CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-938**

ADMINISTRATIVE DOCUMENTS

REQUEST FOR PROPRIETARY/ESTABLISHED NAME REVIEW

To: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D., Chair
HFD-530
9201 Corporate Blvd, Room S447

From: Sue-Ching Lin, Review Chemist
Division of Anti-inflammatory, Analgesic, and Ophthalmic Products,
HFD-550 Phone: 827-2525

Date: January 14, 1999

NDA#: 20-938

Proposed Proprietary Name: Mobic

Trademark registration status/Countries registered(if known): "Mobic" has been registered in many countries outside of the U.S., mostly in Europe.

Company name: Boehringer Ingelheim Pharmaceuticals, Inc.

Other proprietary names by same firm for companion products: N/A

United States Adopted Name, dosage form, strength and dosing schedule: Meloxicam, 7.5 mg tablet, one to two tablets once daily

Indication for use: For relief of the signs and symptoms of osteoarthritis

Comments from submitter (concerns, observations, etc.):

1. This is a new molecular entity in the U.S.. However, according to the sponsor, meloxicam is currently marketed in over 70 countries for the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.
2. Other trade names used in foreign countries for this product: Movalis (Austria, Bulgaria, Czech, Greece, and others) , Movatec (Brazil, and etc.), Mobex (Chile..), Loxitan, Mobicox.....

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1142	550	Mobic	meloxicam tablets
ATTENTION:	Sue-Ching Lin		

A. Look-alike/Sound-alike

	Potential for confusion:		
Mobigesic	XXX Low	____ Medium	____ High
Mobisyl Crème	XXX Low	____ Medium	____ High
Moban	XXX Low	____ Medium	____ High
	____ Low	____ Medium	____ High
	____ Low	____ Medium	____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

xxx Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 4/9/99

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
20-938

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.	September 14, 1999
TELEPHONE NO. *(Include Area Code)* (203) 798-4486	FACSIMILE (FAX) NUMBER (Include Area Code) (203) 791-6262
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DISCRIPTION

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

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Meloxicam	Mobic®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME (if any)
4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide	UH AC 62 XX

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	7.5 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

INDICATED FOR RELIEF OF THE SIGNS AND SYMPTOMS OF OSTEOARTHRITIS

SEP 15 1999
MEDICAL REVIEW

APPLICATION INFORMATION

APPLICATION TYPE (check one) [X] 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 [X] 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 [X] 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: **RESPONSE TO FDA REQUEST FOR INFORMATION**

PROPOSED MARKETING STATUS (check one) [X] PRESCRIPTION PRODUCT (Rx) [ ] OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS [X] 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.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

FORM FDA 356H (7/97)

G:\DRA\Meloxicam\fda356h.doc

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	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) (i), 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) (vi) (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 (j) (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 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify): General Correspondence

CERTIFICATION

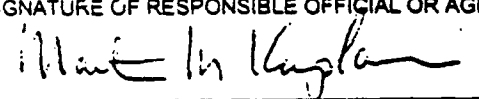
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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	DATE
	Martin M. Kaplan, J.D., M.D. Vice President, Drug Regulatory Affairs	September 14, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877	(203) 798-4486

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

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Meeting Minutes

DATE: December 13, 1999

NDA: 20-938

DRUG: Mobic® (meloxicam) 7.5 mg Tablets

SPONSOR: Boehringer Ingelheim Pharmaceuticals, Inc.

Representatives of BIPI
Manfred Hale, M.D.
David Hall, Ph.D.
Martin Kaplan, M.D., J.D.
Steven Lanes, Ph.D.
Alan, McEmber
Michel Pairet, Ph.D.
Gurkapal Sihng, M.D.
Chet Wood, M.D.

Representatives of FDA
Robert DeLap, M.D., Ph.D.
Lawrence Goldkind, M.D.
John Hyde, M.D., Ph.D.
Kent Johnson, M.D.
Karen Midthun, M.D.
Anthony M. Zeccola

BACKGROUND: This face-to-face meeting was scheduled as a continuation/follow-up to the December 2, 1999 labeling discussion between the Division and Applicant. The purpose of this meeting was to try to reach agreement on the issues of COX-2 Selectivity, GI Tolerability and PUB analysis.

DISCUSSION: Following introductions, the issues mentioned above were discussed.

