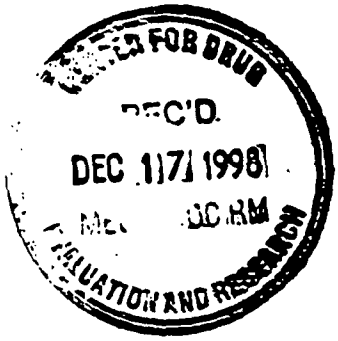
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-938**

CORRESPONDENCE

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

December 15, 1998



Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Re: MOBIC® (meloxicam) 7.5 mg Tablets **ORIGINAL NEW DRUG APPLICATION**
NDA 20-938 **USER FEE #3755**

Attention: Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)
Document Control Room N115

Dear Dr. DeLap:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act and CFR 314.50, Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is submitting archive and review copies of an original New Drug Application (NDA) No. 20-938 for MOBIC® (meloxicam) Tablets 7.5 mg.

The proposed indication for meloxicam is for the relief of the signs and symptoms of osteoarthritis.

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid class. Information from 149 clinical trials is presented in this NDA to support the safety of MOBIC®. Of these 149 trials, 86 trials have been integrated for presentation in the Integrated Summary of Safety (ISS). These 86 trials contain data from over 16,000 patients on meloxicam with painful rheumatic conditions including osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). Of these 86 trials, 7 well-controlled European trials (107.042, 107.043, 107.044, 107.045, 107.063, 107.153, 107.154) provide confirmatory evidence for the safety and efficacy of meloxicam tablets in the target osteoarthritis patient population. As agreed to at a December 15, 1997 meeting with the Division, the 12-week US OA trial (107.181) serves as the pivotal trial to secure NDA approval for this indication.

Meloxicam is currently approved in over 70 countries for the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in doses from 7.5 to 15 mg. Meloxicam is currently marketed outside the U.S. as 7.5 and 15 mg tablets, 7.5 and 15 mg capsules, 7.5 and 15 mg ampules (for injection) and 7.5 and 15 mg suppositories.

This NDA is comprised of 903 original volumes, and follows the format and content regulations as specified in 21 CFR 314.50, applicable FDA guidelines and those modifications discussed/communicated with the Division on April 21, 1997 (pre-NDA meeting), September 4, 1997 (submission Serial No. 018) and July 24, 1998 (submission Serial No. 079).

In accordance with Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, 21 USC 335a(k)(1), a debarment certification statement is included in the NDA following the FDA Form 356h.

This application contains electronic copies of the case report forms (CRFs) and case report tabulations (CRTs). The content of the CRFs and CRTs were communicated to the Division on July 24, 1998 (submission Serial No. 079). No paper copies are provided. Also included in this application are the electronic carcinogenicity datasets. As an aid to the reviewer, we will submit under a separate cover electronic files containing the text of the index, label, application summary, preclinical technical summary, HPB/clinical technical summaries, clinical trial supplemental analyses, ISS/ISE with datasets and programs, and Trial 107.181 with datasets and programs. These will separately be submitted to the Division within two weeks of the NDA submission. The format and content of the electronic submission are described in correspondences and telephone conversations dated May 22, 1998 (submission Serial No. 065) and June 30,1998 (telephone conversation with Mr. Ken Edmunds), respectively.

One certified "true" copy of the Application Summary Section, Chemistry, Manufacturing & Controls Section (including batch record data) and Samples, Methods Validation and Labeling Section is being submitted concurrently to the Stoneham, Massachusetts District Office, as required under Section 314.50(k)(3).

Please note that BIPI has submitted, under separate cover, the required User Fee [redacted] The User Fee number assigned to this application is 3577.

BIPI will forward a request for priority review of this application, under separate cover.

We hope that you share our enthusiasm for a supportive, highly interactive working relationship with the Division during the forthcoming NDA review process.

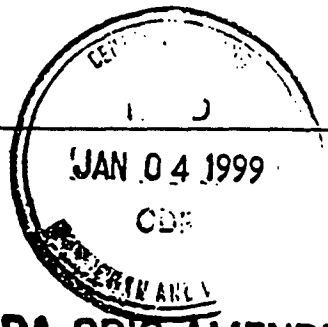
Sincerely,

Alan V. McEmber

Alan V. McEmber
DRA Associate Director
Tel: (203) 798-4366
Fax: (203) 791-6262

APPEARS THIS WAY
ON ORIGINAL

= 12/28/98
12/30/98



ORIGINAL

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

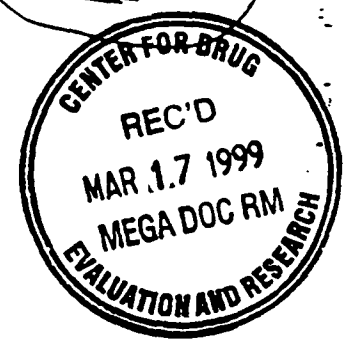
December 28, 1998

NDA ORIG AMENDMENT

BM Dianna Gunter PM
Kint Johnson MD

FDA Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

BM



Attention: Robert DeLap, M.D., Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
CDER

Re: NDA # 20-938 MOBIC (meloxicam) 7.5 mg tablet
Electronic Items 11 and 12 (Replacement DLT Tape)

Dear Dr. DeLap:

Please refer to the original NDA submission which was sent on December 15, 1998. In the original NDA, Sections 11 and 12 were included as an electronic component on DLT tape.[1] Also referenced is the telephone contact between Lt. Commander D'Annie Gunter of your Division and me on December 23, 1998, regarding the DLT tape from the original NDA being unreadable by the Central Document Room.

We are now providing replacement DLT tapes containing Sections 11 and 12. We have determined that additional software on the server was used to back-up the Sections 11 and 12 on the DLT tape. In the replacement tapes included in this submission, the additional software has been removed.

The CRTs and CRFs meet in electronic form per FDA Guidance for Industry - Archiving Submissions in Electronic Format - NDAs (September 1997), Subsection 1.1: Index (NDA Table of Contents), Subsection 1.11: Case Report Tabs (CRTs) and Subsection 1.12: Case Report Forms (CRFs).

[1] Section 11, Case Report Tabulations (CRTs) included CRTs for all patients in controlled studies. Section 12, Case Report Forms (CRFs) included CRFs for all patients who died and patients who withdrew due to adverse events.

We certify and agree to the following:

We have taken precautions to ensure the data files are free of computer viruses and authorize CDER to use anti-virus software as appropriate.

We understand that the data is an official part of the application and so may be retained indefinitely by the agency as an archive of the application.

The material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331 (J).

If there are any questions concerning this application, please contact me.

