

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20905**

**CORRESPONDENCE**

<p align="center"><b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b>  <b>FOOD AND DRUG ADMINISTRATION</b></p> <p><b>APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b>  <i>(Title 21, Code of Federal Regulations, 314 &amp; 601)</i></p>	<p><i>Form Approved OMB No. 0916-0306</i>  <i>Expiration Date: April 30, 2000</i>  <i>See OMB Statement on page 2.</i></p>
	FOR FDA USE ONLY
	APPLICATION NUMBER

<b>APPLICANT INFORMATION</b>	
NAME OF APPLICANT <b>Hoechst Marion Roussel, Inc.</b>	DATE OF SUBMISSION <b>8/21/98</b>
TELEPHONE NO. (Include Area Code) <b>(816) 966-7297</b>	FACSIMILE (FAX) Number (Include Area Code) <b>(816) 966-3594</b>
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): <b>10236 Marion Park Drive Kansas City, MO 64137</b>	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE <b>Quintiles BRI, Inc. 1801 Rockville Pike, Suite 300 Rockville, MD 20852 (301) 530-9222 FAX (301) 272-2150</b>

<b>PRODUCT DESCRIPTION</b>	
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) <b>leflunomide (INN, USAN pending)</b>	PROPRIETARY NAME (trade name) IF ANY <b>ARAVA<sup>CR</sup> Tablets</b>
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) <b>N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide</b>	CODE NAME (if any) <b>HWA 486, A77 1486</b>
DOSAGE FORM: <b>Immediate Release Film-Coated Tablets</b>	STRENGTHS: <b>10mg, 20mg, 100mg.</b>
ROUTE OF ADMINISTRATION: <b>Oral Tablets</b>	
(PROPOSED) INDICATION(S) FOR USE: <b>Rheumatoid Arthritis</b>	

<b>APPLICATION INFORMATION</b>	
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507	
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____	
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION (053) <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER	
REASON FOR SUBMISSION	
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (P) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED: <b>1</b>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

<b>ESTABLISHMENT INFORMATION</b>
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INOs, NDAs, PMAs, S10(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1. Index	
2. Labeling (check one)	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))	
X 4. Chemistry section	
A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (1), 21 CFR 601.2)	
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (v) (b), 21 CFR 601.2)	
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (i) (2) (A))	
15. Establishment description (21 CFR Part 600, if applicable)	
16. Debarment certification (FD&C Act 306 (k)(1))	
17. Field copy certification (21 CFR 314.50 (k) (3))	
18. User Fee Cover Sheet (Form FDA 3397)	
19. OTHER (Specify)	

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 608, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Douglas M. Hunt</i>	TYPED NAME AND TITLE Douglas M. Hunt, Director QSRD	DATE 8/21/98
ADDRESS (Street, City, State, and ZIP Code) 1801 Rockville Pike, #300, Rockville, MD 20852		Telephone Number (301) 530-9222

Public reporting burden for this collection of information is estimated to average 40 hours 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 (0910-0338)  
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.

**Q**  
**INTILES**

Quintiles, Inc.  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
<http://www.cro.quintiles.com>

BZ

April 20, 1998

VIA FACISIMILE

Division of Anti-Inflammatory, Analgesic,  
and Dental Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn:** Ms. Sandra Cook, Consumer Safety Officer  
**Subject:** Informational Amendment: Response to Written Request (Dated 4/13/98)  
NDA 20-905  
Serial No. 001

Dear Ms. Cook:

In response to the FDA's written request dated 13 April 1998, Please find the enclosed two copies of the following:

1) CMC section:

An electronic version and Hard Copy of the CMC summary from the Summary Application (Section 2.4) to be provided in Word 7.0.

2) Hardware for the PK reviewers, two sets:

QBRI has been informed from FDA that the two external CD drive and associated software for installation are not needed. Therefore we have not enclosed the external CD drive.

3) Statistical Requests.

3.1 Data sets provided in SAS 6.12 and SAS 6.12 transport on CD - ROM and Hard Copy containing all the data sets used to support the ISE and ISS separated by study.

3.2 Annotated case report forms for the phase III studies, separated by study.

3.3 CD- ROM containing the integrated tables in Word 6.0.



QUINTILES

4) Index for all the technical sections of the NDA:

One inclusive Index ( 7 volumes, consecutively) containing the following:

- 1) The current Master Table of Contents (Section 1.0 Index)
- 2) Technical Sections, Table of Contents (all)
- 3) Individual Volume Indexes

5) Pharmacology Requests:

5.1 Replacement Requests for the Preclinical Reports.

- 1) Volume 22: Full Document for report number C16176.
- 2) Volume 24: Full Document for report number 13001.
- 3) Replacement documents requested from the pharmacology/toxicology reviewer are provided in full replacement volumes for volumes 25,27,28,33-37,39, 40-42 and 59. These replacement volumes are identical to the original NDA volumes.

5.2 Sponsor Coding:

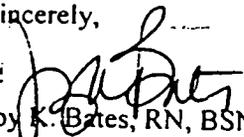
A table with the code name and compound names have been submitted in a separate binder.

Finally QBRI would like to inform the division that our address has changed. The New address is:

Quintiles BRI, Inc.  
Suite 300  
1801 Rockville Pike  
Rockville, MD 20852-1633  
Tel. 301-530-9222  
Fax. 301-272-2150

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

  
QUINTILES

Quintiles, Inc.  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
<http://www.cro.quintiles.com>

April 21, 1998



**VIA COURIER & FACSIMILE**

Division of Anti-Inflammatory, Analgesic,  
and Dental Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

Attn: **Ms. Sandra Cook, Consumer Safety Officer**  
Subject: **Informational Amendment: Response to Clinical Request (Dated 4/8/98)**  
**NDA 20-905**  
**Serial No. 002**

Dear Ms. Cook:

In response to Clinical request from Dr. Johnson dated 8 April 1998, please find the enclosed two copies (hard and electronic) of Scatter Plot Graphs of Changes from Baseline in Efficacy Parameters (SJC, TJC, MHAQ) vs. Days on Study Treatment for Dropouts for Studies US301, MN301, MN302, and YU203.

Each scatter plot graph contains data for all treatment groups, with individuals from the different treatment groups coded as such. All dropouts are included, regardless of the reasons for discontinuation.

**Please Note:** There are sections of the graphs (particularly in US301) in which many points overlap and the treatment groups are difficult to separate visually. Therefore, QBRI enclosed, for the US301 study, graphs of mean changes in efficacy parameters vs. endpoint visits.

**Also Note:** The endpoint visits on these graphs are the last visits on which the parameters in question were assessed for a subject prior to/at discontinuation, and should approximate the days on study treatment from the scatter plot divided by 7.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122. Dr. Frank Hurley from QBRI will call Dr. Johnson to discuss these graphs and any other information he may require.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

BB



QUINTILES

Quintiles, Inc.  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
<http://www.cro.quintiles.com>

April 24, 1998

VIA COURIER



Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Response to Written Request (Dated 4/13/98)**  
**NDA 20-905 (Section 6.0: Electronic Version of the Phase I**  
**Pharmacokinetic and Phase III Population Pharmacokinetic Data on CD-**  
**ROM)**  
**Serial No. 003**

Dear Ms. Cook:

In response to Written Request dated 13 April 1998, please find enclosed two copies (hard and electronic) of the analysis of the Phase I Pharmacokinetic and Phase III Population Pharmacokinetic Data on CD-ROM.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

DUPLICATE

DUPLICATE

ORIGINAL

NTILES

Quintiles BRI  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
<http://www.cro.quintiles.com>



April 27, 1998

**VIA COURIER AND FACSIMILE**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

ORIG AMENDMENT

BM

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Response to Clinical Verbal and Faxed Request**  
**(Dated 4/8/98)**  
**NDA 20-905**  
**Serial No. 004**

Dear Ms. Cook:

In response to a Clinical request, with a follow-up fax, from Dr. Kent Johnson dated April 8, 1998, please find the enclosed two copies in this submission of the following analyses, A Reanalysis of the Results of X-rays of Hands and Feet and An Analysis of the Subjects Who Were Non-Responders at Week 16.

