Technical Supply Leader  
Rose-Marie Meier, Ph.D., Galenical Development Analytics  
Heinz Wiederkehr, Ph.D., Technical Registration

**AND: Representatives of DAVDP**

Steve Miller, Ph.D., Chemistry Team Leader  
Dan Boring, Ph.D., Chemistry Reviewer  
Linda Lewis, Medical Officer  
Jim Farrelly, Ph.D., Pharmacology/Toxicology Team Leader  
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer  
Grace Carmouze, Regulatory Project Manager

**SUBJECT: Additional Oral Suspension Formulation CMC Issues**

**Background:** During the previous teleconference with the sponsor (May 2, 2000), the sponsor indicated that due to manufacturing issue with homogeneity, they would need to investigate some new manufacturing processes. It was agreed that the sponsor would produce        batches to see if the homogeneity issues were resolved. In facsimile transmission (serial number 218), dated May 25, 2000, the sponsor indicated that the homogeneity issue had been resolved, however, higher levels of degradation product        were observed in the trial batches. The purpose of this meeting was to discuss the sponsor's plans to resolve this new issue.

1. The sponsor's proposal to submit the Master Batch Record during the NDA review is acceptable to DAVDP

2. The sponsor indicated that the list of Sample and Method-Validation have been completed and will be submitted with the NDA. Also, the sponsor indicated that the certificate of analysis may need to be submitted as an amendment to the NDA.
3. In response to the sponsor site inspection availability, DAVDP stated that discussion of scheduling should be referred to Office of Compliance. DAVDP will provide the name of a contact person at the Office of Compliance. The sponsor was advised that a foreign inspection late in the review cycle can result in an unfavorable action if unexpected issues arise that cannot be resolved by the action date.
4. The sponsor understood that specification negotiation is a review issue. It was also noted that the specifications will be dependent on the outcome on the stability profile; statistical analyses, due in September, will also be factored into specification negotiation.
5. The sponsor provided information regarding the Qualification of Impurities data facsimile dated May 26, 2000. DAVDP stated that although the information was reasonable, it would be a review issue.
6. The sponsor was informed that discussion of the bioequivalence study would need to take place at a later date.
7. The Division requested that the sponsor provide a table with process improvements and degradants that will include the study number and specifications used.
8. The sponsor indicated that they would include the content uniformity testing information. Additionally, the sponsor will provide additional validation data on \_\_\_\_\_ batches in the Rationale for Specifications section of the NDA.

Concurrence:

- HFD-530/ChemTL/Miller
- HFD-530/Chem/Boring
- HFD-530/PharmToxTL/Farrelly
- HFD-530/PharmTox/Yuen ESC
- HFD-530/RPM/Carmouze

19  
15  
151

cc:

- Original IND 53,093
- Division File
- HFD-530/ChemTL/Miller
- HFD-530/Chem/Boring
- HFD-530/PharmTox/Yuen
- HFD-530/MO/Lewis
- HFD-530/RPM/Carmouze

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**RECORD OF TELECONFERENCE**

7/13/00

14 Page(s) Withheld



**Record of Teleconference**

**IND:** 53,093

**Date:** May 2, 2000

**Drug:** Oseltamivir phosphate oral capsules

**Sponsor:** Hoffmann-La Roche Pharmaceuticals

**BETWEEN:** Representatives of Hoffmann-La Roche Pharmaceuticals

- Duane Voss, CMC Regulatory Affairs
- Joanna McNamara, Regulatory Affairs Leader
- Barbara Taylor, Ph.D., Program Director, Regulatory Affairs
- Penelope Ward, M.D., Clinical Scientific Leader
- Joanne Barrette, Ph.D., Clinical Pharmacology
- Daniel O'Day, Program Leader
- Rudolf Hausmann, Ph.D., Technical Project Manager
- Mathias Usteri, Ph.D., Technical Registration
- Jim Rider, Ph.D., Pharmaceutical Development
- Sarah Orris, Pharmaceutical Development
- Peter Collum, Package Development
- Ronald Tscherne, Quality Management-Analytical Development