Sincerely,
Alan V. McEmber
Associate Director
Drug Regulatory Affairs
Phone: (203) 798-4366
Fax: (203) 791-6262

/S/

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-938

JAN 5 1999

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Alan V. McEmber
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877

Dear Mr. McEmber:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Mobic (meloxicam) tablet

Therapeutic Classification: Standard (S)

Date of Application: 12-15-98

Date of Receipt: 12-16-98

Our Reference Number: 20-938

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 14, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 16, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, contact LCDR D'Annie Gunter, P.D., Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

/S/

Anthony M. Zeccola
Chief, Projeet Management Staff
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 20-938
HFD-550/Div. Files
HFD-550/DAG
HFD-550/DDir/Hyde
HFD-550/TLChem/Patel
HFD-550/TLBiopharm/Bashaw
HFD-550/TLStat/Lin
HFD-550/TLPharmTox/Weir
DISTRICT OFFICE

Drafted by: dag/December 21, 1998
Initialed by:
final:

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

NC

Boehringer Ingelheim Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

January 27, 1999

LT. CMDR D'Annie Gunter
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, MD 20850

Re: MOBIC® (meloxicam) 7.5 mg Tablets
NDA 20-938
DESK COPIES of Text Module and Data Module

Attention: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)
Document Control Room N115

Dear LT. CMDR D'Annie Gunter:

As per our agreement in a telephone contact on January 27, 1999, please find enclosed additional desk copies of electronic information intended to support the review of the Mobic® NDA. Five copies of the **text module** (on CD-ROM) are provided and one additional copy of the **data module** (set of two DEC tapes) is provided. These are identical to what was submitted to you previously. Two attachments to this letter briefly describe the content of the modules.

Please distribute copies of the CD-ROM to: Dr. Johnson (Medical Officer), Dr. Yang (Pharmacology), Dr. Lu (Statistics), and Dr. Bashaw (Pharmacokinetics). One extra copy of the CD-ROM is provided.

In addition, please forward the DEC tapes to Dr. Lu (Statistics).

Please do not hesitate to contact me immediately if you require additional copies this data or if you have any questions.

Sincerely,

Alan McEmber 1/6.

Alan V. McEmber
DRA Associate Director
Tel: (203) 798-4366
Fax: (203) 791-6262

ORIGINAL

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

ORIG AMENDMENT

B2

February 4, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Re: Mobic® (meloxicam) 7.5 mg Tablets

AMENDMENT #1
NDA 20-938

Attention: Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
(HFD-550)

Dear Dr. DeLap:

Reference is made to the teleconference of January 27, 1999 between your Division and our company and [redacted] in which we discussed the issues raised at the 45-day Meeting regarding NDA Sections 5 (preclinical), 6 (HBP), and 10 (Statistical). Further reference is made to the discussion between Lt.Cmdr D. Gunter of your Division and myself on February 1, 1999, in which we reviewed the agreement of the proposal to submit an amendment for Sections 5 and 6. Based on these discussions, the trial reports found in Sections 5 and 6, have been reordered, the index has been improved in detail by the addition of the study trial reports, and the legibility of the trial reports has been improved. Other minor modifications also have been made.

Under the provisions of 21 CFR 314.60, Boehringer Ingelheim Pharmaceuticals, Inc., (BIPI), is now submiting the archival and review copies of the Amendment to the unapproved NDA 20-938 (dated December 15, 1998). Enclosed are the following volumes:

NDA Section	Title	Volume No.	# of Volumes
Index/Form FDA 356H		2.1	1
Section 5	Nonclinical Pharmacology And Toxicology	2.5 to 2.52	48
Section 6	Human Pharmacokinetics And Bioavailability	2.53 to 2.99	47

Volumes 2.5 to 2.52 (Section 5) and Volumes 2.53 to 2.99 (Section 6) supersede the original NDA volumes 1.5 to 1.52 (Section 5) and Volumes 1.53 to 1.99 (Section 6), respectively. Volumes 2.2, 2.3, and 2.4 of this amendment are intentionally unassigned so that the Section 5 and 6 volume numbering in this

amendment will correlate to the numbering of the volumes in the original NDA. Due to the reordering of the content of the reports in these volumes, these volumes may not directly match with the original NDA volumes.

No new information is provided in this amendment. This amendment makes the following changes in both sections, based upon the points raised by the Division in the January 27, 1999 teleconference:

Section 5 (Nonclinical Pharmacology and Toxicology)

Provided in Amendment #1:

1. The study reports are physically organized together by category and by type.
2. The INDEX for Section 5.5.3 (individual trial reports) now contains a detailed list of study report titles and report locations organized by category (pharmacology, toxicology, ADME), and by type/subtype. This list is duplicated in the reference section that follows each individual narrative summary of the nonclinical pharmacology, toxicology, and ADME subsections.
3. The legibility of the technical reports was reviewed and efforts were made to improve either the size and/or clarity of the contents of the illegible pages.

Pending Information to be submitted within the next 10 days:

1. An electronic text module of this Amendment will be provided on CD-ROM. This information will supersede the Section 5 electronic text module desk copies submitted on January 11, 1999 with the revised Section 5 technical summary.
2. A reformatted annotated package insert will be provided. The package insert referencing will be updated to specify the new locations of the technical report.
3. A table will be provided which provides the human dose equivalent from the carcinogenicity/reproduction toxicology study results.
4. An electronic file will be provided as a reviewer's aid to help locate trial reports and their contents within the section. Report numbers and index categories are hyperlinked to provide the location of the report.

Section 6 (Human Pharmacokinetics and Bioavailability)

Provided in Amendment #1:

1. The study reports are physically organized together by group and by type.
2. The section INDEX adds the detailed listing of the trial report titles in Section 6.7 (Individual Study Reports). In this expanded listing, the trial reports are organized by group headings, subheadings, and by trial number. Location of the reports is given. In Section 6.6 (references), the trial report titles are organized by report number for cross-referencing purposes. Location of the reports is given.
3. Section 6.1 (tabular summary) includes the *in vitro* studies and the analytical validation report information per the request of the Biopharmaceutics Reviewer. The analytical validation reports are paired under the appropriate clinical report tabular entry.
4. The legibility of the technical reports reviewed and efforts made to improve either the size and/or clarity of the pages found to be illegible.

Pending Information to be submitted to the NDA within the next 10 days:

1. An electronic text module of this Amendment will be provided on CD-ROM. This information will supersede the Section 6 electronic text module desk copies submitted on January 11, 1999 with the revised Section 6 technical summary.
2. A reformatted annotated package insert will be provided. The package insert referencing will be updated to specify the new locations of the technical report.
3. An electronic file will be provided as a reviewer's aid to help locate trial reports and their contents within the section. Trial numbers, report numbers, and index categories are hyperlinked to the volume index.

An electronic dataset of the PK data was provided in a separate submission as a separate desk copy on February 3, 1999 to the biopharmaceutics reviewer, Dr. Veneeta Tandon.

Reference is made to the discussions between Dr. Laura Lu (Office of Biostatistics) and BIPI on February 1, and 2, 1999 in which we reviewed the specific datasets subsets from the overall database which are needed to assist in the Division's efficacy review. The efficacy, demographic and medical history datasets (along with the appropriate descriptor files) will be supplied to her on CD-ROMs in the SAS PC (v.6.12) format, as desk copies.

Please do not hesitate to contact me immediately if you have any questions.