- **A Reanalysis of the Results of X-rays of Hands and Feet**

The analytic approach was modified in accordance with the request to present the final x-ray for each patient at the end of therapy (i.e., not using the 12 month x-ray for subjects who discontinued prior to month 12). Three tables are provided in the attachment:

-An accountability table showing the number of subjects included in the original analysis and the available x-rays for each subject who discontinued early. This table can be used to determine the number of subjects available for the modified approach to the analysis.

For example, the original analytic approach included 131 leflunomide subjects with an endpoint x-ray. Some of the subjects included in that analysis were early discontinuations who had only a 12 month x-ray. Those subjects are not included in the new analytic approach as the reanalysis used only x-rays taken at the end of initial therapy. Thus, the number of subjects in the new analysis can be determined as follows:

- 83 subjects who completed the protocol and had a 12 month x-ray
- 2 subjects who entered alternate therapy, but who also had an x-ray taken at early termination
- 13 subjects who discontinued early and had an x-ray taken at early termination and at month 12
- 14 subjects who discontinued early and had only an early termination x-ray
- 112 subjects with an x-ray at the end of initial therapy

Thus, a total of 112 leflunomide subjects are included in the modified analytic approach.

TILES

-A copy of the tables showing the results of the original analysis for reference (Table 37 of the integrated tables, included in Appendix A to Section 8.0, Volume 1.112, pg. 8-537).

-Table 37(revised) providing the results of the reanalysis. The reanalysis shows that all three treatment groups have slightly less progression (i.e., smaller mean change in total score) than found in the original analysis. This is as expected, given that the results reflect a shorter time interval for the subjects who discontinued early. The pattern between the treatment groups, nonetheless, remains the same as seen in the original analysis: leflunomide is statistically significantly superior to placebo. The difference between leflunomide and methotrexate is no longer statistically significant due to the smaller sample sizes, but the mean change in the leflunomide group is numerically better than in the methotrexate group and the relative difference between the two groups is similar to that using the original analytic approach.

The results of the modified approach, therefore, support the findings of the original analysis and support the conclusion that leflunomide effectively retards disease progression as evidenced by x-rays of the hands and feet.

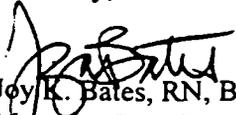
- **An Analysis of the Subjects Who Were Non-Responders at Week 16**

An analysis of subjects who were eligible to discontinue from the initial therapy phase and enroll in alternate active therapy. The first table presents the number and percentage of subjects who enrolled into alternate active therapy who were not responders at week 16. A review of this table indicates that more of the placebo subjects discontinued and enrolled in alternate therapy than subjects on both active therapies. Since ACR responder status requires simultaneous improvement in multiple parameters, further analysis was done to determine if the subjects, in all treatment groups, who did not enter the alternate therapy phase at week 16 had, in fact experienced some degree of improvement, though not enough to achieve ACR responder status.

The remaining tables present these results and support the conclusion that subjects who chose to remain in initial therapy had experienced some improvement, while those who entered alternate therapy showed little, if any, improvement on initial therapy.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



Quintiles BRI  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
<http://www.cro.quintiles.com>

NC  
NEW CORRECT  
TRIPHOSPHATE

May 1, 1998

**VIA COURIER AND FACSIMILE**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



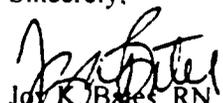
**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Official Request for Marketing Exclusivity for**  
**ARAVA™**  
**NDA 20-905**  
**Serial No. 005**

Dear Ms. Cook:

Enclosed are two copies of an official letter from Hoechst Marion Roussel, Inc. requesting extended marketing exclusivity for ARAVA™.

If you have any questions regarding the attached documentation, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN  
ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338  
Expiration Date: April 30, 2000  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Hochst Marion Roussel, Inc.

DATE OF SUBMISSION

May 1, 1998

TELEPHONE NO. (Include Area Code)  
(816) 966-7297

FACSIMILE (FAX) Number (Include Area Code)  
(816) 966-3594

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,  
and U.S. License number if previously issued):

10236 Marion Park Drive  
Kansas City, MO 64137

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,  
ZIP Code, telephone & FAX number) IF APPLICABLE

Quintiles BRI, Inc.  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
(301) 530-9222 FAX (301) 272-2150

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

leflunomide (INN, USAN pending)

PROPRIETARY NAME (trade name) IF ANY

ARAVA<sup>™</sup> Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

-N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide HWA 486, A77 486

CODE NAME (if any)

DOSE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

Immediate Release Film-Coated Tablets 10mg, 20mg, 100mg. Oral Tablets

(PROPOSED) INDICATION(S) FOR USE:

Rheumatoid Arthritis

APPLICATION INFORMATION

APPLICATION TYPE  
(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION  
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION  
(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

Official Request for marketing Exclusivity for ARAVA<sup>™</sup>

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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<input type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
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<input type="checkbox"/>	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k) (3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. OTHER (Specify) Official Request for Marketing Exclusivity for ARAVA™

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Douglas M. Hunt, Director QSRD	DATE May 1, 1998
ADDRESS (Street, City, State, and ZIP Code) 1801 Rockville Pike, #300, Rockville, MD 20852		Telephone Number (301) 530-9222

Public reporting burden for this collection of information is estimated to average 40 hours 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 (0910-0338)  
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.

# Hoechst Marion Roussel

April 28, 1998

Hoechst Marion Roussel, Inc.

Mail Stop H4-M2630

10236 Marion Park Drive

Mail: P.O. Box 9627

Kansas City, MO 64134-0627

Telephone (816) 966-5000

Dr. Michael Weintraub  
Acting Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-105)  
Room S219  
Corporate 2  
9201 Corporate Blvd.  
Rockville, MD 20850

Subject: **ARAVA™**

Dear Dr. Weintraub:

As requested, this letter serves as an official request for a period of extended marketing exclusivity for ARAVA™ under 21CFR 314.50(j) and 21CFR 314.108(b)(2). As a new chemical entity, ARAVA™ is entitled to five (5) years of exclusivity pursuant to 505(j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). If you have any questions concerning this request, please contact the undersigned.

L.E. (Mick) Roebel, PhD -- H4-M2630  
Hoechst Marion Roussel, Inc.  
P.O. 9627  
Kansas City, MO 64134-0627  
(816-966-7297)

Sincerely,



L.E. Roebel, PhD  
Director, US Regulatory Affairs

kmh

Hoechst Marion Roussel  
A member of the Hoechst Group

**Hoechst** 

# Hoechst Marion Roussel

April 28, 1998

Hoechst Marion Roussel, Inc.

Mail Stop H4-M2630

10236 Marion Park Drive

Mail: P.O. Box 9627

Kansas City, MO 64134-0627

Telephone (816) 966-5000

Dr. Michael Weintraub  
Acting Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-105)  
Room S219  
Corporate 2  
9201 Corporate Blvd.  
Rockville, MD 20850

Subject: **ARAVA™**

Dear Dr. Weintraub;

As requested, this letter serves as an official request for a period of extended marketing exclusivity for ARAVA™ under 21CFR 314.50(j) and 21CFR 314.108(b)(2). As a new chemical entity, ARAVA™ is entitled to five (5) years of exclusivity pursuant to 505(j)(4)(D)(ii) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355). If you have any questions concerning this request, please contact the undersigned.

L.E. (Mick) Roebel, PhD -- H4-M2630  
Hoechst Marion Roussel, Inc.  
P.O. 9627  
Kansas City, MO 64134-0627  
(816-966-7297)

Sincerely,



L.E. Roebel, PhD  
Director, US Regulatory Affairs

kmh

Hoechst Marion Roussel  
A member of the Hoechst Group

**Hoechst** 

**Q**  
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Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
<http://www.cro.quintiles.com>

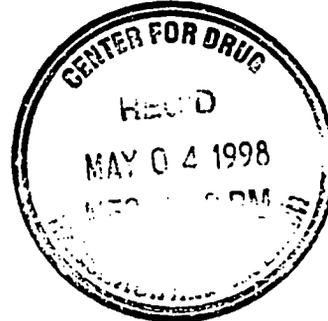
BZ

**ORIGINAL**

May 1, 1998

**VIA COURIER AND FACSIMILE**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Response to Statistical Request (Dated 4/7/98)**  
**and Response to Pharmacology/Toxicology Request for Nonclinical**  
**Summary Handbook**  
**NDA 20-905**  
**Serial No. 006**

Dear Ms. Cook:

Enclosed are two copies of the following:

**Volume 1: Statistical Request**

Program Documentation for Sample SAS Programs for Integrated Efficacy Tables provided on diskette and Hard Copy containing the list of program name and Description.