- COX-2 Selectivity of meloxicam - The Applicant discussed their rationale for inclusion of some mention of COX-2 Selectivity in the label and suggested alternative wording. The Division reiterated its position regarding this issue. Any description of COX-2 selectivity needs to be based upon *in-vivo* studies, as discussed during recent meetings of the Arthritis Advisory Committee. The Division still recommends removal of the discussion of COX-2 selectivity. The Applicant once again disagreed. Dr. Kaplan indicated that this would require further discussion with the upper management of BIPI.

- PUB Analysis and GI Tolerabilty -The Applicant discussed their rationale for inclusion of this information in the Clinical Trials section of the label and suggested alternative wording. In the case of GI tolerability, given the lack of endoscopic data, this information is more appropriately reported in the Adverse Reactions section of the label. The PUB analysis data is also not appropriate given that this is a pooled analysis which was not described *a priori*. The Applicant once again disagreed with the Division's suggestion. Dr. Kaplan indicated that this would require further discussion with the upper management of BIPI.

Having arrived at an impasse, Dr. Kaplan inquired as to possible actions. Dr. DeLap stated that given that the FDAMA/PDUFA due date for this NDA is December 15, 1999, and the need for further internal discussions within BIPI, if an agreement were not reached by the due date, an Approvable, rather than an Approval letter would be issued. Dr. Kaplan indicated that he would take this into consideration and would get back to the Division.

Follow-Up: During the late morning of December 15, 1999, the Project Manager received a call from Mr. McEmber, stating that BIPI was unable to accept the labeling as suggested by the Division, and requested the issuance of an Approvable letter.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Meeting Minutes

DATE: December 2, 1999

NDA: 20-938

DRUG: Mobic® (meloxicam) 7.5 mg Tablets

SPONSOR: Boehringer Ingelheim Pharmaceuticals, Inc.

Representatives of BIPI
Chris Corsico, M.D.
Frank Degner, Ph.D.
Manfred Hale, M.D.
David Hall, Ph.D.
Martin Kaplan, M.D., J.D.
Steven Lanes, Ph.D.
Alan, McEmber
Michel Pairet, Ph.D.
Paul Rozko
Gunter Terummlitz, Ph.D.
Chet Wood, M.D.

Representatives of FDA
Robert DeLap, M.D., Ph.D.
Lawrence Goldkind, M.D.
John Hyde, M.D., Ph.D.
Kent Johnson, M.D.
Karen Midthun, M.D.
Anthony M. Zeccola

BACKGROUND: This teleconference was scheduled as a continuation/follow-up to the November 24, 1999 labeling discussion between the Division and Applicant. The Applicant submitted additional information, as amendments to the NDA, dated November 30 and December 1, 1999. These amendments contained information discussing the COX-2 selectivity of meloxicam, as well as additional information regarding the PUB analysis and GI tolerability of meloxicam.

DISCUSSION: Following introductions, the contentious sections of the November 19, 1999 version of the label were once again discussed.

- COX-2 Selectivity of meloxicam - Following review of the December 1, 1999 submission, the Division's position remains unchanged regarding this issue. Any description of COX-2

selectivity needs to be based upon *in-vivo* studies, as discussed during recent meetings of the Arthritis Advisory Committee. Therefore, the Division still recommends removal of the discussion of COX-2 selectivity. The Applicant once again disagreed with the Division's suggestion, stating that the *in-vitro* studies suggested that meloxicam was as COX-2 selective as at least one of the currently marketed agents with regard to this type of information. The Division countered that since there is no currently validated/standard *in-vitro* assay to quantify COX-2 selectivity, this was not an unequivocal finding.

- PUB Analysis and GI Tolerabilty - Following review of the December 1, 1999 submission, the Division's position remains unchanged regarding these issues. In the case of GI tolerability, given the lack of endoscopic data, this information is more appropriately reported in the Adverse Reactions section of the label. The PUB analysis data is also not appropriate given that this is a pooled analysis which was not described *a priori*. The Applicant once again disagreed with the Division's suggestion.

- Adverse Reactions Section - While there is still a need for further discussion of the format of this section, it was agreed that it is progressing via normal channels between the review team and the Applicant. It was agreed that discussions of this section would continue as they have been.

The Applicant requested a face-to-face meeting with the FDA to discuss these issues further. A meeting was scheduled for Monday December 13, 1999.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Meeting Minutes

DATE: November 24, 1999

NDA: 20-938

DRUG: Mobic® (meloxicam) 7.5 mg Tablets

SPONSOR: Boehringer Ingelheim Pharmaceuticals, Inc.