Sincerely,

Alan V. McEmber
Associate Director, Drug Regulatory Affairs
Tel: (203) 798-4366
Fax: (203) 791-6262

ORIGINAL

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

February 17, 1999

Dr. Robert DeLap, Director
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Re: MOBIC® (meloxicam) 7.5 mg Tablets
NDA 20-938

RESPONSE TO FDA
REQUEST FOR INFORMATION
Reformatted Annotated Package Insert

Attention: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)

Dear Dr. DeLap:

Reference is made to the Amendment dated February 4, 1999 in which we provided revised versions of Sections 5 (preclinical) and 6 (human pharmacokinetics and bioavailability) for MOBIC (meloxicam) 7.5-mg tablets NDA 20-938. Further reference is made to the teleconference of January 27, 1999 between your Division and our company in which you requested the annotated package insert be reformatted.

Per your request, attached is the reformatted annotated package insert that supercedes the labeling that was provided in the original NDA 20-938 dated December 15, 1998. The package insert references have been updated to specify the new locations of references in the February 4th amendment containing Sections 5 and 6. Also attached is an electronic copy of the annotated package insert in Word 97 format.

Please do not hesitate to contact me immediately if you require additional copies this data or if you have any questions.

Sincerely,

Alan McEmber

Alan V. McEmber
DRA Associate Director
Tel: (203) 798-4366
Fax: (203) 791-6262

Desk Copy: Dr. J. Yong
Dr. Vaneeta Tandon
LCDR. D'Annie Gunter (3 copies)
Dr. Kent Johnson

DISTRIBUTION (Cover letter only)

[redacted]

BM DUPLICATE

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

February 18, 1999

Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville MD 20850

Attention: Robert DeLap, M.D., Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550) CDER

Re: **Mobic® Tablets**
NDA 20,938

Response to FDA Request for Information

Summary Study Information - Japanese Controlled OA Studies (107.129, 107.131)

Dear Dr. DeLap:

Per the conversation of February 2, 1999 between Dr. Kent Johnson of your Division and BIPI, we are now providing copies of the following controlled Japanese clinical trials that Dr. Johnson had expressed interest in reviewing within the context of the meloxicam OA NDA (NDA 20-938) submission.

107.129 Late Phase II Clinical Study of UH AC 62 (meloxicam) Capsules in the Treatment of Osteoarthritis of the Knee Joint. (Japan)

107.131 Phase III Comparative Study of UH AC 62 (meloxicam) Capsule on Osteoarthritis of the Knee. (Japan)

These studies were not included in the integrated analysis of the efficacy of Mobic® in the treatment of the signs and symptoms of OA per agreement during pre-NDA discussions. They expand upon the summary information provided in the initial NDA submission of December 15, 1998.

The nature of the endpoints analyzed, doses used and homogeneity of the patient population(s) tested in the Japanese studies (107.129, 107.131) make it difficult to evaluate these studies in the same manner as the European and US studies.

Telephone: (203) 798-9988

If you require any additional information that will assist in your review of the clinical data for Mobic®, please do not hesitate to give me a call at the number listed below.

Sincerely,

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs
Phone: (203) 798-4366
Fax: (203) 791-6262

Desk Copies: Dr. Kent Johnson

DUPLICATE

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
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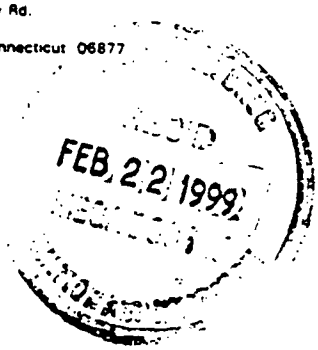
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877



February 19, 1999

Dr. Robert DeLap, Director
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Attention: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)

Re: MOBIC® Tablets, 7.5 mg
(meloxicam)
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION
Safety Tables

Dear Dr. DeLap:

Reference is made to the teleconference held on January 28, 1999 between Dr. Kent Johnson and the following Boehringer Ingelheim scientists: Dr. Chet Wood, Dr. David Hall, and Mr. Paul Roszko. In the teleconference we agreed to run specific safety tables and efficacy tables for specific studies. Also referenced is the fax sent to Dr. Kent Johnson on February 17, 1999 in which we provided an advanced copy of the safety tables.

Per this request, the following executed safety tables are now officially being submitted to the NDA:

- Tables A.1 and A.2: Contain two 6-month OA trials (107.063 and 107.045)
- Tables B.1 and B.2: Contain two 3-month OA trials (107.099 and 107.181)
- Tables C.1 and C.2: Contain two 4-week OA trials (107.153 and 107.154)
- Tables D.1 and D.2: Contain two 6-week OA trials (107.044 and 107.043) and combined data
- Tables E.1 and E.2: Contain one 3-week OA trials (107.042)

The efficacy tables you requested will be provided under a separate submission.

I will contact you within the next few days to discuss these tables.

Sincerely,

3/4/99

Alan V. McEmber
Associate Director, Drug Regulatory Affairs
Tel: (203) 798-4366
Fax: (203) 791-6262

3-3-99

G:\DRA\Meloxicam\Amend003.doc

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
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Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

February 26, 1999

Robert DeLap, M.D., Director
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville MD 20850

NDA 3/11/99

Re: Mobic® Tablets, 7.5 mg (meloxicam) NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Summary Efficacy Tables

Attention: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) CDER

Dear Dr. DeLap:

Reference is made to the conversation of January 28, 1999 between Dr. Kent Johnson of your Division and Dr. Chet Wood, Dr. David Hall, and Mr. Paul Roszko of BIPI in which we agreed to run specific safety and efficacy tables for specific studies. Also reference is made to the fax sent to Dr. Kent Johnson on February 19, 1999 and February 24, 1999, in which we provided an advanced copy of the efficacy tables. We are now officially submitting the following requested executed efficacy tables to the NDA:

- Trial 107.042, Three-Week, Double Blind, Placebo Control Study
- Trial 107.043, Six-Week, Double Blind, Active Control Study
- Trial 107.044, Six-Week, Double Blind, Active Control Study
- Trial 107.045, Six-Month, Double Blind, Active Control Study
- Trial 107.063, Six-Month, Double Blind, Active Control Study
- Trial 107.153, Four-Week, Double Blind, Active Control Study
- Trial 107.154, Four-Week, Double Blind, Active Control Study
- Trial 107.181, Three-Month, Double Blind, Placebo/Active Control Study

Please include this information in the file for NDA 20-938.

Telephone. (203) 798-9988

Please note that previously, an advance copy of the requested safety tables were provided to Dr. Johnson by fax on February 17, 1999, followed by an official submission to the NDA on February 19, 1999. At this point in time, all requests for safety and efficacy tables from the January 28, 1999 telconference have been met.

Sincerely,

Alan V. McEmber

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs
Phone: (203) 798-4366
Fax: (203) 791-6262

Desk Copy: Dr. Kent Johnson

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
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900 Ridgebury Rd.
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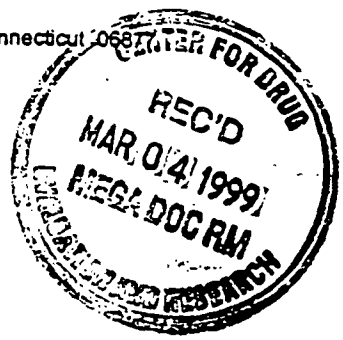
Ridgefield, Connecticut 06877

ORIG AMENDMENT
BC



March 3, 1999

Dr. Robert DeLap
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville MD 20850

Attention: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) CDER

Re: **Mobic® Tablets, 7.5 mg**
(meloxicam)
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION:
Electronic NDA CMC Text Files

Dear Dr. DeLap:

Reference is made to our meeting of February 8, 1999 in which Dr. Sue Ching Lin of your Division requested electronic MS Word 97 files of the specifications, packaging component description, synthesis flow chart, and description of the manufacturing procedure that were found in Section 4 (CMC) of NDA 20-938. The NDA was submitted on December 15, 1998.