**Volumes 2-9: Nonclinical Pharmacology/Toxicology Request**

**Nonclinical Summary Handbook**

**Note:** This handbook also contains the Summary Table of Macroscopic Findings for the Oral Carcinogenicity Studies in Mice (Document- 13384) and Oral Carcinogenicity Studies in Rats (Document- 13211)

If you have any questions regarding the attached documentation, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Jon K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



Quintiles BRI  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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BM  
ORIG AMENDMENT  
TRIP



May 5, 1998

**VIA COURIER AND FACSIMILE**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Response to Verbal and Faxed Request (Dated 4/8/98)**  
**NDA 20-905**  
**Serial No. 008**

Dear Ms. Cook:

In response to a telephone request from Dr. Kent Johnson on April 29, included in this submission are two copies of the following analyses:

- **Presentation of individual efficacy measure results for all subjects who discontinued early in Protocol US301.**

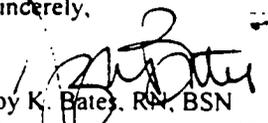
These tables show the mean change from baseline for all subjects who discontinued early; the results are presented overall as well as separately for subjects who did and did not enter alternate therapy. Also included is a table showing the number of subjects who enrolled into the alternate therapy phase based on reason for early discontinuation. The results show that the relationship among the three treatment groups are similar in the subjects who discontinued early to those in the overall group, though as would be expected, less improvement is seen in those who discontinued early. Those who enrolled into the alternate therapy phase showed poorer results than those who did not, reflecting the fact that most who entered alternate therapy did so after discontinuing initial therapy due to lack of efficacy. Those who did not enter alternate therapy had discontinued initial therapy for reasons other than lack of efficacy, and thus, some did show some level of improvement.

- **Flow charts showing subject and x-ray of hands and feet accountability.**

These flow charts are provided for the three Phase III studies, US301, MN301, and MN302.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



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BC

~~ORIG AMEND~~

ORIGINAL

May 5, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Response to Written Request (Dated 4/13/98)  
for NDA 20-905 (Section 3.0 and 4.0: Electronic Version of the CMC  
Section in Word Format)  
Serial No. 007**

Dear Ms. Cook:

In response to FDA's Written Request dated 13 April 1998, enclosed please find two electronic copies containing the available electronic files the Chemistry, Manufacturing, and Controls (CMC) section (Section 3.0, volumes 1.3 to 1.7) and the Samples, Methods Validation and Labeling section (Section 4.0, volumes 1.8 to 1.9). The electronic versions are provided on CD ROM and are in MS Word v. 6.0 format.

To facilitate your use of the enclosed electronic version of Sections 3.0 and 4.0, please refer to the informational "Read Me" file which is intended to serve as a general guide for the reviewer. This file is provided in hard copy and electronically (NDA.doc) in MS Word v. 6.0.

The files are named according to the corresponding individual document number. For example, the document entitled "Stability Testing for the Drug Product," with document number #PDA-ST 38/98 and NDA page number 3-772, has been given the filename: PDA-ST 38\_98.

**Please Note:** Every effort has been made to electronically capture all of the information that was submitted to the NDA. All files that are electronically provided in this submission are indicated as REDLINED text in the Table of Contents, which is included electronically as well as in hard copy.



LES

Items which could not be electronically captured include documentation relating to packaging, previous validation reports (for methods used during stability testing), the environmental assessment document, completed batch records, information on the proposed labeling, signatures on final documents, and certain figures.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

- Cc: Kansas City District Office

**Q**  
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98 157  
**ORIG AMENDMENT**

**DUPLICATE**



May 6, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

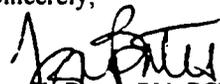
**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Section 5.0: Electronic Version of the Study Data for the Oral Carcinogenicity Studies in Mice (Document- 13384) and Oral Carcinogenicity Studies in Rats (Document- 13211) on CD-ROM**  
**NDA 20-905**  
**Serial No. 009**

Dear Ms. Cook:

In response to Written Request dated 13 April 1998, please find enclosed two copies of the electronic version of the Study Data for the Oral Carcinogenicity Studies in Mice (Document- 13384) and Oral Carcinogenicity Studies in Rats (Document- 13211). The electronic document has been provided on CD ROM. The study data has been formatted according to the FDA Guidelines for the Formats and Specifications for Submission of Animal Carcinogenicity Study Data (Dated 3/12/97) and per the reviewing statistician requests.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy R. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

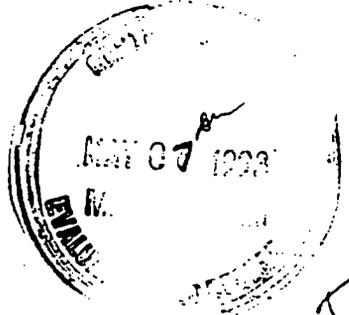
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<sup>BL</sup>  
**ORIG AMENDMENT**  
**ORIGINAL**



*note KJ  
6/11/98*

May 7, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Section 2.0: Request for Electronic Version of the Summary Application Provided in Word Perfect Format on Diskette**  
**NDA 20-905**  
**Serial No. 010**

Dear Ms. Cook:

Per the Clinical Reviewer's request, enclosed please find enclosed two copies of the Section 2.0: Summary Application and the Annotated Labeling for ARAVA™ provided in hard copy and electronically in WordPerfect format on diskette.

**Please Note:** The hard copy version of the Summary Application and Annotated Labeling are presented as printouts from the files enclosed. Also, due to the conversion process from Word to WordPerfect, the formatting for the Summary Application and Annotated Labeling may not exactly match page for page the version previously submitted in the NDA Application.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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*313*  
ORIG AMENDMENT  
**ORIGINAL**



May 15, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Section 6.0: Request for Electronic Version of the Human Pharmacokinetic and Bioavailability Text Provided in Word 6.0 on Diskette**  
**NDA 20-905**  
**Serial No. 011**

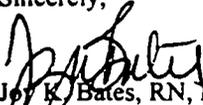
Dear Ms. Cook:

Per the PK Reviewer's request, enclosed please find enclosed two copies of Section 6.0: Human Pharmacokinetic and Bioavailability text provided electronically in Word 6.0 on diskette.

**Please Note:** Due to the size of the electronic file, we have provided it as executable file. When opened, the file will prompt the viewer to save the file in another location.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

**Q**  
**UINTILES**

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*BC*  
**ORIG AMENDMENT**

**ORIGINAL**

May 22, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Response to Telephone Request (Dated 5/13/98)**  
**NDA 20-905 (Section 3.0: Electronic Version)**  
**Serial No. 012**

Dear Ms. Cook:

In response to FDA's Telephone Request dated May 13, 1998, enclosed please find two electronic copies of the available electronic files of the Chemistry, Manufacturing, and Controls (CMC) section (Section 3.0, volumes 1.3 to 1.7). A previous amendment to the NDA (Serial No.007) was submitted on May 5, 1998 that contained two electronic copies of these files. However, based on the May 13 teleconference, these files have been reorganized to better facilitate the use and review of Section 3.0. The revised CD-ROMs are enclosed in this amendment.

The electronic documents are divided into two main folders: "Info" and "Section3". The "Info" folder contains the informational "Read Me" file which is intended to serve as a general guide for the reviewer. The "Section3" folder contains sub-folders that correspond to the NDA Section numbers (e.g., A, B1, B2, B3, etc.). Sub-sub-folders have been created where necessary. The individual files have been placed in the following sub-folders:

- A
- Appendix
- B1
- B2
- B3
- B4
- B5
- B6
- B7
- B8
- Introduc

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As indicated in Serial No.007, items which could not be electronically captured include documentation relating to packaging, previous validation reports (for methods used during stability testing), the environmental assessment document, completed batch records, information on the proposed labeling, signatures on final documents, and certain figures.