**AND:** Representatives of DAVDP

- Steve Miller, Ph.D., Chemistry Team Leader
- Dan Boring, Ph.D., Chemistry Reviewer
- Jeffrey Murray, M.D., M.P.H., Medical Team Leader
- Grace Carmouze, Regulatory Project Manager

**SUBJECT:** Oral Suspension Formulation Manufacturing Issues

**Background:** On April 24, 2000, the sponsor informed DAVDP that there were problems with the manufacture of the oral suspension that would delay NDA filing. The sponsor indicated that they would be submitting a summary of the issues and would request a teleconference to discuss the next course of action. On April 28, the sponsor submitted a facsimile (sn 215) outlining their proposed plan for submitting the Tamiflu oral suspension NDA. The purpose of this teleconference was to discuss the issues outlined in submission number 215.

**Discussion:**

1. The sponsor indicated that they have had ongoing formulation development problems in providing an oral suspension, which would support a pediatric indication. First, the sponsor has observed \_\_\_\_\_ in the suspension and physical instability (discoloration on aging) from the high sorbitol content. These problems have been resolved by reformulation, however, analysis of the most recently prepared batches has revealed that the assay of samples from the

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beginning, middle and end of a production run were decreasing out of specification

2. Five samples from each batch were pulled from the beginning, middle and end of a production run and the samples were then pooled for assay. Three batches were assayed and the results were as follows (in %LS):

	Beginning	Middle	End
Batch 1	—	—	—
Batch 2	—	—	—
Batch 3	—	—	—

3. The sponsor believes that these phenomena are caused by a loss in homogeneity due to \_\_\_\_\_ period that comprises a manufacturing run.
4. The sponsor has proposed two process improvements and will evaluate both options against pre-defined acceptance criteria. These criteria are the sponsor's standard manufacturing criteria used for product formulations of this type. The improvements involve \_\_\_\_\_ The sponsor does not expect these changes to have any adverse impact on either the physical or chemical stability of the product.
5. If these improvements result in acceptable material as defined, then the sponsor will move forward with filing as outlined in their facsimile correspondence dated April 28, 2000. If the improvements do not provide batches that meet the acceptance criteria, the sponsor will discuss the data with DAVDP and propose a new strategy.
6. Specific additional modifications to the proposed submission schedule are:
- A. The analytical release data on \_\_\_\_\_ batches manufactured at \_\_\_\_\_ scale \_\_\_\_\_ will be provided in the first half of August 2000.
  - B. DAVDP recommends that content uniformity be included in the release specification for the Tamiflu Suspension NDA and that the testing protocol proposed in Appendix 1 of the April 28, 2000 facsimile be used at present. If a different testing protocol is preferred for post-approval release testing, the sponsor may propose this as part of the NDA submission.
  - C. Release data on the validation batches will be submitted in \_\_\_\_\_ and release data on all additional launch batches will be provided as soon as they become available.
7. New studies on direct evidence for a \_\_\_\_\_ of the active drug substance have indicated that the substance is indeed \_\_\_\_\_. This information will be submitted in the NDA and is important in deciding if dissolution specifications will be required for this product.

8. Regarding the sponsor's use of the " \_\_\_\_\_ " closure system, DAVDP stated that it concurred with the proposal if the March 20, 2000 Pre-NDA meeting commitments pertaining to the closure were honored.
9. The sponsor was reminded that the pediatric indication is linked with the suspension NDA and should not be submitted separately.
10. DAVDP stated that a response to the proposed bioavailability study, outlined in submission number 215, would be discussed at a later date.