Representatives of BIPI
Chris Corsico, M.D.
Frank Degner, Ph.D.
Manfred Hale, M.D.
David Hall, Ph.D.
Martin Kaplan, M.D., J.D.
Steven Lanes, Ph.D.
Alan, McEmber
Michel Pairet, Ph.D.
Paul Rozko
Gurkapal Sihng, M.D.
Gunter Terummlitz, Ph.D.
Chet Wood, M.D.

Representatives of FDA
Lawrence Goldkind, M.D.
John Hyde, M.D., Ph.D.
Kent Johnson, M.D.
Karen Midthun, M.D.
Veneeta Tandon, Ph.D.
Lourde Villalba, M.D.
Mary Jane Walling, Ph.D.
Anthony M. Zeccola

BACKGROUND: NDA 20-938 was submitted December 15, 1999. The label included with the initial submission was reviewed by the full review team and suggested modifications were forwarded to the Applicant via facsimile on November 5, 1999. The Applicant did not accept the changes and this teleconference was schedule. The Applicant submitted counter proposals in an amendment to the NDA dated November 19, 1999. These counter proposals involved the COX-2 statement in the Clinical Pharmacology section, statements regarding the PUB analysis and GI tolerability in the Clinical Trials section and safety information in the Adverse Reactions section.

DISCUSSION: Following introductions, the contentious sections of the November 19, 1999 version of the label were discussed section by section.

- COX-2 Selectivity - The November 19, 1999, label put forth by the Applicant contained revised wording concerning COX-2 selectivity, based on *in-vitro* studies. The Division's position is that any description of COX-2 selectivity needs to be based upon in-vivo studies, as discussed during recent meetings of the Arthritis Advisory Committee. Therefore, the Division still suggests removal of the discussion of COX-2 selectivity. The Applicant indicated that they would propose revised wording, along with additional data relating to the COX-2 selectivity of meloxicam and would like to discuss this following review of that information by the Division.

- PUB Analysis and GI Tolerability - In the November 5, 1999 facsimile, the Division suggested that the Applicant remove the discussion of the GI tolerability and PUB from the Clinical Trial section. In the case of GI tolerability, given the lack of endoscopic data, this information is more appropriately reported in the Adverse Reactions section of the label. The PUB analysis data is also not appropriate given that this is a pooled analysis which was not described *a priori*. The Applicant disagreed with both suggestions and indicated that they would submit additional background information for future discussion of these issues.

- Adverse Reactions Section - This part of the meeting focused on the format and presentation of this section. This was not an area of contention, but it was agreed that additional discussions between the Division and the Applicant would be necessary to complete this section.

It was agreed that another telecon would be scheduled to discuss the pending issues. The Division will review additional information submitted by the Applicant in an expedient manner. The telecon was scheduled for Thursday, December 2, 1999.

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

MEETING DATE: 3/27/00 **TIME: 2:00** **LOCATION:** Corp S-314

HFD-550 Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

NDA 20-938
DRUG: **Mobic®(meloxicam) Proposed Indication: Signs and Symptoms of Osteoarthritis**

APPLICANT:Boehringer Ingelheim Pharmcaceuticals, Inc.

TYPE of MEETING: Pre-Approval Safety Conference

REVIEW DIVISION PARTICIPANTS:
Karen Midthun, Division Director, DAAOPD
Kent Johnson, Medical Officer
Leslie Vaccari, Acting, Chief Project Management Staff
Anthony Zeccola, Project Manager

OPDRA PARTICIPANTS:
Julie Beitz - Division Director, DDRE I
Claudia Karwoski - Safety Evaluator Team Leader, DDRE I
Renan Bonnel - Safety Evaluator, DDRE I
Patrick Guinn - Project Manager, DDRE I

MEETING OBJECTIVES:

To provide a routine, formal mechanism for communications between the Office of Drug Evaluation (ODE) review divisions and the Office of Post-Marketing Drug Risk Assessment (OPDRA) risk evaluation divisions prior to the approval of a new chemical entity (NCE) or certain other applications in order to:

(1) Ensure that OPDRA is aware of potential post-marketing safety problems of drugs about to be approved,

(2) Consider, jointly, the need for any special post-marketing analyses or post-marketing safety studies or other evaluations to be implemented by or agreed to by the sponsor prior to the approval of a drug product, and

(3) Determine if there is any special information or feedback that the ODE review division would like from the OPDRA risk evaluation division during the immediate post-launch life of the soon-to-be-approved drug product.