In response to this request, enclosed is a diskette containing the following files:

4.1 Drug Substance.doc (Linker Text)
4.2 Drug Product.doc (Linker Text)
CMC Summary.doc (Application Summary)

These files should provide the relevant information useful to the written chemistry review.

Sincerely,

Alan V. McEmber
Senior Associate Director,
Drug Regulatory Affairs
Phone: (203) 798-4366

Desk Copy: Dr. Lin
LCDR Gunter

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

March 9, 1999

NEW CORRESP
NC

Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville MD 20850

Attention: Robert DeLap, M.D., Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550) CDER

Re: Mobic® Tablets
NDA 20-938

Response to FDA Request for Information
Summary Study Information - Taiwanese Controlled OA Studies (107.196 and 107.213)

Dear Dr. DeLap:

Per the contact of March 9, 1999 between Dr. Kent Johnson of your Division and me, we are now providing copies of the following Taiwanese controlled DRAFT trial reports for studies:

107.196	Multicenter, Double-blind, Double-dummy, Randomized Trial of Patients with Osteoarthritis. (Taiwan)
107.213	A 4 weeks, double-blind, parallel group, controlled study to compare the efficacy and safety of Meloxicam (7.5mg) with Diclofenac sodium slow release tablet (100mg) in patients with osteoarthritis of the knee. (Taiwan)

The Taiwanese studies, while clinically complete, are not administratively complete and ongoing reconciliation of the data may quantitatively affect some results. It is not anticipated that there will be qualitative changes that result from the ongoing reconciliation of the data from these studies. Appendicies are not yet available.

Telephone: (203) 798-9988

If you require any additional information that will assist in your review of the clinical data for Mobic®, please do not hesitate to give me a call at the number listed below.

Sincerely,

Alan V. McEmber

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs
Phone: (203) 798-4366
Fax: (203) 791-6262

DESK COPY: Dr. Kent Johnson

ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

NEW CORRESP
NC

K T
4/29/99

March 16, 1999

Dr. Robert DeLap
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville MD 20850

Attention: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) CDER

Re: Mobic® Tablets, 7.5 mg (meloxicam) NDA 20-938

OTHER: Final Plan for Four-Month Safety Update

Dear Dr. DeLap:

Reference is made to the facsimiles dated February 3, 1999 and February 17, 1999 to Dr. Kent Johnson and to the facsimile dated February 24, 1999 to LCDR. D'Annie Guenter of your Division in which we provided the proposed content and format for the four month safety update. This plan is now being submitted officially to the NDA file. This submitted plan differs from the faxed version in that the list of trials is now finalized to what will be included in submission. The table of contents is reordered to improve the flow of information in the submission. We intend to follow the attached plan for the four-month safety update and submit it to the Divison around April 14, 1999.

If you have any questions or comments, please feel free to contact me.

Sincerely,

Alan V. McEmber

Alan V. McEmber
Senior Associate Director,
Drug Regulatory Affairs
Phone: (203) 798-4366

ORIGINAL

Boehringer Ingelheim

NDA ORIG AMENDMENT

EP

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

March 30, 1999

RE: MOBIC® Tablets
NDA 20-938

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION:
Toxicology: Rat Carcinogenicity Tumor/Mortality Dataset

Alan McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Delap

Reference is made to the teleconference of March 25, 1999 between Mr. Anthony Zeccola, Dr. Constance Lewen, Dr. Laura Lu, and Dr. Jose Yang of your Division and Dr. Horst Lehmann (Toxicology), Mr. Doug Ball (Toxicology), and myself of Boehringer Ingelheim Pharmaceuticals (BIPI). In the teleconference, BIPI agreed to provide to your Division on March 30, 1999, a diskette containing the rat tumor/mortality dataset. Enclosed is a copy of the rat tumor mortality ASCII dataset which has been 100% quality controlled checked against the source animal reports. Typographical errors have been corrected and the tumor-free animal data has been included in this version. We have separated the dataset into three files: 3805.FDA (tumor/mortality table file), 3805.org (organ code file), 3805.dig (diagnosis code file). These data replace that submitted to the NDA on December 15, 1998 Volume 5, Page A.

As agreed in the teleconference of March 25, 1999, we will send you a diskette of the mouse tumor/mortality dataset at the end of this week.

Please contact me with any further requests or comments at (203) 798-4366.

Sincerely,

Alan V. McEmber
DRA Senior Associate Director

G:/DRA/Meloxicam/NDA Communications/9let0330 carcinogenicity dataset

ORIGINAL

NDA ORIG AMENDMENT

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

March 29,1999

RE: **MOBIC® Tablets**
NDA 20,938

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION:
Toxicology Carcinogenicity/Reproductive Studies
Exposure Table Modification to Table 5.3.4.2:1

Alan McEmber
Telepnone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Delap

Reference is made to the teleconference between your Division and BIPI of January 27, 1999 in which Dr. Jose Yang of your Division discussed the need for an exposure table for the carcinogenicity and reproductive studies in mg m2 day. Further reference is made to the meeting between Dr. Yang, LCDR. D'Annie Gunter, and Dr. Abraham Varghese, [redacted] and myself on February 8, 1999, in which we further discussed the exposure table. Reference is made to the facsimile to Dr. Constance Lewen, of your Division dated March 24, 1999, in which we provided an advance copy of the exposure data in mg m2 day. In that facsimile, we also included a modified table 5.3.4.2:1 (Reference February 4, 1999: Volume 3.5, Page 165) to replace the table provided in the NDA.

We are now providing you with a formal copy of the facsimile to you officially for the NDA files. Please contact me with any further requests or comments.

Sincerely,

Alan V. McEmber
DRA Senior Associate Director

DUPLICATE

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

BP
ORIG AMENDMENT

April 1, 1999

RE: MOBIC® Tablets
NDA 20-938

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION:
Toxicology: Mouse Carcinogenicity Tumor/Mortality Dataset

Alan McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Delap

Reference is made to the teleconference of March 25, 1999 between Mr. Anthony Zeccola, Dr. Constance Lewen, Dr. Laura Lu, and Dr. Jose Yang of your Division and Dr. Horst Lehmann (Toxicology), Mr. Doug Ball (Toxicology), and myself of Boehringer Ingelheim Pharmaceuticals (BIPI). In the teleconference, BIPI agreed to provide to your Division on April 1, 1999, a diskette containing the mouse tumor/mortality dataset. Enclosed is a copy of the mouse tumor/mortality ASCII dataset which has been 100% quality controlled checked against the source animal reports. Typographical errors have been corrected and the tumor-free animal data has been included in this version. We have separated the dataset into three files: 4184.FDA (tumor/mortality table file), 4184.org (organ code file), 4184.dig (diagnosis code file). These data replace that tumor/mortality data for the mouse submitted to the NDA on December 15, 1998 Volume 1.5, Page A. Note that the high dose group had a total of 100 animals with 51 being male and 49 being female mice.