Concurrence:

HFD-530/ChemTL/Miller  
HFD-530/Chem/Boring  
HFD-530/MOTL/Murray  
HFD-530/RPM/Carmouze

LS  
LS  
LS

cc:

Original IND 53,093  
Division File  
HFD-530/ChemTL/Miller  
HFD-530/Chem/Boring  
HFD-530/MOTL/Murray  
HFD-530/MO/Wu  
HFD-530/RPM/Carmouze

Record of Teleconference

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DFS 6/23/00



Carmouze - 53

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

## MEMORANDUM OF INDUSTRY MEETING

**Date of Meeting:** February 18, 2000      **Time:** 1:00 P.M.

**IND:** 53,093

**Drug:** Oseltamivir phosphate (Ro 64-0796)

**Indication:** Treatment of Influenza

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

**Type of Meeting:** Pre-NDA Meeting

**Meeting Chair:** Linda Lewis, M.D.      **Sponsor Chair:** Joanna McNamara

**Project Manager:** Grace Carmouze

### DAVDP Attendees:

Heidi Jolson, M.D., M.P.H., Division Director  
Debra Birnkrant, M.D., Deputy Director  
Walla Dempsey, Ph.D. Associate Director  
Jeffery Murray, M.D., M.P.H., Medical Team Leader  
Teresa Wu, M.D., Ph.D., Medical Reviewer  
Linda Lewis, M.D., Medical Reviewer  
Stephen Miller, Ph.D., Chemistry Team Leader  
Daniel Boring, Ph.D., Chemistry Reviewer  
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader  
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer  
Narayana Battula, Ph.D., Microbiology Reviewer  
Kellie Reynolds, Pharm.D., Clinical Pharmacology/Biopharmaceutics Team Leader  
Prabhu Rajagopalan, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer  
Girish Aras, Ph.D., Statistical Team Leader  
Thomas Hammerstrom, Ph.D., Statistical Reviewer  
Thomas Hassall, R.Ph., Associate Director for Regulatory Affairs  
Antoine El-Hage, Ph.D., Branch Chief, Division of Scientific Investigations  
Charles Frost, Pharm.D., Visiting Post-Doctoral Fellow  
Farah Hanitt, M.S., Visiting Regulatory Scientist  
Grace Carmouze, Regulatory Project Manager

**External Constituents:**

**Hoffmann-La Roche, Inc:**

Joanne Barrett, Ph.D., Project Clinical Pharmacologist  
Regina Dutkowski, M.D., Pediatric Program Clinical Scientist  
Rudolph Hausmann, Ph.D., Technical Team Leader  
David Ipe, Pediatric Program Statistician  
Joanna McNamara, Regulatory Leader  
Vis Naranjan, M.D., Pediatric Program Clinical Scientist  
Daniel O'Day, Project Leader  
Ian Small, Project Document Manager  
Lesley Struthers, Ph.D., Project Statistician  
Barbara Taylor, Ph.D., Regulatory Affairs  
Penelope Ward, M.D., Clinical Science Leader

**Gilead Sciences Inc.**

Roger Mills, M.D., Director, Clinical Research

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**Background:** In a facsimile, dated November 23, 1999 (serial no. 182), the sponsor requested a type-B face to face meeting to discuss their filing strategy of the proposed supplemental NDA (sNDA) for a pediatric indication in children 1-18 years. In the briefing package, dated December 21, 1999 (serial no. 186), the sponsor indicated that they plan to submit this sNDA at the end of April 2000. The purpose of the meeting was to discuss the questions and proposals outlined in the briefing package.

**Discussion:**

1. **The sponsor proposes that the single study WV 15758, with supportive safety data, is sufficient to support a label extension for the treatment of influenza to include pediatric patients aged 1-18 years. Does the Agency concur with this proposal?**

In addition to WV15758, the sponsor plans to submit two supportive studies, WV15759 and WV15871, in children with chronic respiratory disease conducted in both the Northern and Southern Hemispheres. It was noted that although these studies were originally powered for over 500 patients, only 335 were enrolled (179 were influenza-positive). However, DAVDP found the sponsor's proposal acceptable.

The sponsor indicated that asthma exacerbation was slightly less frequent in oseltamivir-treated patients and that a treatment benefit was seen in FEV<sub>1</sub>. DAVDP requested that the sponsor submit all pharmacokinetic studies.