Additionally, we have enclosed a hard copy of the Table of Contents.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,



Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

Cc: Kansas City District Office

Q

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TILES



ORIG AMENDMENT  
ORIGINAL

May 22, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

Attn: Ms. Sandra Cook, Project Manager  
Subject: Informational Amendment: Section 10.0: Request for Electronic Version of the ISS and ISE  
Tables and Figures and Additional Detailed AE Information from the ISS and ISE Integrated  
Table Appendices provided in Word and Hard Copy.  
NDA 20-905  
Serial No. 013

Dear Ms. Cook:

The Statistical Reviewer's request, enclosed please find two copies of the electronic version of the ISS and ISE  
Tables and Figures and additional AE Information (Tables 370-409) not previously submitted from the Integrated ISS  
and ISE Table Appendices provided in Word 6.0.

Note: Excel application was used to produce some of the figures in the ISE document, therefore, we have included  
those figures in both Excel and Word format.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

*Joy K. Bates*  
On behalf of Joy Bates

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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ORIGINAL

May 26, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



Attn: Ms. Sandra Cook, Project Manager  
Subject: Informational Amendment: Section 5.0: Request for Summary Table of Clinical Observations for the Rat and Mouse Two-Year Carcinogenicity Studies.  
NDA 20-905  
Serial No. 014

Dear Ms. Cook:

Per the Pharm/Tox Reviewer's request, enclosed please find two copies of the Summary Table of Clinical Observations for the Oral Carcinogenicity Studies in Mice (Document- 13384) and Oral Carcinogenicity Studies in Rats (Document- 13211).

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 530-9222.

Sincerely,

*Judith A. Donnelly on behalf of Joy K. Bates*  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



Quintiles BRI  
Strategic Regulatory Division  
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NC



May 27, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Written Correspondence: Request for a 90 Day Meeting with FDA for**  
**NDA #20-905**  
**Serial No. 016**

Dear Ms. Cook:

Quintiles BRI and HMR would like to request a 90 Day meeting with the FDA Review team assigned to NDA #20-905 to discuss any issues the FDA reviewers may have with the ARAVA™ (leflunomide) product in preparation for the Advisory Panel Meeting scheduled for August 7, 1998.

In order to have both HMR Germany and HMR Kansas City present, we would like to request the date for the meeting either on June 18<sup>th</sup> or 19<sup>th</sup>, 1998.

Please let me know if this is acceptable with the FDA review team.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3106.

Sincerely,

Douglas M. Hunt  
Director, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



Quintiles BRI  
 Strategic Regulatory Division  
 1807 Rockville Pike, Suite 300  
 Rockville, MD 20852  
 301 530 9222 / 301 272 2150 Fax  
 http://www.cro.quintiles.com

BC

May 27, 1998

**VIA COURIER**



Division of Anti-Inflammatory, Analgesic,  
 and Ophthalmologic Drug Products  
 Center for Drug Evaluation and Research  
 Food and Drug Administration, HFD-550  
 9201 Corporate Boulevard  
 Rockville, MD 20850

**Attn:** Ms. Sandra Cook, Project Manager  
**Subject:** Information Request: Annotated Labeling for NDA 20-905  
 Serial No. 015

Dear Ms. Cook:

In response to FDA's request for a thorough review of NDA 20-905 for technical errors, we have found three volume/source document errors in the Human Pharmacokinetic section of the annotated labeling for the ARAVA™ (leflunomide) product. The corrections are as follows:

Line Number	Changed From:	Changed To:
115	Vol.1.101: 6.7.34, p6-17362, 6.7.36, p6-17404	Vol.1.108: 6.7.34, p6-17362, 6.7.36, p6-17056
305	Vol. 1.98: 6.7.17, p6-13574, 6.7.18, p6-13767	Vol. 1.98: 6.7.17, p6-13574, Vol. 1.99: 6.7.18, p6-13767
307	Vol. 1.102: 6.7.19, p6-14068	Vol. 1.102: 6.7.20, p6-14659
312	Vol. 1.103, 1.97: 6.7.21, p6-15193	Vol. 1.103: 6.7.21, p6-15193

Please note that the corrections only consist of location of the source documents. The contents of the labeling have not changed.

We have attached a revised labeling with the correct information HIGHLIGHTED and the deleted information marked by STRIKEOUT.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3106.

Sincerely,

Doug Hunt  
 Director, Regulatory Affairs  
 Strategic Regulatory Division

Enclosures

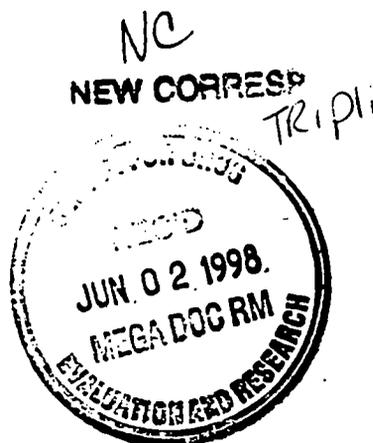


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June 2, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Written Correspondence: Response to FDA Request for X-Ray  
Sensitivity Analysis  
Serial No. 017**

Dear Ms. Cook:

Please find attached a memo to Dr. Kent Johnson. This was faxed last week in draft format and is now being submitted in final version.

If you have any questions regarding this memo, please do not hesitate to contact me at (301) 272-3106.

Sincerely,

*Douglas M. Hunt*  
Douglas M. Hunt  
Director, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

Cc: Dr. Kent Johnson



Quintiles BRI  
Strategic Regulatory Division  
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Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
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CSBP  
ORIGINAL

June 3, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Response to FDA Request for NONMEM Statistical Data Files**  
**Serial No. 018**

Dear Ms. Cook:

Per FDA's request please find two copies of the following NONMEM statistical data files for the Population PK section of NDA #20-905. These are being provided in zip format on diskette. The file listings on the diskette are provided in the attached directories.

If you have any questions regarding this information, please do not hesitate to contact me at (301) 272-3106.

Sincerely,

Douglas M. Hunt  
Director, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

**Q**  
**QUINTILES**

Quintiles BRI  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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<http://www.cro.quintiles.com>

June 11, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Drug Product Stability Data Update**  
**NDA 20-905, ARAVA™ (leflunomide) Tablets**  
**Serial No. 019**

Dear Ms. Cook:

On behalf of Hoechst Marion Roussel, Inc. (HMR), we are submitting an amendment to the above referenced NDA to provide an update to the drug product stability data that was filed in the original NDA.

Enclosed please find two stability reports as follows:

- PDA-ST 189.0/98: 6-month update report on Drug Product batches manufactured at the Compiegne (France) facility with Drug Substance at the Frankfurt (Germany) facility. This report updates the data reported in Doc. No. PDA-ST 03/98 of the original NDA.
- PDA-ST 191.0/98: 3-month update report on Drug Product batches manufactured at the Compiegne (France) facility with Drug Substance at the Vertolaye (France) facility. This study was performed according to the stability protocol no. PDA-ST 169/97 submitted in the original NDA.

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
J. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

Cc: Kansas City District Office

BC  
**ORIG AMENDMENT**  
**DUPLICATE**



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*N*  
**NEW CORRESP  
DUPLICATE**

June 15, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Written Correspondence: List of Participants and Agenda for 90 Day Meeting  
NDA 20-905, ARAVA™ (leflunomide) Tablets  
Serial No. 021**

Dear Ms. Cook:

This letter is to inform FDA of the participants and proposed agenda for the 90 Day meeting for ARAVA™ scheduled for Thursday, June 18, 1998.