Please note that we have submitted a separate dataset for the rat carcinogenicity tumor mortality data on March 30, 1999.

Please contact me with any further requests or comments at (203) 798-4366.

Sincerely,

Alan V. McEmber

Desk Copy: Dr. Laura Lu

ORIGINAL

ORIG AMENDMENT

BX

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

April 2, 1999

RE: **MOBIC® Tablets**
NDA 20-938

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION:
Additional Analyses for Trials 107.043, 44, 45, 63, 99, 181, 196, 213.

Alan McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Delap

Reference is made to the facsimile dated March 29, 1999 from Dr. Kent Johnson of your Division in which he cumulatively summarized the additional analyses requested for selected meloxicam trials. Reference is made to the Boehringer Ingelheim facsimile dated April 1, 1999, in which we provided an advance copy of the Q Statistic analyses on selected efficacy measures for the trials 107.099, 181 (4 weeks), 196(dose corrected), and 213. Further reference is made to the Boehringer Ingelheim facsimile dated March 26, 1999, in which we provided an advance copy of the Q Statistic and rescue medications for the trials 107.043, 44, 45, and 63 and the Q Statistic for 181 (3 months) and 196 (4 weeks). We are now following both facsimiles up with an official copy being submitted as an amendment to the NDA. Attached are the following:

Q Statistic analyses on selected efficacy measures with the rescue medications for the following trials:

Trial 107.043: Six-week, double blind, active control, OA of hip
Trial 107.044: Six-week, double blind, active control, OA of knee
Trial 107.045: Six-month, double blind, active control, OA hip and knee
Trial 107.063: Six-month, double blind, active control, OA knee or hip
Trial 107.181: Three-month, double blind, placebo control/active control, OA (Q at final visit – 3 months)

Q Statistic analyses on selected efficacy measures:

Trial 107.099: Three month, double blind, active control, OA hip (Q at 4 weeks and end trial)
Trial 107.181: Three month, double blind, placebo control/active control, OA (Q at 4 weeks)
Trial 107.196: Four week, double blind, active control, OA hip/knee (Q at 4 weeks) (dose corrected)
Trial 107.213: Four week, double blind, active control, OS knee (Q at 4 weeks)

Boehringer Ingelheim

The information in this amendment addresses some, but not all of the requests outlined in the March 29, 1999 facsimile from Dr. Kent Johnson. We will respond to the remaining requests during the next few weeks.

Please contact me with any further requests or comments at (203) 798-4366.

Sincerely,

Alan V. McEmber

Desk Copy: Dr. Kent Johnson

DUPLICATE

NDA ORIG AMENDMENT

BP

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

April 6, 1999

RE: MOBIC® Tablets
NDA 20-938

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION:
Toxicology: Mouse Carcinogenicity Tumor/Mortality Dataset; Additional Information

Alan McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Delap

Reference is made to the April 1, 1999 amendment in which we provided a copy of the mouse tumor/mortality ASCII dataset which has been quality controlled checked against the source animal reports. In this version, typographical errors have been corrected and the tumor-free animal data has been added. Reference is made to the teleconference of April 6, 1999, between Dr. Constance Lewen and Dr. Laura Lu of your Division and Mr. Doug Ball (Toxicology) and myself of Boehringer Ingelheim Pharmaceuticals (BIPI). In the teleconference, Dr. Lu noted that the diskette containing the mouse tumor/mortality dataset sent on April 1, 1999 did not have the listing for the animal #429. This was an early death animal which did not have a tumor and whose listing was inadvertently not transferred to the final dataset. The listing for the animal is now added in this version.

Please contact me with any further requests or comments at (203) 798-4366.

Sincerely,

Alan V. McEmber

Alan V. McEmber

Desk Copy: Dr. Laura Lu

DUPLICATE

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

NEW CORRESP
NC

April 8, 1999

RE: MOBIC Tablets
NDA 20-938

GENERAL CORRESPONDENCE: Response to Request for Information

Alan McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Delap

Reference is made to the Amendment dated April 2, 1999 which included Additional Analyses for Trials 107.043, 44, 45, 63, 99, 181, 196, 213. In the Amendment, the 356h form was unsigned. Enclosed is a copy of the signed Form 356h for that amendment.

Please contact me with any further requests or comments at (203) 798-4366.

Sincerely,

Alan V. McEmber

DUPLICATE

Boehringer Ingelheim

NEW CORRESP
NC

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

April 6, 1999

RE: MOBIC® Tablets
NDA 20-938

OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION:
Toxicology: Mouse Carcinogenicity Tumor/Mortality Dataset; Additional Information

Alan McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Dr. Delap

Reference is made to the April 1, 1999 amendment in which we provided a copy of the mouse tumor/mortality ASCII dataset which has been quality controlled checked against the source animal reports. In this version, typographical errors have been corrected and the tumor-free animal data has been added. Reference is made to the teleconference of April 6, 1999, between Dr. Constance Lewen and Dr. Laura Lu of your Division and Mr. Doug Ball (Toxicology) and myself of Boehringer Ingelheim Pharmaceuticals (BIPI). In the teleconference, Dr. Lu noted that the diskette containing the mouse tumor/mortality dataset sent on April 1, 1999 did not have the listing for the animal #429. This was an early death animal which did not have a tumor and whose listing was inadvertently not transferred to the final dataset. The listing for the animal is now added in this version.

Please contact me with any further requests or comments at (203) 798-4366.

Sincerely,

Alan V. McEmber

Desk Copy: Dr. Laura Lu

Boehringer Ingelheim

ORIGINAL

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

April 15,1999

Alan V. McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail AMcEmber@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

RE: **MOBIC® Tablets**
NDA 20-938

NDA ORIG AMENDMENT
SU

FOUR MONTH SAFETY UPDATE

Dear Dr. Delap,

Pursuant to 21 CFR 314.50(d)(5)(vi)(b), Boehringer Ingelheim Pharmaceuticals, Inc. is amending the above referenced NDA to provide updated safety information for MOBIC® (meloxicam) 7.5 mg Tablets.

Reference is made to two (2) telefaxes dated February 3, 1999 and February 17, 1999, and 3 BIPI/Agency telephone conversations dated January 19, 1999, February 22, 1999, and February 24, 1999, in which we provided proposals for the content and format of this Four-Month Safety Update.

This safety update covers the period from the cut-off date for the OA NDA 20-938, through January 15, 1999. Based on the evaluation of safety data obtained during this review period, we propose that the following adverse events be added to the "Adverse Reactions" section of the proposed label:

Jaundice
Leg Edema
Interstitial nephritis

Detailed discussions of the information supporting these proposed changes can be found in the attached report.

Report	Author/Title	NDA Section
U99-3066	Paul Roszko	9.0

Please incorporate this information into NDA 20-938 for meloxicam.