2. The sponsor proposes that a dose recommendation for the suspension should be based on \_\_\_\_\_  
\_\_\_\_\_ than dosing based on a \_\_\_\_\_  
basis. Does the Agency concur with this proposal?

The sponsor proposed the following dosing regimens:

\_\_\_\_\_  
\_\_\_\_\_

DAVDP informed the sponsor that this proposal was a review issue.

DAVDP expressed concern that the target exposure for children was based on adult AUC levels observed following 75 mg twice daily and 150 mg twice daily dosing (mean exposure between 2700 ng·h/ml and 5500 ng·h/ml, respectively). DAVDP recommended that the sponsor conduct a regression analysis to obtain an exposure closer to the approved 75 mg twice daily dosing. This would ensure that safety was the basis for dosing instead of convenience.

The sponsor requested that DAVDP consider \_\_\_\_\_  
\_\_\_\_\_, if the repeat bioequivalence study fails. DAVDP agreed to consider this proposal when the study results are submitted.

3. The sponsor proposes that the label should indicate that the capsule formulation \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ Does  
the Agency concur with this proposal?

The sponsor summarized the types of suspension formulations used throughout development. The formulation types are as follows:

- Type 1: Drug powder used during the clinical trials (V20; 6 mg/mL); and
- Type 2: \_\_\_\_\_ product planned as the market formulation (V36; 12 mg/mL)

It was discussed that the first bioequivalence study comparing V20 with V36 failed. The sponsor stated that possible reasons for the failure may be attributed to inconsistent methods of suspension preparation, improper dosing and administration, and problems with the formulation itself. As a result, the sponsor is conducting a repeat bioequivalence study. To ensure proper dosing and administration, patients are now being given the oral suspension directly in the mouth, without the use of a dosing cup.

DAVDP informed the sponsor that this proposal was a review issue.

1 Page(s) Withheld

oral suspension NDA. The sponsor understood and will consider a simultaneous submission.

**MISCELLANEOUS**

1. In response to a query, DAVDP stated that the sponsor could argue for priority review since no pediatric indication is currently approved for the neuraminidase inhibitor drug class. It was also noted that an Advisory Committee meeting would most likely be unnecessary.
2. It was discussed that the submission regarding viral resistance in the pediatric population would be subject to a teleconference at a later date.

Signature, Minutes Preparer: \_\_\_\_\_

LSI

Date: \_\_\_\_\_

4/6/00

Concurrence, Meeting Chair: \_\_\_\_\_

LSI

Date: \_\_\_\_\_

4/6/00

Concurrence:

HFD-530/DivDir/Jolson *LSI*  
HFD-530/AssocDir/Dempsey *LSI*  
HFD-530/MOTL/Murray *LSI*  
HFD-530/MO/Wu *LSI*  
HFD-530/MO/Lewis *LSI*  
HFD-530/BiopharmTL/Kellie *LSI*  
HFD-530/Biopharm/Rajagopalan *LSI*  
HFD-530/RPM/Carmouze

cc:

HFD-530/IND  
HFD-530/Division File  
HFD-530/MOTL/Murray  
HFD-530/MO/Wu  
HFD-530/MO/Lewis  
HFD-530/Boring  
HFD-530/Micro/Battula  
HFD-530/PharmTox/Yuen  
HFD-530/Stats/Hammerstrom  
HFD-530/Biopharm/Rajagopalan  
HFD-530/Biopharm/Reynolds  
HFD-530/RPM/Carmouze