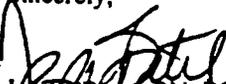
The following Quintiles BRI and HMR participants plan on attending the meeting:

Mick Roebel, Ph.D. – HMR Regulatory – Meeting Leader  
Hans Donaubauer, Ph.D. – HMR Preclinical  
Andrew Wade, Ph.D. – HMR Preclinical  
Mark Eller, Ph.D. – HMR Pharmacokinetic  
Wilhelm Horn, M.D. – HMR Clinical  
Vibeke Strand, M.D. – HMR Consultant  
Frank Hurley, Ph.D. – QBRI Clinical Statistical  
Kit Dorrier, M.S. – QBRI Clinical Statistical  
Joy Bates, RN, BSN – QBRI Regulatory  
Douglas Hunt, B.Sc. – QBRI CMC and Regulatory

The proposed agenda is to discuss any outstanding issues the FDA reviewers may have with NDA 20-905, ARAVA™ (leflunomide) Tablets in preparation for the Advisory Panel Meeting scheduled for August 7, 1998.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division



Quintiles BRI  
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1801 Rockville Pike, Suite 300  
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BP  
ORIG AMENDMENT

DUPLICATE



June 15, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

Attn: Ms. Sandra Cook, Project Manager  
Subject: Response to FDA Request for Additional Pharmacokinetic Analysis  
Serial No. 020

Dear Ms. Cook:

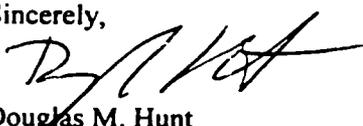
During the June 2, 1998 teleconference between FDA and HMR/Quintiles, Dr. Deneeta Tandon, the reviewer from the Division of Clinical Pharmacology and Biopharmaceutics, had the following requests with respect to the population pharmacokinetic analysis:

1. A secondary analysis excluding data points for which there was incomplete dosing and/or sampling time information, i.e. those for whom assumed times were used. (NONMEM files from this analysis are included electronically in Appendix II.
2. A more extensive discussion of how samples were categorized as outliers.
3. Copies of the NONMEM data in either text (ASCII), SAS, or Excel format and the control files.

The following are the responses to items #1 and #2. The data and control files requested in item #3 were delivered to FDA on June 3, 1998 and are not included in this document.

If you have any questions regarding this information, please do not hesitate to contact me at (301) 272-3106.

Sincerely,

  
Douglas M. Hunt  
Director, Regulatory Affairs  
Strategic Regulatory Division

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BM  
~~ORIG AMENDMENT~~

**ORIGINAL**



June 16, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

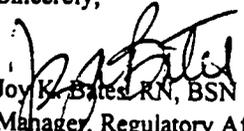
**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Section 8.0: Request for Additional Analysis of X-rays of Hands and Feet**  
**NDA 20-905**  
**Serial No. 022**

Dear Ms. Cook:

Per the Clinical Reviewer's request, enclosed please find two copies of the Additional Analysis of X-rays of Hands and Feet.

If you have any questions regarding the attached information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



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June 17, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Section 10.0: Response to June 11, 1998 Written Request for Additional Information on Liver Function Tests, X-rays and Alternative Therapy NDA 20-905 Serial No. 023**



Dear Ms. Cook:

Per the Statistical Reviewer's written request dated June 11, 1998, enclosed please find two copies of the Additional Information on Liver Function Tests, X-rays and Alternative therapy.

If you have any questions regarding the attached information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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June 19, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Section 10.0: Request for P-values for the Interaction Between Treatment Groups and the Subgroups in the ISE**  
**NDA 20-905**  
**Serial No. 024**

Dear Ms. Cook:

Per the Statistical Reviewer's request, enclosed please find two copies of the P-values for the interaction between the treatment groups and subgroups included in Tables 33-39 of the Integrated Summary of Efficacy.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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BB

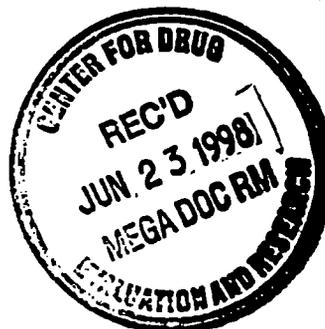
ORIG AMENDMENT

TRIP

June 23, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



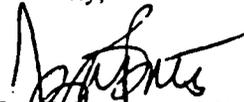
**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Biopharmaceutical Information**  
**NDA 20-905**  
**Serial No. 025**

Dear Ms. Cook:

Enclosed please find two copies of the NDA amendment to report Biopharmaceutical Information regarding the use of 5 x 20 mg tablets as an alternative to 1 x 100 mg tablet as the loading dose regimen for Leflunomide. A report is appendicized to this amendment to provide comparative in vitro dissolution data. This issue was discussed in a teleconference on May 29, 1998 between Dr. Mark Eller of Hoechst Marion Roussel, Inc. (HMR) and Dr. Dennis Bashaw of the FDA.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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ORIG AMENDMENT

TRIP

June 24, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**

**Subject: Information Amendment: Section 5.0: Response to Pharmacology Reviewer's Request (Dated May 27, 1998) for Exposure Ratios at Maximum Doses of Animals to Humans for Carcinogenicity and Reproductive Portions of the Labeling  
NDA 20-905  
Serial No. 027**

Dear Ms. Cook:

In response to the Pharmacology Reviewer's request dated May 27, 1998, we have provided the following attachment tabulating the exposure data for A77 1726, the active metabolite of leflunomide, in animals and humans. Animal data have been obtained from the carcinogenicity and reproductive toxicity studies. Tables summarizing the exposure data for humans have been included for comparison.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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ORIG AMENDMENT  
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June 23, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**

**Subject: Informational Amendment: Section 10: Random Sampling Sensitivity Analysis  
NDA 20-905  
Serial No. 026**

Dear Ms. Cook:

Per the Statistician's request, please find two copies of of the random sampling sensitivity analysis according to our proposal of 5/27/98 (Attachment 1). The results of this analysis are consistent with the sensitivity analysis already provided in accordance with our 5/29/98 memo. That is, (as discussed during our 6/18/98 meeting) the boundary value for the missing Leflunomide data was not quite as large as the observed placebo progression and the boundary value for the placebo missing data was not quite as good as the observed Leflunomide results. In the current analysis where missing values were replaced by randomly selected observations from the opposite group, in the US301 study 55 of the 100 samples still resulted in p-values less than 0.05.

For MN301, the sample results show 35 of the 100 samples result in  $p \leq 0.05$ . Thus, as shown by the previous analysis, the missing cases would have to be dramatically different from the observed results in order to change the conclusions of the primary analysis.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy R. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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June 24, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**

**Subject: Information Amendment: Section 6.0: Response to PK Reviewer's Request for Document No. 16639**  
**"Investigations into the metabolism of HWA 486 using urine from a single human volunteer dosed orally with 100mg unlabelled HWA 486."**  
**NDA 20-905**  
**Serial No. 029**

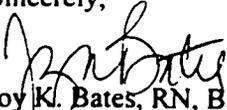
Dear Ms. Cook:

Per the PK Reviewer's request, enclosed please find two copies of Document No. 16639, "Investigations into the metabolism of HWA 486 using urine from a single human volunteer dosed orally with 100 mg unlabelled HWA 486."

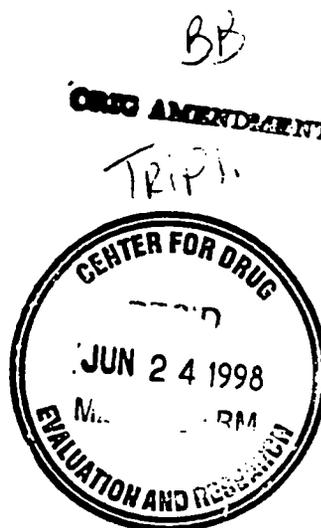
To summarize this report, the human radiolabelled study the slow rate of excretion of radioactivity in urine and feces precluded radiochromatographic profiling at time-points later than 48-96h. Consequently, the metabolic fate of only approximately 35% of the dose was positively established. However, it is very likely that the metabolite pattern exhibited in the last samples investigated i.e. predominantly A77 1726 in feces and TFMA oxanilic acid in urine, would persist and that these metabolites would therefore ultimately account for the majority, if not all, of the remaining dose. The percentages shown in the summary figure for metabolism in man are therefore an extrapolation based on this assumption.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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BH  
ORIG ALZENDANT

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June 24, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**