Sincerely,

Alan V. McEmber
Senior Associate Director, DRA

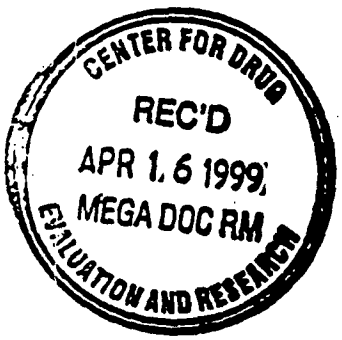
G:\DRA\Meloxicam\9fet0415 4 month saf update jrn.doc

NDA ORIG AMENDMENT

Boehringer Ingelheim

B 5

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850



Boehringer Ingelheim
Pharmaceuticals, Inc.

April 15, 1999

RE: **MOBIC® Tablets**
NDA 20-938

RESPONSE TO REQUEST FOR INFORMATION

Dear Dr. Delap,

Reference is made to the February 3, 1999 submission in which we provided a CD-ROM of the electronic efficacy dataset for the trials 107.042, 043, 044, 045, 063, 153, 154, and 181.

Additional reference is made to the teleconference of April 7, 1999 between Dr. Laura Lu and Dr. Constance Lewin of the Division and the sponsor and representatives from [redacted] in which we discussed the need to provide a revised, efficacy dataset layout for the US trial 107.181. We are now providing a CD-ROM containing the revised electronic efficacy data set for the US Trial 107.181. As agreed, the following attributes are included in the revised efficacy data set.

a. Trial dataset is organized by patient with one record of each patient with the last observation carried forward.
b. The treatment group is provided in the dataset.
c. "Other" is clarified in the revised dataset.
d. The original formatted value in the revised dataset is provided with a codebook.

Please contact me if you have any further questions.

Sincerely,

ORIGINAL

Alan V. McEmber
Senior Associate Director, DRA

Desk copy: Dr. Laura Lu

Alan V. McEmber
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail AMcEmber@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

DUPLICATE

NC

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

April 16, 1999

Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville MD 20850

Attention: Dr. Veneeta Tandon
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550) CDER

Re: Mobic® Tablets
NDA 20-938

DESK COPY
Response to Request for Information
Copy of Section 6 Technical Reports

Dear Dr. Tandon:

Reference is made to the April 9, 1999 telephone discussion between you, Dr. Constance Lewin, Dr. Jose Yang and Dr Tony Zeccola of the Division myself and [redacted] in which you requested a desk copy of specific technical reports photocopied at higher magnification. In agreement to our discussion, we are now providing you desk copies of the following volumes photocopied at higher magnification: 70-77.

These volumes are essentially the same, with the exception of the text magnification, as those volumes submitted to the NDA in the February 4, 1999 amendment. We will provide you with desk copies of the remainder of the reports in separate mailings over the next couple of weeks.

If you require any additional information that will assist in your review, please do not hesitate to give me a call at the number listed below.

Sincerely,

Abraham Vaghese Jr.

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs
Phone: (203) 798-4366
Fax: (203) 791-6262

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analagesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

NDA ORIG AMENDMENT

RE: MOBIC® Tablets
NDA 20-938

April 16,1999

Alan McEmber
Sr. Associate Director
Drug Regulatory Affairs
Telephone 203/798-4366
Telefax 203/791-6262

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

RESPONSE TO FDA REQUEST FOR INFORMATION :
Preclinical: Rat and Mouse Carcinogenicity Study – Body Weight, Organ Weight and Food Consumption Data Sets

Dear Dr. DeLap

Reference is made to the ASCII data set of the mouse and rat carcinogenicity studies provided in the December 15, 1999 NDA located in Section 5. Further reference is made to the March 25, 1999 teleconference between Dr. Laura Lu, Dr. Jose Yang, Dr. Constance Lewin and Mr. Tony Zeccola of your division and Boehringer Ingelheim in which we discussed providing a corrected version of the ASCII data sets from the mouse (U91-0332) and rat carcinogenicity (U92-0645) studies. Additional reference is made to the March 30, 1999 and April 6, 1999 submissions in which we provided the corrected tumor mortality data sets from the rat study and the mouse study respectively. We are now providing a copy of the diskettes containing the quality control-checked ASCII data sets of the body weight, organ weight and food consumption data from the rat and mouse carcinogenicity reports. Typographical errors have been corrected and each data set has been 100% verified by Boehringer Ingelheim Pharma KG.

The following files are provided in the attached diskette:

1. 3805_2FDA:	Rat –	Body Weight
		Food Consumption
		Organ Weight
2. 4184_2FDA:	Mouse –	Body Weight
		Food Consumption
		Organ Weight

A full paper copy of each of the ASCII files from this submission is attached to this cover letter.

ORIGINAL

Please contact me with any further requests or comments at (203) 798-4366.

Sincerely,

Alan V. McEmber

Alan V. McEmber

Desk copy: Dr. Laura Lu

ORIGINAL
BP

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

April 22,1999

Meloxicam Tablets
NDA 20-938

Response to FDA Request for Information
Carcinogenicity Data Tables

Alan V. McEmber
Telephone 203.798.4366
Telefax 203.791.6262

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. DeLap:

Reference is made to the teleconference of March 25, 1999 between your Division and Boehringer Ingelheim in which we discussed the mouse and rat carcinogenicity datasets and study reports. In the discussion, you requested that we provide clarification of tables 17/18 from those reports. Specifically, you requested calculated p-values listed by male and female animals. Please find the requested tables attached to this letter.

Copies of these tables were submitted via facsimile to Dr. Laura Lu on April 21, 1999.

Sincerely,

Alan V. McEmber
Sr. Associate Director

DUPLICATE

NC

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.
a subsidiary of
Boehringer Ingelheim Corporation
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, Connecticut 06877

April 23, 1999

Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville MD 20850

Attention: Dr. Jose Yang
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550) CDER

Re: Mobic® Tablets
NDA 20-938

DESK COPY
Response to Request for Information
Copy of Section 5 Technical Reports

Dear Dr. Yang:

Reference is made to the April 9, 1999 telephone discussion between you, Dr. Constance Lewin, Dr. Veneeta Tandon and Dr Tony Zeccola of the Division myself and [redacted] in which you requested a desk copy of specific technical reports photocopied at higher magnification. In agreement to our discussion, we are now providing you desk copies of the following volumes photocopied at higher magnification: 44-49.

These volumes are essentially the same, with the exception of the text magnification, as those volumes submitted to the NDA in the February 4, 1999 amendment. We will provide you with desk copies of the remainder of the reports in separate mailings over the next couple of weeks.

If you require any additional information that will assist in your review, please do not hesitate to give me a call at the number listed below.

Sincerely,

for Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs
Phone: (203) 798-4366
Fax: (203) 791-6262

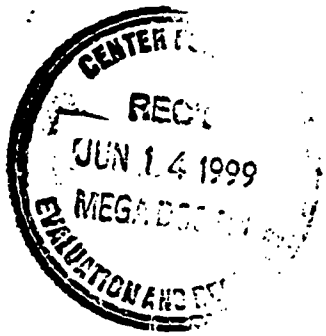
Boehringer Ingelheim

[redacted]

BM

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-550)
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.