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MEETING MINUTES

*DFS 4/6/00*



◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	✗ Materials requested in AP letter
◆ Post-marketing Commitments	✗
Agency request for Phase 4 Commitments.....	✗
Copy of Applicant’s commitments .....	✗
◆ Was Press Office notified of action (for approval action only)?.....	✗ Yes <input type="checkbox"/> No
Copy of Press Release or Talk Paper.....	_____
◆ Patent	
Information [505(b)(1)] .....	✗
Patent Certification [505(b)(2)].....	_____
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	_____
◆ Exclusivity Summary .....	✗
◆ Debarment Statement .....	✗
◆ Financial Disclosure	
No disclosable information .....	✗
Disclosable information – indicate where review is located .....	_____
◆ Correspondence/Memoranda/Faxes .....	✗
◆ Minutes of Meetings .....	✗
Date of EOP2 Meeting <input checked="" type="checkbox"/> _____	
Date of pre NDA Meeting <input checked="" type="checkbox"/> _____	
Date of pre-AP Safety Conference <u>N/A</u> _____	
◆ Advisory Committee Meeting .....	N/A
Date of Meeting .....	_____
Questions considered by the committee .....	_____
Minutes or 48-hour alert or pertinent section of transcript .....	_____
◆ Federal Register Notices, DESI documents .....	N/A

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

◆ Summary memoranda (e.g., Office Director’s memo, Division Director’s memo, Group Leader’s memo) .....	✗
◆ Clinical review(s) and memoranda .....	✗

- ◆ Safety Update review(s) ..... See MO review
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver) ✖ Deferred Pediatric Page..... ✖
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable No
- ◆ Statistical review(s) and memoranda ..... ✖
- ◆ Biopharmaceutical review(s) and memoranda..... ✖
- ◆ Abuse Liability review(s) ..... N/A  
 Recommendation for scheduling .....
- ◆ Microbiology (efficacy) review(s) and memoranda ..... ✖
- ◆ DSI Audits .....  
 ✖ Clinical studies  bioequivalence studies .....

**CMC INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ CMC review(s) and memoranda ..... ✖
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ◆ DMF review(s) ..... ✖
- ◆ Environmental Assessment ..... N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ◆ Facilities Inspection (include EES report)  
 Date completed \_\_\_\_\_ ✖ Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed ✖ Not Completed  
 April 11, 2000

**PRECLINICAL PHARM/TOX INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Pharm/Tox review(s) and memoranda ..... ✖
- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A

- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297  
Expiration Date 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1 APPLICANT'S NAME AND ADDRESS <b>Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199</b>		3 PRODUCT NAME <b>Tamiflu™ (oseltamivir phosphate) Suspension</b>	
2 TELEPHONE NUMBER (Include Area Code) <b>(973 ) 562-3664</b>		4 DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT STOP HERE AND SIGN THIS FORM <b>YES</b> IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO CONTAINING THE DATA)	
5 USER FEE I D NUMBER <b>3952</b>		6 LICENSE NUMBER / NDA NUMBER <b>NDA 21-246</b>	
7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD DRUG AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7 reverse side before checking box) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7 reverse side before checking box ) <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug and Cosmetic Act (See item 7, reverse side before checking box ) <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) <b>FOR BIOLOGICAL PRODUCTS ONLY</b> <input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION <input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT <input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY <input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT <input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/82			
8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See reverse side if answered YES)			

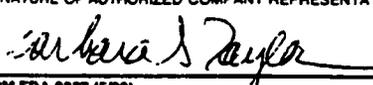
**A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.**

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0297)  
Hubert H Humphrey Building, Room 531-H  
200 Independence Avenue, S W  
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE <b>Barbara S. Taylor, Ph.D. Program Director, DRA</b>	DATE <b>June 14, 2000</b>
---------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------	------------------------------



June 9, 2000

Mellon Bank  
Three Mellon Bank Center  
27<sup>th</sup> Floor (FDA 360909)  
Pittsburgh, Pennsylvania 15259-0001

Ladies and Gentlemen:

**RE: NDA 21-246 - TAMIFLU™ (oseltamivir phosphate) Suspension**  
**HUMAN DRUG APPLICATION FEE - I.D. No. 3952**

Enclosed please find a check in the amount of \$285,740.00 made payable to the U.S. Food and Drug Administration. This payment represents the user fee required for our New Drug Application for Tamiflu™ (oseltamivir phosphate) Suspension, which is planned for submission on June 14, 2000

Should you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

**HOFFMANN-LA ROCHE INC.**

A handwritten signature in cursive script, appearing to read "Jill M. Serra".