DISCUSSION and DECISIONS REACHED:

A brief history of the application was provided, including a synopsis of labeling discussions between the Division and Applicant.

No post-marketing surveillance issues were identified and the product appears to be appropriately labeled at this time.

The meeting was concluded at 2:35 There were no unresolved issues or discussion points.

/S/ 3/29/00
Anthony M. Zeccola Date
Project Manager

/S/ 3/29/00
Karen Midthun Date
Division Director

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TELECONFERENCE MEETING MINUTES

Meeting Date: March 25, 1999 **Time:** 1:30 – 2:30 p.m. **Location:** CORP S-300

NDA #/Drug Name: NDA 20,938 Mobic (meloxicam)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Type of meeting: Pharmacology-Toxicology

Attendees:

FDA	Sponsor
John E. Hyde, Ph.D., M.D, Deputy Division Director	Douglas J. Ball, M.S., Toxicologist.
Constance Lewin, M.D., Project Manager	Horst Lehmann, Ph.D., Toxicologist
Laura Hong Lu, Ph.D., Statistician	Alan McEmber, M.S., Reg Affairs
Josie Yang, D.V.M., Ph.D., Pharmacology-Toxicology Reviewer	Guenter Trummlitz, Ph.D., International Project Planning
Anthony M. Zeccola, Chief, Project Management Staff	

Meeting Chair: John E. Hyde, Ph.D., M.D. **External Participant Lead:** Horst Lehmann, Ph.D.

Meeting Recorder: Constance Lewin, M.D.

Meeting Objective:

Clarification of underlying basis for preclinical carcinogenicity dataset inconsistencies which include the following:

1. Mislabeling of animal death types (natural death vs. sacrifice);
2. Mismatching of animals and dose groups;
3. Discrepancies in numbers of animals included in electronic datasets vs. such numbers in study report; and
4. Exclusion of animals without tumor from data analyses

Discussion Points:

1. Regarding items 1, 2 and 3 above, sponsor reported that such discrepancies were the result of limiting quality-control check to several pages which were error-free and relying on outside assurances that the data had been previously checked for quality-control purposes. In addition, sponsor stated that the original analyses were done by what is now an outdated computer system, and errors of a typographical nature were made when transcribing ASCII computer files to currently used electronic format.

2. Regarding item 4 above, sponsor indicated that there had been a misinterpretation of the format which was being requested by FDA: Sponsor thought FDA wanted to analyze only the data from animals with tumor. As a result, animals without tumor were excluded from analyses submitted.

3. Further clarification was requested on p values in trend analyses reported in Tables 17 and 18: It is not clear whether the trend p-values are for male or female animals.

4. Inquiry was made by FDA regarding rat-study control group. Specifically, a question was raised whether the two control groups were created artificially by separating one control group into two. Sponsor indicated that, while normally there would be two independent control groups, in this case the one group was separated by counting off the first 50 and then the next 50. FDA responded that such procedure was not randomized and that the two control groups should be combined for statistical analyses.

5. Inquiry was made by FDA regarding quality assurance of clinical data. Sponsor indicated the need to defer response at this time, as the appropriate parties were not present. Sponsor was advised to check QA procedures applied to clinical data, given the inconsistencies found thus far in pre-clinical data.

Decisions/Agreements reached:

1. Sponsor will perform complete quality assurance checks on all preclinical (mouse and rat) tumor and mortality datasets and will resubmit such datasets as follows: Rat dataset to be resubmitted on Wednesday, March 31, 1999; and mouse dataset to be resubmitted on Friday, April 2, 1999.

2. Sponsor will perform a complete quality assurance check on body-weight, organ-weight, and food-consumption datasets and will resubmit such datsets on or about April 15, 1999.

3. Sponsor will completely recheck ASCII computer files against individual animal data.

4. Sponsor will combine the two rat control groups into one for the purposes of statistical analyses.

5. Sponsor will provide gender-related (male and female) p values.

Unresolved Issues/Issues requiring Further Discussion:

1. Sponsor will follow up with FDA to respond to question regarding quality assurance check of clinical data.

Action Items:

1. Sponsor will fax to FDA Tables 17 and 18.

2. Sponsor will follow up on this teleconference by submitting to NDA 20,938 the appropriate official amendments in response to agreements made today.