**Subject: Information Amendment: Section 8.0: Response to Clinical Reviewer's Request for Additional Information on Adverse Events  
NDA 20-905  
Serial No. 028**

Dear Ms. Cook:

Per the Clinical Reviewer's request, enclosed please find two copies of tables summarizing the adverse events for patients treated with leflunomide. The tables provide additional information for the following five adverse events: hypertension, alopecia, infections, allergic reactions, and weight decrease.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy E. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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NC  
**DUPLICATE**

June 26, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Section 3.0: Chemistry, Manufacturing, and Controls**  
**NDA 20-905**  
**Serial No. 030**

Dear Ms. Cook:

Enclosed please find the letter of authorization for the FDA to reference information contained in the Type II Drug Master File #8116 for Leflunomide (HWA 486). The file was last updated on June 26, 1998, with Hoechst Marion Roussel's responses to FDA requests for information dated June 17, 1998.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

*JKB*  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

*On behalf of Joy Bates*

Enclosures





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NC  
NEW CORRESP  
ORIGINAL

June 30, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: General Correspondence: Section 8.0: Clinical: Materials for US Clinical Site Inspections**  
**NDA 20-905**  
**Serial No. 031**

Dear Ms. Cook:

Enclosed please find the cover letter, which accompanied the materials required by the Division of Scientific Investigations for US clinical site inspections for NDA 20-905.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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Q  
NTILES

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Strategic Regulatory Division  
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ORIG AMENDMENT  
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July 2, 1998

VIA FACSIMILE AND COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



Attn: Ms. Sandra Cook, Project Manager  
Subject: Information Amendment: Section 6.0: Biopharm Request for Polymorphic Composition of the batches for 10, 20, and 100 mg tablets used in phase III and specific PK studies.  
NDA 20-905  
Serial No. 034

Dear Ms. Cook:

Per the Biopharm Reviewer's written request dated June 30, 1998, enclosed please find two copies of polymorphic composition (Form I or II or its ratio) for the batches of 10, 20, and 100 mg tablets used in the pivotal clinical trials (US301, MN301, and MN302) and the PK studies (multiple dose studies, food effect, drug interaction, and study in dialysis patients).

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

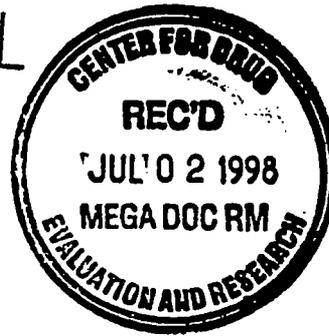
Sincerely,

*Joy K. Bates on behalf of*

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

NEW COPY  
ORIGINAL



Document

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July 2, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

Attn: Ms. Sandra Cook, Project Manager  
Subject: General Correspondence: Draft Briefing Package  
NDA 20-905  
Serial No. 033

Dear Ms. Cook:

Enclosed for your review and comments please find 12 copies of the draft version of the Hoechst Marion Roussel Advisory Committee Meeting Briefing Package.

Please forward the copies to the Reviewing Team and return your comments to my attention by July 8, 1998. After incorporating your comments, the final copy of the Advisory Committee Meeting Briefing Package will be forwarded July 13, 1998 to the Arthritis Advisory Committee for the panel meeting scheduled August 7, 1998.

Please send your comments to my attention via fax (301-272-2150) or by phone (301-272-3122).

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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July 2, 1998

**VIA FACSIMILE AND COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

BL

ORIGINAL

**Attn:** Ms. Sandra Cook, Project Manager  
Dr. Kent Johnson, Clinical Medical Reviewer  
**Subject:** Information Amendment: Section 8.0: Clinical Reviewer's Request for Suggested  
Revisions to the proposed labeling for ARAVA™ Tablets (leflunomide)  
NDA 20-905  
Serial No. 035

Dear Ms. Cook:

Per the Clinical Reviewer's request, enclosed please find two copies of the revised proposed labeling for ARAVA™ Tablets (leflunomide) with the suggested revisions from the Clinical Reviewer. This submission is provided in hard copy and electronically in Word 7.

To assist in the review of the document:

All additions to the labeling have been marked by an underline/highlight and  
All deletions to the labeling have been marked by a strikeout.

**Note:** At this time, annotations information (i.e. volume, section, page number) have not been updated to reflect the new suggested revisions. This section of the labeling will be revised upon the division's official recommendations.

We welcome the opportunity to interact cooperatively on label construction. Our desire is to move the process along as much as possible, without limiting the possibility of negotiating specific important details of the labeling at a later time.

We have incorporated many of the suggested alterations into this version of the label. However, areas that still need to have detailed discussion include, but are not limited to, the carcinogenicity area, the teratology/pregnancy area and the efficacy display area.

With regard to efficacy presentation, we have maintained the draft version of the Clinical Trials section as proposed by Dr. Kent Johnson for discussion purposes. However, we would like to continue to discuss the question of inclusion of the MN302 trial in the efficacy presentation, since we feel that the efficacy results have very limited applicability.



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Strategic Regulatory Division  
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July 9, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: General Correspondence: Response to FDA Written Request (Dated June 16, 1998),  
Regarding the Proposed Proprietary Name for NDA 20-905  
NDA 20-905; Serial No. 037**

Dear Ms. Cook:

Enclosed please find two copies of Hoechst Marion Roussel, Inc. response to FDA Written Correspondence (Dated June 16, 1998), regarding the Nomenclature Committee decision not to accept ARAVA™ as the proposed proprietary name for NDA 20-905.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

## Hoechst Marion Roussel

July 7, 1998

Ms. Sandra Cook, Project Manager  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Blvd.  
Rockville, MD 20850

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive  
Mail: P.O. Box 9627  
Kansas City, MO 64134-0627  
Telephone (816) 966-5000

Dear Ms. Cook

This note is in regard to your FAX of 6/16/98 to Joy Bates (copy attached) in which you mention that the nomenclature committee has found the proposed proprietary name (ARAVA) for NDA 20-905 unacceptable. The reason for unacceptability was listed as "A common oncolytic regimen is termed "ara-a" and the proposed name is very close to this common designation". We strongly disagree with the nomenclature committee's opinion.

The results of a trademark database search (attached) indicates that "ara-a" has not been registered or applied for as a trademark. "ara-a" is also not listed anywhere as a generic name. The only reference to "ara-a" is found in a product monograph for vidarabine (generic name), marketed as an anti-viral with the trade name of Vira-A. The product monograph for Vira-A (attached) states that vidarabine is also known as adenine arabinoside and ara-a. Vidarabine is marketed as an ophthalmic ointment for herpes simplex keratitis and intravenously for the treatment of herpes simplex encephalitis and neonatal herpes simplex virus infections. The 1997 sales for Vira-A (vidarabine) amounted to (based on IMS America sales data).

In summary, "ara-a" is not a registered trade name nor generic name, but only an informal "code-designation" for a compound used in an ophthalmic ointment with very limited sales. ARAVA (leflunomide) is a tablet formulation that will have much more extensive use in a very different patient population. To allow the short-hand term "ara-a" to prevent the

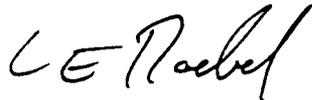
Hoechst Marion Roussel  
A member of the Hoechst Group

**Hoechst** 

adoption of the name ARAVA is, in our opinion, extremely inappropriate. We feel that the possibility of prescription dispensing situations arising where "ara-a" and ARAVA are confused to be extremely limited or non-existent.

Based on the above, we ask the Division to accept the trade name ARAVA as the proprietary name for NDA 20-905.

Best Regards,

A handwritten signature in cursive script, appearing to read "L E Roebel".