Jill M. Serra  
Coordinator, Regulatory Submissions Group  
Drug Regulatory Affairs  
(973) 562-3726 (telephone)  
(973) 562-3700/3554 (fax)

/JS  
HLR 2000-1398  
Enclosure: Check No. 01344749

Hoffmann-La Roche Inc.  
Nutley NJ 07110 (973-235-4381)

Check No. 01344749  
VENDOR 24903731

DOCUMENT NUMBER	INVOICE NUMBER	PURCHASE ORDER	INVOICE DATE	AMOUNT	DISCOUNT	NET
120009499	0001043165	3050006291	06/02/2000	285,740.00	0.00	285,740.00
D. Vecchione 1/2D47 x56987						
TOTALS				285,740.00	0.00	285,740.00

031100209:38827273 01344749 24903731 \*\*\*\*\*285,740.00\* FOOD & DRUG ADMINISTRATION

Hoffmann-La Roche Inc.

340 Kingsland Street  
Nutley, NJ 07110 (973-235-4381)

02-20  
311

DATE CHECK NO. NET AMOUNT  
06/02/2000 01344749 \*\*\*\*\*285,740.00\*

PAY  
\*\*\* TWO HUNDRED EIGHTY FIVE THOUSAND SEVEN HUNDRED FORTY DOLLARS and 00/100 CENTS \*\*\*

TO THE ORDER OF FOOD & DRUG ADMINISTRATION  
PITTSBURGH PA 15251-8903

CITIBANK DELAWARE  
ONE PENNS WAY  
NEW CASTLE DE 19720-2400



⑆01344749⑆ ⑆031100209⑆

38827273⑆

☐☐

☐☐☐☐

☐☐

**CERTIFICATION: FINANCIAL INTERESTS AND  
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d)

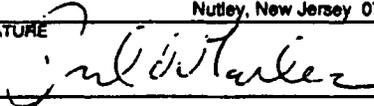
Please mark the applicable checkbox

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators

See attached list

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	Donald Maclean, Ph.D.	TITLE	Vice President of Drug Regulatory Affairs	
FIRM/ORGANIZATION	Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110			
SIGNATURE			DATE	June 6, 2000

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville MD 20857

<b>Investigator &amp; Address</b>	<b>Investigators &amp; Sub-Investigators For Tamiflu – Protocol NP15810</b>	<b>Country</b>	<b>Protocol Number CRTN/Site Code</b>
<b>Principal Investigator: Dr. R. Schulz</b> <u>Sub-investigators:</u> =	<b>Location</b> Clinical Pharmacology Unit Produits Roche S.A. 1, Place de l'Hopital B.P. 20 F-67064 Strasbourg Cedex, France	France	NP15810 22078

<b>Investigator &amp; Address</b>	<b>Investigators &amp; Sub-Investigators For Tamiflu – Protocol NP15826 Location</b>	<b>Country</b>	<b>Protocol Number CRTN/Site Code</b>
<b>Principal Investigator: Dr. J. Ruckle</b> <u>Sub-investigators:</u>	Northwest kinetics, L.L.C. 1401 North 5 <sup>th</sup> Street Tacoma, WA 98403	United States	NP15826 22546

**Investigator & Address**  
**Principal Investigator: Dr. S. Nave**  
**Sub-investigators:**

**Investigators & Sub-Investigators  
For Tamiflu - Protocol WP15979**  
**Location**  
Clinical Pharmacology Unit  
Produits Roche S.A.  
1, Place de l'Hopital B.P. 20  
F-67064 Strasbourg Cedex, France