June 10, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938
Other: Request for Information

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bipharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. DeLap:

Reference is made to the telefax sent to Dr. Constance Lewin on June 7, 1999, in which we requested clarification of the FDA case definition for clinically relevant (serious) UGI Endpoints. Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is in the process of using the FDA case definition for clinically relevant (serious) UGI endpoints to conduct additional analyses of meloxicam clinical trials by a blinded independent review committee. Enclosed are our questions and a copy of the FDA case definition.

Sincerely,

Alan V. McEmber
Senior Associate Director
Drug Regulatory Affairs

DUPLICATE

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-550)
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

[redacted]

June 16, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938
Response to FDA Request for Information

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. DeLap:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc., in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide examples of two revised toxicology reports for Dr. Josie Yang's evaluation. Enclosed are the revised reports entitled, " Teratogenicity Study in the Rabbit with the Substance UH-AC 62 XX, Segment II", U82-0078, and Toxicity Study on UH-AC 62 XX in Mini-Pigs by Oral Application over a period of 12 Months", U92-0253.

I will contact Dr. Constance Lewin within the next couple of days to schedule a teleconference to discuss the two study reports.

Sincerely,

Alan V. McEmber
Drug Regulatory Affairs

Desk Copies: Dr. Josie Yang
Dr. Constance Lewin (cover letter only)

DUPLICATE

NC

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-550)
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

NEW CORRESP

Boehringer Ingelheim
Pharmaceuticals, Inc.

June 24, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938
Response to FDA Request for Information: Electronic Copy

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
Telefax (203) 791-6262
E-Mail Amcember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. DeLap:

Reference is made to our "Response to FDA Request for Information" submission filed to this NDA on June 16, 1999, in which we provided paper copies of two revised toxicology reports entitled "Teratogenicity Study in the Rabbit with the Substance UH-AC 62 XX, Segment II", U82-0078, and Toxicity Study on UH-AC 62 XX in Mini-Pigs by Oral Application over a period of 12 Months", U92-0253.

Enclosed is an electronic copy of only the text portion of these revised reports.

Also enclosed is a revised replacement Page 4a for report U92-0253, which includes Table 18: Female Individual Animal Body Weights. This table was inadvertently omitted from the Table of Contents of this report submitted on June 16, 1999.

Sincerely,

Alan V. McEmber
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

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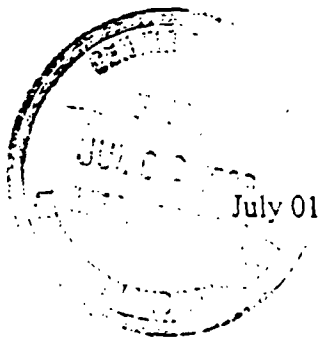
ORIGINAL

Boehringer Ingelheim

ORIG AMENDMENT

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals Inc.



July 01,1999

Mobic® (meloxicam) 7.5mg Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. DeLap:

Alan McEmber, M.S.
Telephone 203-798-4366
Telefax 203-791-6262
E-Mail Amcember@bi-pharm.com
900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Reference is made to the meeting between your Division and Boehringer Ingelheim on May 24, 1999, in which a request was made for additional statistical analyses for the rat carcinogenicity study U92-0645.

Attached is the final report containing the analyses. In addition, separately attached is a summary page entitled, "Table A: Statistical Summary of Specific Tumor Incidence in Sprague-Dawley Rats Administered UH-AC 62XX (BI study report U92-0645)." This table combines Tables 1, 2, 3 and 4 from the attached report into one summary table.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Alan McEmber, M.S.
Senior Associate Director
Drug Regulatory Affairs

ORIGINAL

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
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Rockville, MD 20850

ORIG AMENDMENT
BZ

Boehringer Ingelheim
Pharmaceuticals Inc.

July 7, 1999

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Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION: Additional Statistical Analyses from mouse carcinogenicity study U91-0333 (paper/electronic copy); Additional Statistical Analyses from rat carcinogenicity study U92-0645 (electronic copy).

Dear Dr. DeLap:

Reference is made to the meeting between your Division and Boehringer Ingelheim on May 24, 1999, in which a request was made for additional statistical analyses to be conducted for the mouse carcinogenicity study U91-0333.

Attached is the final report containing the analyses. In addition, separately attached is a summary page entitled, "Table A: Statistical Summary of Specific Tumor Incidence in Mice Administered UH-AS 62xx (BI study/report U91-0333)." This table combines Tables 1, 2, 3 and 4 from the attached report into one summary table. Also attached is an electronic copy of the tables from this report.

Reference is made to our "Response to FDA Request for Information" submission filed to this NDA on July 1, 1999, in which we provided a paper copy of the final report of the rat carcinogenicity study U92-0645 containing the additional statistical analyses requested by Dr. Josie Yang in a meeting on May 24, 1999. Attached is an electronic copy of the tables from this report.

Sincerely,

Alan McEmber
Senior Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

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ORIGINAL

Boehringer Ingelheim

ORIG AMENDMENT

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals Inc.

July 8, 1999

Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION: Population Kinetics – PK NONMEM Electronic Data Set from Studies 107.014, 107.030, and 107.036.

Dear Dr. DeLap:

Reference is made to the facsimile transmission record dated July 1, 1999, in which it was requested to provide additional electronic data sets from selected studies. Regarding the PK data set from studies 107.014, 107.030, and 107.036, attached is an electronic copy of the [redacted] data files, control files and the output files used for report U97-2656. Additionally, attached is a guide to the datasets followed by a print-out of the datasets. The PD files will be submitted to you under a separate amendment.

Dr. Veneeta Tandon may contact Dr. John Sabo with any technical questions regarding the data set at (203) 798-5355.

Sincerely,

Alan V. McEmber

Alan McEmber
Senior Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Veneeta Tandon

Alan McEmber
Senior Associate Director
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ORIGINAL

BP

Boehringer Ingelheim

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-550)
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.

ORIG AMENDMENT

July 12, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938
Response to FDA Request for Information

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
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900 Ridgebury Rd/P.O. Box 368
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Telephone (203) 798-9988

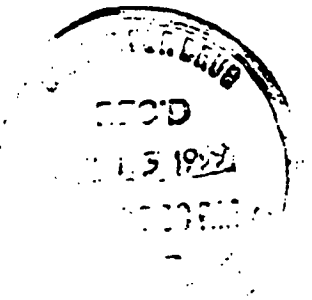
Dear Dr. DeLap:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc., in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports for Dr. Josie Yang's evaluation.
Attached is a revised report entitled "Teratogenicity Study with the Substance UH-AC 62 XX in Rats, Segment II (Test of Organogenesis)", U82-0079. Also attached is an electronic copy of the text portion of the report.

Sincerely

Alan V. McEmber
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang



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ORIGINAL

Boehringer Ingelheim

NC

Dr. Robert DeLap, Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Food and Drug Administration
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals Inc.

July 16, 1999

Alan McEmber
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Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938

RESPONSE TO FDA REQUEST FOR INFORMATION: PD Electronic Data Set from Studies 107.014, 107.030, and 107.036.