L. E. Roebel, Ph. D.  
Director, U.S. Regulatory Affairs  
Hoechst Marion Roussel, Inc.

  
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BL  
DUPLICATE



July 9, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

Attn: Ms. Sandra Cook, Project Manager  
Subject: Information Amendment Request: Section 8.0: Clinical Request (Dated July 8, 1998) for  
Suggested Revisions to Labeling and Response to "Message to Readers" for NDA 20-905  
NDA 20-905; Serial No. 038

Dear Ms. Cook:

Enclosed please find two copies of Hoechst Marion Roussel, Inc.'s response to the Clinical Reviewer's request for the following :

1. Hoechst Marion Roussel, Inc.'s "Response to Message to Readers" and
2. Revised Sections to Selected Portions of the Labeling

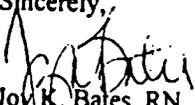
Note: The revised labeling only contains suggest wording for the following :

1. Black Box Statement,
2. Warning Section (Dealing with Pregnancy),
3. Information for Patients,
4. Laboratory Tests, and
5. Informed Consent Section

This information has been provided in hard copy and electronically in Word 7. Due to computer technology, the number lines on the document have been updated to reflect the new numbering. Therefore, for reviewing ease, we have added the previous line numbers from the July 2, 1998 document in front of the new numbers.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

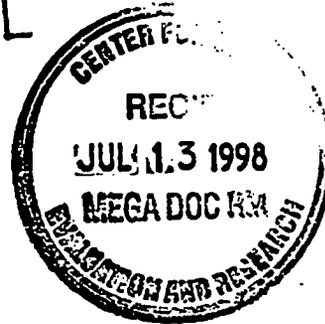
  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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ORIG AMENDMENT  
ORIGINAL



July 10, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

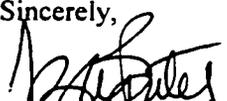
**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Section 9.0: Safety Update Report :Four Month Safety Update for ARAVA™ (leflunomide) Tablets NDA 20-905 Serial No. 040**

Dear Ms. Cook:

Pursuant to Section 505(b) of 21 CFR 314.50 (d)(5)(vi)(b), we are submitting to Section 9.0: Safety Update Report: The Four Month Safety Update for NDA 20-905, ARAVA™ (leflunomide) Tablets.

If you have any questions regarding the enclosed document, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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 Strategic Regulatory Division  
 1801 Rockville Pike, Suite 300  
 Rockville, MD 20852  
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BL  
 ORIG AMENDMENT  
 TRIP!



July 10, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
 and Ophthalmologic Drug Products  
 Center for Drug Evaluation and Research  
 Food and Drug Administration, HFD-550  
 9201 Corporate Boulevard  
 Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment Request: Labeling Request (Dated July 8, 1998) for Suggested Revisions to Labeling for NDA 20-905 Serial No. 039**

Dear Ms. Cook:

Enclosed please find two copies of the FDA request for the revised Clean Version of the Labeling for NDA 20-905. Provided in hard copy and Word 7. This labeling contains the following new information:

1. Correction to Line Number 312- the Liver Function Test Table with Elevations of > 3x the Upper Limits of Normal (ULN) for US301, MN301 and MN302. The correction only involve the titles for the treatment groups.

Table 2. LFT Elevations > 3x Upper Limits of Normal (ULN)								
US301			MN301			MN302		
LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX	

3. Additional Liver Function Test Table with Elevations of > 2x to 3x the Upper Limits of Normal (ULN) for US301, MN301 and MN302
4. The clean version of revised sections submitted in Submission No. 038 on July 9, 1998. The submission contained the following revisions for:
  - Black Box Statement,
  - Warning Section (Dealing with Pregnancy),
  - Information for Patients,
  - Laboratory Tests, and
  - Informed Consent Section

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
 Joy K. Bates, RN, BSN  
 Manager, Regulatory Affairs  
 Strategic Regulatory Division

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 Rockville, MD 20852  
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BL  
 ORIG AMENDMENT  
 Tripl.

July 13, 1998

**VIA COURIER**



Division of Anti-Inflammatory, Analgesic,  
 and Ophthalmologic Drug Products  
 Center for Drug Evaluation and Research  
 Food and Drug Administration, HFD-550  
 9201 Corporate Boulevard  
 Rockville, MD 20850

Attn: Ms. Sandra Cook, Project Manager  
 Subject: Information Amendment: Request for Clarification of Revisions to Labeling for NDA 20-905  
 (Serial Number 039, Date 7/10/98)  
 Serial No. 041

Dear Ms. Cook:

Per our telephone conversation this morning, enclosed please find two copies of the Clarification to the Clean Version of the Labeling for NDA 20-905 submitted as Serial number 039.

1. Correction to Page 18 Table 3 The Liver Function Test Table with Elevations of > 2x to 3x the Upper Limits of Normal (ULN) for US301, MN301 and MN302. The correction only involves the following cell

Table 3. LFT Elevations > 2x to 3x Upper Limits of Normal (ULN)								
	US301			MN301			MN302	
	LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX
ALT (SGPT) > 2x to 3x UNL (n %)	12 (6.6)	-	12 (6.6)	1 (0.8)	-	6 (4.5)	22 (4.4)	74 (14.9)
Reversed to ≤3x ULN:	12	-	11	1	-	5	20	70
Reversed to ≤ 2x ULN:								

2. Correction for Page 27, 4<sup>th</sup> Paragraph: The following paragraph should not have been presented in **BOLD** Type:

**Drug Elimination Procedure**

**Drug Elimination Procedure**

After discontinuing ARAVA, your doctor will prescribe a drug elimination procedure consisting of a full 10-day course of drug elimination medication followed by a laboratory blood test to assure a very low drug level in your body plus an additional waiting period of at least one month (one menstrual cycle). If your drug levels are too high, a repeat drug elimination procedure may be necessary. Repeat blood test will be required.



If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

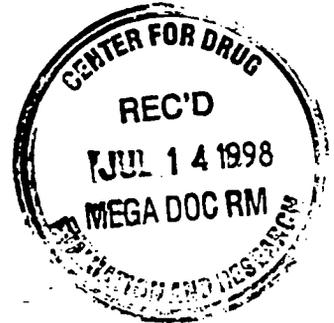
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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NC  
NEW CORRESP  
DUPLICATE



July 14, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: General Correspondence: Briefing Document for the Arthritis Advisory Committee Meeting on August 7, 1998 for ARAVA™ (leflunomide) Tablets**  
**NDA 20-905**  
**Serial No. 042**

Dear Ms. Cook:

Enclosed please find the cover letter, which accompanied the materials required by the Arthritis Advisory Committee for the panel meeting for NDA 20-905.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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July 15, 1998

**VIA FACSIMILE and COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Informational Amendment: Response to FDA Request for CMC Information**  
**NDA 20-905, ARAVA™ (leflunomide) Tablets**  
**Serial No. 043**

Dear Ms. Cook:

W reference your facsimile dated July 8, 1998, and the teleconference held on July 14, 1998.

On behalf of Hoechst Marion Roussel, Inc. (HMR), we are submitting an amendment to the above referenced NDA to respond to the Chemistry Reviewer's request.

Based on the July 14<sup>th</sup> teleconference, it is our understanding that the stability data requested by the Reviewer have been identified (Serial No.019, June 11, 1998), and will not be included within this submission.

However, based on our teleconference, we are submitting the standard 3 point stability commitment (request number 3 in the fax) as requested in the July 8<sup>th</sup> fax. Please find the commitment and July 8<sup>th</sup> fax attached.

In addition to being faxed, two hard copies of this submission will also be sent to you via courier.

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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Strategic Regulatory Division  
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Rockville, MD 20852  
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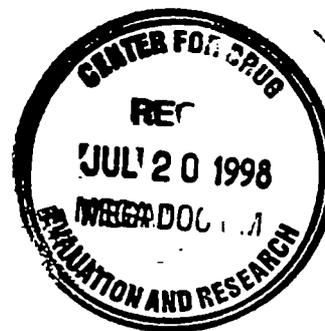
BM  
OFFICE OF THE DIRECTOR

Triple

July 17, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: General Correspondence: Section 8.0: Clinical: Materials for European Clinical Site Inspections**  
**NDA 20-905**  
**Serial No. 044**

Dear Ms. Cook:

Enclosed please find the cover letter, which accompanied the materials required by the Division of Scientific Investigations for European clinical site inspections for NDA 20-905.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

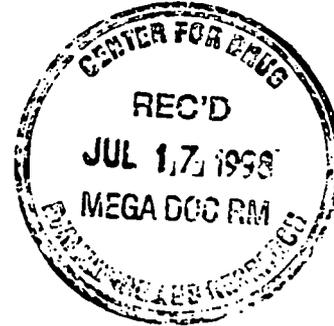
  
Joy R. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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NC  
NEW CORRESP  
**ORIGINAL**



July 17, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

NOTED  
IC 3  
7/23/98

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: General Correspondence: Briefing Document for the Arthritis Advisory Committee Meeting on August 7, 1998 for ARAVA™ (leflunomide) Tablets NDA 20-905 Serial No. 042**

Dear Ms. Cook:

Per your request July 17, 1998, enclosed is a archive copy of the documentation submitted to the Arthritis Advisory Committee for the panel meeting for NDA 20-905 on July 14, 1998.