**Country**  
France

**Protocol Number  
CRTN/Site Code**  
WP15979  
25209



Investigator & Address	Investigators & Sub-Investigators For Tamiflu – Protocol WV15758 Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. Francois Boucher Sub-investigators:	Centre de Recherche du CHUL 2705 Boul, Laurier Ste Foy, Quebec G1V 4G2	Canada	WV15758 23354
Principal Investigator: Dr. Francisco Diaz- Mitoma Sub-investigators:	Herridge Community Health Clinic 59 Herridge Street Ottawa, Ontario K1S 0G8	Canada	WV15758 23356
Principal Investigator: Dr. Jeanette Janzen Sub-investigators:	Kells Medical Research Group Inc. 175 Stillview Suite 235 Pointe-Claire, Quebec H9R 4S3	Canada	WV15758 23364
Principal Investigator: Dr. Jacques Leroux Sub-investigators:	ZOOM International Hotel-Dieu de St. Jerome 290 Rue Montigny local F-19 St Jerome, Quebec J7Z 5T3	Canada	WV15758 23366



Investigator & Address	Investigators & Sub-Investigators For Tamiflu - Protocol WV15758 Location	Country	Protocol Number CRTN/Site Code
Principal Investigator: Dr. Daniel Shu Sub-investigators:	Gain Medical Centre 1199 Austin Avenue Coquitlam, British Columbia V3K 3P4	Canada	WV15758 23359
Principal Investigator: Dr. Pradeep Vohora	6682 Fraser Street Vancouver, B.C. V5H 3T5	Canada	WV15758 23362
Principal Investigator: Dr. Elaine Wang Sub-investigators:	Clinical Epidemiology Unit Hospital for Sick Children 555 University Avenue Toronto, Ontario M5G 1X8	Canada	WV15758 23363

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 21246/000  
Stamp: 15-JUN-2000 Regulatory Due: 15-DEC-2000  
Applicant: ROCHE  
340 KINGSLAND ST  
NUTLEY, NJ 07110

Priority: P  
Action Goal:  
Brand Name: TAMIFLU (OSELTAMIVIR  
PHOSPHATE) 12MG/ML  
Established Name:  
Generic Name: OSELTAMIN VIR PHOSPHATE  
Dosage Form: FOS (FOR ORAL SUSPENSION)  
Strength: 12 MG/ML

Org Code: 530

District Goal: 16-OCT-2000

FDA Contacts: G. CARMOUZE (HFD-530) 301-827-2330 , Project Manager  
D. BORING (HFD-530) 301-827-2396 , Review Chemist  
S. MILLER (HFD-530) 301-827-2392 , Team Leader

Overall Recommendation:

**ACCEPTABLE on 01-DEC-2000 by S. FERGUSON (HFD-324) 301-827-0062**

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No:  
AADA No:

Profile: CRU OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 17-AUG-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: \_\_\_\_\_

Establishment: 9692013  
HOFFMANN LA ROCHE  
GRENZACHERSTRASSE 124  
BASEL, , SZ

DMF No:  
AADA No:

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 20-JUN-2000  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE  
MANUFACTURER  
DRUG SUBSTANCE STABILITY  
TESTER  
FINISHED DOSAGE  
MANUFACTURER

Profile: POW OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 30-NOV-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Establishment: 2210844  
HOFFMANN LA ROCHE INC  
340 KINGSLAND ST

DMF No:  
AADA No:

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

NUTLEY, NJ 071101199

Profile: POW	OAI Status: OAI ALERT	Responsibilities: FINISHED DOSAGE LABELER
Last Milestone: OC RECOMMENDATION		FINISHED DOSAGE MANUFACTURER
Milestone Date: 01-DEC-2000		FINISHED DOSAGE PACKAGER
Decision: ACCEPTABLE		FINISHED DOSAGE RELEASE TESTER
Reason: DISTRICT RECOMMENDATION		FINISHED DOSAGE STABILITY TESTER

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No:  
AADA No:

Profile: CRU	OAI Status: NONE	Responsibilities: _____
Last Milestone: OC RECOMMENDATION		
Milestone Date: 24-AUG-2000		
Decision: ACCEPTABLE		
Reason: DISTRICT RECOMMENDATION		

Establishment: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

DMF No:  
AADA No:

Profile: POW	OAI Status: NONE	Responsibilities: _____
Last Milestone: OC RECOMMENDATION		
Milestone Date: 20-SEP-2000		
Decision: ACCEPTABLE		
Reason: BASED ON PROFILE		

4 Page(s) Withheld