/S/

Constance Lewin, M.D.
Project Manager/Minutes Preparer

Concurrence, Chair:

/S/ 4-28-99

John E. Hyde, Ph.D., M.D.
Deputy Division Director

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

TELECONFERENCE MEETING MINUTES

Meeting Date: April 6, 1999 Location: CORP N102

NDA #/Drug Name: NDA 20-938 Mobic (meloxicam)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Type of meeting: Biostatistics

Attendees:

FDA	Sponsor
Constance Lewin, M.D., Project Manager	Douglas J. Ball, M.S., Toxicologist.
Laura Hong Lu, Ph.D., Statistician	Alan McEmber, M.S., Reg Affairs

Meeting Chair: Laura Hong Lu, Ph.D. External Participant Lead: Douglas J. Ball, M.S.

Meeting Recorder: Constance Lewin, M.D.

Background Summary:

Teleconference was requested by FDA to inquire about missing mouse data from mouse carcinogenicity dataset. Specifically, it appeared that all data relating to mouse #429 had been omitted from the mouse carcinogenicity dataset which, due to dataset inconsistencies, was resubmitted on March 31, 1999, by agreement between FDA and sponsor at March 25, 1999, telecon.

Discussion Points:

1. Inquiry was made by Dr. Lu regarding missing data for mouse #429. Sponsor indicated that all data related to mouse #429 had been erroneously omitted when revising mouse carcinogenicity datasets to include mice without tumor. Sponsor reported that there were 500 such mice and that this data had been entered manually, leading to an error of omission. Sponsor stated that mouse #429 was male; was in dose group three; was 97 weeks at time of death; had death status code of "1"; had animal microscopic exam code of "1"; and that one record exists for this animal. Per sponsor, this animal was without tumor and had early death.

2. Upon inquiry by sponsor, Dr. Lu reported that she had briefly looked at the corresponding rat data and that, based on her limited inspection, there are no apparent problems with it.

Agreements reached/Action Items:

Sponsor agreed to send today, by Federal Express, revised mouse carcinogenicity datasets that will include all data pertaining to mouse #429. Also by agreement, sponsor will submit today to NDA 20-938 an official copy of such materials.

/S/

Constance Lewin, M.D.
Project Manager

Concurrence, Chair:

/S/

Laura Hong Lu, Ph.D.
Statistician

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

TELECONFERENCE MEETING MINUTES

Meeting Date: April 7, 1999 Time: 1:30 – 1:50 p.m. Location: CORP N-102

NDA #/Drug Name: NDA 20-938 Mobic (meloxicam)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Type of meeting: Biostatistical

Attendees:

FDA	Sponsor
Constance Lewin, M.D., Project Manager Laura Hong Lu, Ph.D., Statistician	Susan Bassion Program Director, PPD-Pharmaco David Hall, Ph.D., Biostatistics Alan McEmber, M.S., Regulatory Affairs Matt Snowden, Data Management George Strong, Ph.D. Associate Director, Biostatistics PPD-Pharmaco

Meeting Chair: Laura Hong Lu, Ph.D.

External Participant Lead: David Hall, Ph.D.

Meeting Recorder: Constance Lewin, M.D.

Background History: Teleconference requested by FDA to discuss statistical layout issues regarding clinical datasets submitted.

Meeting Objectives:

1. Relay to sponsor the need to provide per-patient clinical data, as opposed to the per-visit clinical data which has been submitted;
2. Relay to sponsor the need for therapeutic-group identification in clinical statistical submission;
3. Clarification regarding the definition of "other" in the reason-for-discontinuation column in datasets; and
4. Clarification of the reason for a protocol change in statistical analysis plan.

Discussion Points:

1. Trial 181 clinical datasets provided by sponsor - FDA informed sponsor that it was previously requested that this submission be organized by patient ID and not by visit, the format which has been received. Sponsor agreed to submit this data organized by patient ID, with one record per patient, with last observation carried forward.
2. Therapeutic-group identifier – FDA informed sponsor that therapeutic-group identifier was not found in the clinical data submitted. Sponsor agreed to include this when submitting data organized by patient ID.