Please have document control add this letter and the enclosed materials to Submission Serial No. 042.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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QUINTILES

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Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
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NC  
ORIGINAL

July 28, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

*Handwritten notes:*  
2081  
100  
8/10/98

Attn: Ms. Sandra Cook, Project Manager  
Subject: Information Amendment: Section 9.0: Four Month Safety Update Report: Revisions to Section 2.4: Malignancies (Serial Number 040, Date 7/10/98) NDA 20-905  
Serial No. 046

Dear Ms. Cook:

Enclosed please find two copies of an updated table to the Four-Month Safety Update Report (submitted as Serial number 040 on July 10, 1998) for NDA 20-905.

Changes to the table entitled "Malignancy Data through December, 1997," obtained during RA studies with leflunomide and presented in the original four-month safety update, are listed in Attachment 1.

The originally submitted table included benign conditions, as well as malignant conditions. The revised table shows a lower incidence of malignancies in all treatment groups. The conclusion reached in the four-month update remains the same and is reiterated here: "The table indicates that the relative incidence (based on years of patient experience) of malignancies is similar among all study treatment groups, with the lowest rate of occurrence in the leflunomide group."

For ease of review, we are also providing the following:

1. Attachment 2: The table originally submitted with the safety update
2. Attachment 3: A table delineating both the deletions and additions made to the original table

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

*Handwritten signature:* Joy K. Bates

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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BP  
ORIG AMENDMENT  
Tripi



August 4, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Section 5.0: Response to FDA Carcinogenicity Panel**  
**Request Regarding Thymoma Verification**  
**NDA 20-905**  
**Serial No. 049**

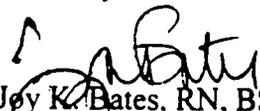
Dear Ms. Cook:

Enclosed please find two copies of the response to FDA's request dated July 29, 1998 from the FDA Carcinogenicity Panel regarding:

Verify that the thymomas identified in the Carcinogenicity Studies are epithelial in origin with non-neophyte lymphocyte infiltration.

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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3P  
ORIG. AMENDMENT

ORIGINAL



August 11, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Section 5.0: Response to FDA Pharmacology  
Reviewer Request Regarding Historical Vehicle Control Data for Metaphase  
Aberrations from Report No. 91.0115  
NDA 20-905  
Serial No. 050**

Dear Ms. Cook:

Enclosed please find two copies of the response to FDA's request dated August 8, 1998 from the FDA Pharmacology Reviewer regarding:

Historical vehicle control data for metaphase aberrations from study report no. 91.0115 entitled "A77 1486 (HWA 486) in the In Vivo Cytogenetic Test in Bone Cells of the Chinese Hamster - Chromosome Analysis".

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy R. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

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**D**  
**NTILES**

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Strategic Regulatory Division  
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Rockville, MD 20852  
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**ORIG AMENDMENT**

**DUPLICATE**



August 13, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment Request: Labeling Request (Dated August 7, 1998) for Revisions to Labeling for NDA 20-905 Serial No. 051**

Dear Ms. Cook:

Enclosed please find two copies of the FDA request for the revised ARAVA™ Tablets labeling for NDA 20-905. The following has been provided:

1. Clean version of the labeling provided in hard copy and Word 7.
2. Redline version which containing all edits to FDA's version of the labeling submitted to the Arthritis Advisory Committee for review in preparation of the August 7<sup>th</sup> panel meeting.

To assist in the review of the edited document:

All additions to the labeling have been marked by an underline/highlight and All deletions to the labeling have been marked by a strikeout.

The revised labeling contains the following revisions:

- Suggested wording per the outcome of the Arthritis Advisory Committee meeting held on August 7, 1998,
- Incorporation of the trade name ARAVA™,
- Black Box Statement,
- Revisions to the Mechanism of Action and Pharmacokinetics,
- Revisions to the Clinical Studies Section,
- Revisions to the Contraindications and Warning Section (Dealing with Pregnancy),
- Laboratory Tests, and
- Guidance for Counseling Female Patients of Childbearing Potential

We welcome the opportunity to interact cooperatively on label construction. Our desire is to move the process along as much as possible, without limiting the possibility of negotiating specific important details of the labeling.



NTILES

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



**QUINTILES**

Quintiles, Inc.  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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August 14, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Response to FDA Pharmacokinetics Reviewer's  
Written Request (Dated August 6, 1998) Regarding Smoking, Drug Clearance,  
and Required Dose of Arava™  
NDA 20-905  
Serial No. 052**

Dear Ms. Cook:

Enclosed please find two copies of the response to the FDA Pharmacokinetics Reviewer's written request regarding smoking, drug clearance, and required dose of Arava™ in your fax dated August 6, 1998. A copy of your August 6<sup>th</sup> fax is also enclosed for your reference.

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



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Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
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BC  
ORIG AMENDMENT

TRIP1

August 21, 1998  
**VIA COURIER**



Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Response to FDA CMC Reviewer's Written Request**  
**(Dated August 19, 1998) for Arava™ Tablets**  
**NDA 20-905**  
**Serial No. 053**

Dear Ms. Cook:

Enclosed please find two copies of the response to the FDA CMC Reviewer's written request regarding Arava™ dated August 19, 1998. A copy of your August 19<sup>th</sup> fax is also enclosed for your reference.

**Please Note:** This response answers Questions 1 to 12.

We will inform FDA as to the date when the information for Question 13 will be available.

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



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Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
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August 28, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Response to FDA Draft Version of the Labeling**  
**(Dated August 27, 1998) for Arava™ Tablets**  
**NDA 20-905**  
**Serial No. 054**

Dear Ms. Cook:

Enclosed please find two copies of the response to the FDA draft version of the labeling for Arava™ dated August 27, 1998. Hoechst Marion Rousell, Inc. would like to include the following revised Modified Health Assessment Questionnaire (MHAQ) statement insert for the Arava labeling.

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

Joy A. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

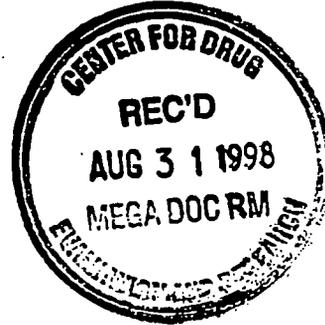


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August 31, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Response to FDA Draft Version of the Labeling**  
**(Dated August 31, 1998) for Arava™ Tablets**  
**NDA 20-905**  
**Serial No. 055**

Dear Ms. Cook:

Enclosed please find two copies of the response to the FDA draft version of the labeling for Arava™ dated August 31, 1998. Hoechst Marion Rousell, Inc. The following has been enclosed:

1. Clean version of the labeling provided in hard copy and Word 7.
2. Redline version which containing all edits to FDA's version of the labeling.

To assist in the review of the edited document:

All additions to the labeling have been marked by an underline/highlight and  
All deletions to the labeling have been marked by a strikeout.

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy R. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures



Quintiles, Inc.  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
<http://www.cro.quintiles.com>



September 1, 1998

**VIA COURIER**

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850

**Attn: Ms. Sandra Cook, Project Manager**  
**Subject: Information Amendment: Revised Package labeling for**  
**10 mg, 20mg, and 100 mg for Arava™ Tablets**  
**NDA 20-905**  
**Serial No. 056**

Dear Ms. Cook:

Enclosed please find two copies of the revised package labeling for 10 mg, 20 mg, and 100 mg tablets for the Arava (leflunomide).

If you have any questions regarding the enclosed information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
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Enclosures