Dear Dr. DeLap:

Reference is made to the facsimile transmission record dated July 1, 1999, in which it was requested additional electronic data sets from selected studies. Regarding studies 107.014, 107.030, and 107.036, attached is a copy of the PD electronic data set.

Sincerely,

Alan McEmber
Senior Associate Director
Drug Regulatory Affairs

Desk Copy: Dr. Veneeta Tandon

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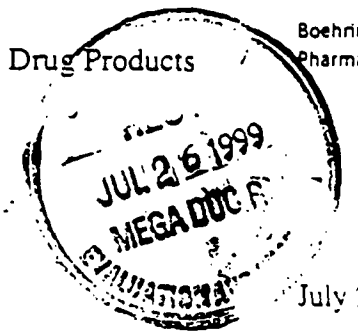
Boehringer Ingelheim

BP

Dr. Karen Midthun, Director
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-550)
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

Boehringer Ingelheim
Pharmaceuticals, Inc.



July 23, 1999

Re: Mobic® (meloxicam) 7.5 mg Tablets
NDA 20-938
Response to FDA Request for Information

Alan McEmber
Senior Associate Director
Telephone (203) 798-4366
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E-Mail Amember@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Midthun:

Reference is made to the telephone conference call of May 14, 1999 between the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Boehringer Ingelheim Pharmaceuticals, Inc., in which we discussed the specific comments generated by the Pharmacology reviewer, Dr. Josie Yang. Further reference is made to the meeting of May 24, 1999 between the Division and Dr. Wolfgang Neumann, Dr. Ray Stoll and myself in which we agreed to provide revised toxicology reports for Dr. Josie Yang's evaluation. Attached is a revised report entitled "Chronic Toxicity Study of UH-AC 62 XX in Rats Following Oral Administration over a Period of 26 weeks."

Also attached is an electronic copy of the text portion of the report.

Sincerely

Alan V. McEmber
Drug Regulatory Affairs

Desk Copy: Dr. Josie Yang

TRIP
BC

Boehringer Ingelheim

ORIG AMENDMENT

Boehringer Ingelheim
Pharmaceuticals Inc.

Food and Drug Administration
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products (HFD-550)
Document Control Room N115
9201 Corporate Blvd.
Rockville, MD 20850

July 28, 1999

Attention: Karen Midthun, MD, Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD 550)

Alan V. McEmber
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E-Mail amcember@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

MOBIC (meloxicam) 7.5 mg Tablets
NDA 20-938
CMC Amendment / Response to FDA Request for Information

Dear Sir or Madam:

Please amend Section 4.0 CHEMISTRY of our NDA with the following chemistry, manufacturing and controls (CMC) information:

Section 4.1.9 Drug Substance Controls
Section 4.1.9.2 Specifications and Test Methods
(Original NDA Vol. 1.2 pages 43 - 44)

In our original submission we listed both an [redacted] HPLC assay method and a [redacted] assay method in the specifications for meloxicam drug substance. Reference is made to the telephone message dated July 20, 1999, from Dr. Sue-Ching Lin, Review Chemist, to Alan McEmber, in which Dr. Lin requested that one regulatory assay method be designated.

We agree to designate the [redacted] HPLC assay method as the regulatory method, and to consider the [redacted] assay method as an alternate method. Enclosed in this amendment is a revised Section 4.1.9.2, where TABLE 4.1.9.2:1 is amended accordingly.

Boehringer Ingelheim

In our original submission, the analytical methods for testing meloxicam were incorporated by reference to the document "Drug Substance Testing Specifications for Meloxicam (UH-AC 62 XX) [redacted] for meloxicam. At Dr. Lin's request in a telephone conversation dated July 20, 1999, Section 4.1.9 is also revised to physically include a copy of this document.

Section 4.2.4 Name and Address of Manufacturer
Section 4.2.4.2 Packaging, Labeling and Final Product Release
(Original NDA Vol. 1.2, page 151)

Enclosed in this amendment is a revised Section 4.2.4.2 in which the following sentence is deleted: "MOBIC Tablets will be distributed by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)." Identification of the distributor is not specifically required in the CHEMISTRY section of our NDA. We would prefer not to mention the distributor in order to avoid the need to maintain this section with current information as distribution agreements change.

Section 4.2.6 Drug Product Controls
Section 4.2.6.2 Specifications and Test Methods
(Original NDA Vol. 1.2, pages 212-215)

Reference is made to the FDA Biopharmaceutics and Chemistry Information Request dated July 19, 1999 (facsimile, copy attached), in which FDA recommended that the dissolution specification be changed to either [redacted] We agree to tighten the dissolution specification for MOBIC Tablets to [redacted]

In a July 22, 1999, telephone discussion with Dr. Lin, she requested that the tabulation of the drug product specifications in Section 4.2.6.2 be organized differently to show the regulatory specifications more clearly differentiated from the internal controls, and to more clearly identify which tests are performed only on stability.

According to Dr. Lin's request, enclosed in this amendment is a revised Section 4.2.6.2, in which TABLE 4.2.6.2:1 presents the regulatory specifications amended with the tightened dissolution specification, and a separate TABLE 4.2.6.2:2 presents the internal non-regulatory controls.

BIPKG's Testing Specification Number 1015715-008R-03 will be re-issued under a new document number with the revised dissolution specification of [redacted] For purposes of this amendment, this revised specification is shown as hand-written notations on the document.

Boehringer Ingelheim

Section 4.2.9.2 Accelerated and Long Term Stability Studies
Section 4.2.9.3 Proposed Storage Conditions and Expiry Dating
(Original NDA Vol. 1.3, pages 43-44, pages 64 - 104)

Enclosed in this amendment is an updated stability report, *Stability Report UH-AC 62 XX tablets 7.5/180 mg* (T1482-03-03-04), with twenty-four (24) months stability data for MOBIC Tablets stored at the long-term 25°C storage condition, in both bottle and blister package systems. Also included in this report are twenty-four (24) months stability data for the blister-packaged tablets stored at the intermediate condition 30°C

Please note that this updated stability report was written prior to FDA's request to change the dissolution specification and therefore, the report still contains the originally proposed dissolution specification of Following is an assessment of the dissolution results versus the revised dissolution specification of

bottles with induction seal and desiccant, 30 and 100 count:

The results for tablets stored at 40°C (3 and 6 months) retrospectively fail the new specification in most cases for stage 1 dissolution testing. But at the time the batches were tested, the dissolution specification was lower and it was met by the data. So, according to the USP requirements, only 6 tablets were tested.

However, if stage 2 testing had been carried out, it is highly probable that the results would have complied with the specification Mean values of 78.8% to 83.8%, and no individual value below 77.0%, were observed for the three NDA batches (30 and 100 count) stored at

The results obtained for tablets stored at 25°C for up to 24 months usually meet stage 1 requirements. Although a few individual values are slightly below 80%, the batches would have easily passed stage 2 requirements if additional testing had been performed.

Based on these data, we propose a revised expiration dating period of 30 months for tablets packaged in bottles / 30 and 100 count.

As previously reported, the results for tablets stored at failed the stage 2 requirements based on the specification Therefore, testing was initiated at 30°

The results obtained for tablets stored at 30°C for up to 18 months fail the new specification for stage 1. However, for stage 2 they would likely meet the new