3. "Other" reason for discontinuation – FDA informed sponsor that the term "other" appears to be used for a large number of blocks under the heading "Reason for Discontinuation," and it is unclear what "other" actually refers to, given that no definition has been provided. Sponsor agreed to provide clarification on this point, adding that a comment field is needed for some of these blocks.

4. Formatted values used in clinical datasets submitted – FDA requested the codebook for variable formatting, which sponsor agreed to provide.

5. Protocol for US trial – In the original protocol of the US study, only treatment and center were specified to be included in the ANOVA model for primary efficacy endpoints. In the actual analysis, target joint was also included. FDA inquired about the basis for this change. Sponsor explained that the results for the primary analysis were similar with or without target joint included in the ANOVA model.

Agreements reached/Action Items:

1. Sponsor will provide, by one week from today, Trial 181 datasets reorganized to provide one record per patient, with the last observation carried forward.

2. Sponsor will include therapeutic-group identifiers in the Trial 181 reorganized datasets to be submitted.

3. Sponsor will provide clarification regarding use of the term "Other" under "Reason for Discontinuation," and sponsor will include this clarification in the datasets to be submitted within one week from today.

4. Sponsor will provide the codebook for formatted values used in the clinical datasets.

Concurrence, Chair:

/S/

Constance Lewin, M.D.
Project Manager

/S/

Laura Hong Lu, Ph.D.
Statistician

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

TELECONFERENCE MEETING MINUTES

Meeting Date: July 12, 1999 **Time:** 1:15 – 2:30 p.m.

NDA 20-938

Drug Name: Mobic (meloxicam)

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Type of meeting: Pharmacology-toxicology

Attendees:

FDA

John E. Hyde, Ph.D., M.D,
Deputy Division Director
Constance Lewin, M.D., Project Manager
Karen Midthun, M.D.,
Acting Division Director
Josie Yang, D.V.M., Ph.D.,
Pharmacology-Toxicology Reviewer
Andrea Weir, Ph.D.,
Pharmacology-Toxicology Team Leader
Anthony M. Zeccola,
Chief, Project Management Staff

Sponsor

Martin Kaplan, M.D.,
Vice President, Regulatory Affairs
Alan McEmber, M.S.,
Director, Regulatory Affairs
Wolfgang Neumann, Ph.D.,
Head, Corporate Non-Clinical Safety/Efficacy
Ray Stoll, Ph.D.,
Director, Toxicology & Safety Assessment

Meeting Chair: Karen Midthun, M.D.

Meeting Recorder: Constance Lewin, M.D.

Background Summary:

In a July 7, 1999, telephone call to the Division, the sponsor conveyed their expectation to have fully and completely submitted, by September 15, 1999, the revised pharm-tox submissions which have been coming in. In that same telephone call, the sponsor requested this teleconference in order to discuss further that timeline; and to discuss their request that the Division agree to consider these submissions a major amendment and thereby extend the review clock by three months.

Meeting Objectives:

- Discussion of sponsors' timeline for completion of revised pharm-tox submissions; and
- Discussion of the option to agree that these submissions constitute a major amendment.

Discussion Points:

- The sponsor opened the teleconference by explaining to the Division that they have 15 toxicologists working to try to meet the mid-September timeline and asked whether the Division would be agreeable to moving the review clock from a ten-month clock to twelve months. The Division explained that the ten-month date is the primary goal date, and the Division is not empowered to change the primary goal date simply by agreement. However, the Division stated that it would consider the possibility of agreeing to consider these pharm-tox submissions a major amendment, which could extend the goal date three months.

  The sponsor stated that they expected that the rest of the toxicology revisions to be completed in August and early September; and that they would like the review clock moved to January 16, 2000; if the Division would be agreeable to such extension. The Division responded that, if all revised pharm-tox submissions were received in the Division by September 16, 1999, the Division would consider these a major amendment and thereby extend the review clock to January 16, 2000. The sponsor agreed with this plan. Additionally, the Division informed the sponsor that, if the complete pharm-tox information is not received by September 16, 1999, the Division would be prepared to take an action on this application based on the status of the application before that date.

- The sponsor inquired about the Division's willingness to consider the PUB re-analysis that they are currently doing and plan to submit. The Division informed the sponsor that it was not aware of the full details surrounding this request and would discuss this issue with sponsor at a later date.

- The Division closed the teleconference by summarizing its understanding regarding the revised pharm-tox submissions: These reports are to be submitted in their entirety by September 16, 1999, or one month prior to the action date. If this can be accomplished, the Division would consider making these submissions a major amendment and thereby extend the primary goal date three months. Conversely, if all revised reports are not received by September 16, 1999, then the October 1999 goal date would not be changed. The sponsor was in agreement with that plan.

Action Items/Agreements reached:

- Provided that sponsors submit the revised pharm-tox reports in their entirety by September 16, 1999, the Division and sponsor will agree to consider these submissions a major amendment and thereby extend the primary goal date to January 16, 2000. However, the Division will be prepared to take an action on this application by the October 1999 goal date if all revised reports are not fully received by September 16, 1999.

Minutes prepared by:

/S/

Constance Lewin, M.D.
Project Manager

APPEARS THIS WAY
ON ORIGINAL

FEB 10 1999

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 20-938 Applicant: Boehiger Ingelheim Original Stamp Date: 12/12/1998

Drug Name: Mobic (Meloxicam) Amendment StampDate: 2/5/1999

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL the required and requested IND studies completed and submitted in this NDA?	√		
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?			N/A
6	Are the proposed labeling sections relative to animal Pharmacology/Toxicology appropriate (including human dose multiples bsed on comparative serum/plasma levels or expressed in mg/m^2) and in accordance with CFR21, part 201.57?		√	Under the sections of Carcinogenesis, Mutagenisis. Impairment of Fertility and Preganacy (Teratogenic Effect), the sponsor need to provide human dose-multiples based on comparative serum/plasma levels or expressed in mg/m^2. The sponsor will send the revised labeling in the next two weeks.
7	Has the sponsor submitted all special studies/data requested by the Division during pre-NDA meeting?	√		

Reviewing Pharmacologist: /S/ 2/10/1999

Josie W.C. Yang Date:

Team Leader: /S/ 10 Feb 99

Andrea Weir Date:

cc:
Original NDA 20-938
HFD-550/Division File
HFD-550/Pharm-Tox/JYang
HFD-550/DGunter
HFD-550/Pharm-ToxTL/AWeir

APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 20-938 Applicant: Boehiger Ingelheim Stamp Date: 12/12/1998

Drug Name: Mobic (Meloxicam)

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? (Yes or No) No

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section organized adequately?		√	The sponsor need to oganized studies under each subsection (e.g. Parmacology, Toxicology, and ADME...et at.) and arrange them consectively in each vol.
2	Is the section indexed and paginated adequately?		√	For each sub section, the sponsor need to provide a master index including study Nº, study title, report Nº, vol. Nº, and page Nº.
3	On its face, is the section legible?		√	Tables for some studies are illegible (such as vol 11, U82-0509, p 32-51), the sponsor need to provide them in better quality with larger prints (increase in font size).
4	Are ALL the required and requested IND studies completed and submitted in this NDA?	√		
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?			N/A
6	Are the proposed labeling sections relative to animal Pharmacology/Toxicology appropriate (including human dose multiples bsed on comparative serum/plasma levels or expressed in mg/m^2) and in accordance with CFR21, part 201.57?		√	Under the sections of Carcinogenesis, Mutagenisis, Impairment of Fertility and Preganacy (Teratogenic Effect), the sponsor need to provide human dose multiples based on comparative serum/plasma levels or expressed in mg/m^2.
7	Has the sponsor submitted all special studies/data requested by the Division during pre-NDA meeting?	√		

Reviewing Pharmacologist: /S/ 1/26/99

Josie W.C. Yang Date:

Team Leader: /S/ 27 Jan 99

Andrea Weir Date:

cc:
Original NDA 20-938
HFD-550/Division File
HFD-550/Pharm-Tox/JYang
HFD-550/CSO
HFD-550/Pharm-ToxTL/AWeir
HFD-550

20-920-DLV.

45 DAY MEETING CHECKLIST

ILEABILITY:

Initial overview of the NDA application: MOBIC N 20-938 YES NO

BIOPHARMACEUTICAL:

(1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓

(3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? ✓

(4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic pharmacokinetic characterization requirements for approvability of this product? ✓

(5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparisons of and establish the equivalence of the product to be marketed and the product(s) used in the clinical development? ✓

(6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? ✓

/S/ 2/10/99
Reviewing Medical Officer

/S/ 2/10/99
Supervisory Medical Officer

APPEARS THIS WAY ON ORIGINAL