CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40306

CORRESPONDENCE

ANDA 40-306

MAY 5

Medeva Pharmaceuticals Manufacturing, Inc.
Attention: Robert B. Parker, Ph.D.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated April 20, 1998 and your correspondence dated April 24, 1998.

NAME OF DRUG: Methylphenidate Hydrochloride Extended-release Tablets USP, 10 mg

DATE OF APPLICATION: April 10, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 13, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Attachment L-A

L: Perrigo Company
Attention: Virginia Lutke
502 Eastern Avenue
Allegan, MI 49010

AUG 21 1997

Reference Number: Bio 97-096

Dear Madam:

This letter is in response to your correspondence dated April 19, 1997, requesting confirmation of the reference listed drug (RLD) for a generic copy of the over-the counter Ibuprofen Capsule, 200 mg. The Office of Generic Drugs has reviewed your request and the following comments are provided for your consideration:

> The reference listed drug for your proposed over the counter (OTC) Ibuprofen Capsule, 200 mg product should be McNeil's Motrin IB Gelcap (ANDA 73-019), as specified in the "Approved Drug Products with Therapeutic Equivalence Evaluations" or FDA's Orange Book.

The comments provided in this correspondence are based on the submitted information, current scientific knowledge, and the proposed issue(s) at hand. The Office may modify the bioequivalence testing requirements if needed.

If you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rockville MD 20857

#680

Rec'd 6/27/97

Perrigo Company
Attention: Ms. Virginia G. Lutke
117 Water Street
Allegan, Michigan 49010

JUN 23 1997

Reference Number: OGD 97-093

Dear Ms. Lutke:

This letter is in response to your April 19, 1997, correspondence requesting guidance on an acceptable reference listed drug (RLD) to perform a bioequivalence study in support of an abbreviated new drug application (ANDA) for Ibuprofen Capsules, 200 mg. The Office of Generic Drugs (OGD) has reviewed your request and provides the following comments.

Perrigo has stated the proposed product will consist of a clear coated white ibuprofen tablet (capsule shaped), which will be encapsulated in a hard shell gelatin capsule and banded in the middle. OGD agrees that this is a capsule dosage form and that a bioequivalence study should compare Perrigo's proposed product with the RLD. Perrigo has stated that there are two ANDA's (70-626 and 71-002) for Ibuprofen Capsules, 200 mg, listed in the discontinued section of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). In addition, OGD has noted that the 17th edition of the Orange Book lists the approval of NDA 20-402 (Provel, Sandoz) in the discontinued section. As noted in Perrigo's correspondence, the Agency published (Federal Register, Vol.61, No. 222, pg 58565-58566; 11/15/96) a determination that Ibuprofen Capsules, 200 mg (Midol; Bayer), was not withdrawn from sale for reasons of safety or effectiveness.

Perrigo's proposal to use a tablet dosage form (ANDA 73-019; Motrin IB Gelcap; McNeil) as the RLD in a bioequivalence study would be acceptable if no capsule dosage form is commercially available.

If you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

MEDEVA
PHARMACEUTICALS

Medeva Pharmaceuticals Mfg., Inc.
755 Jefferson Road
Post Office Box 1710
Rochester, New York 14603

Telephone: (716) 475-9000
Fax: (716) 272-3952

Federal Express

August 3, 1998

Dale Connor, M.D.
Director, Division of Bioequivalence, HFD-612
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 40-306
Methylphenidate Hydrochloride Extended-Release USP, 10 mg
General Correspondence:

Dear Dr. Connor:

At the request of Ms. Nancy Chamberlin and Ms. Lizzie Sanchez of your office, we are providing diskettes in ASCII format which contain pharmacokinetic parameters and plasma concentration data for the three bioequivalence studies included in the above referenced application.

These studies are:

- **Medeva Study # 93-023** A Single Dose, Fasting Bioequivalence Study, Comparing Methylphenidate ER 10 mg Tablets to Ritalin-SR® 20 mg Tablets
- **Medeva Study # 392-04** A Single Dose, Fed, Bioequivalence Study, Comparing Methylphenidate ER 10 mg Tablets to Ritalin-SR® 20 mg Tablets
- **Medeva Study # 392-06**
  A Multiple Dose, Bioequivalence Study, Comparing Methylphenidate ER 10 mg to Ritalin-SR® 20 mg Tablets

A print-out of the data found on the diskettes is also provided for reference purposes.

Should you have any questions regarding this communication, please contact the undersigned at (716) 274-5826.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Director, Regulatory Affairs

Copy Cover Letter: Kassandra Sherrod, Project Manager, OGD
Greg Davis, Regulatory Project Manager, OGD

3/2/99

Medeva

Medeva Pharmaceuticals Mfg., Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5826
Fax: (716) 272-3952

Regulatory Affairs

Certified 013/99

March 1, 1999

DR Label

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 40-306 Methylphenidate Hydrochloride Extended-Release Tablet USP, 10 mg
Minor Amendment to a Pending Application: Response to October 22, 1998 Facsimile
Addition of Medeva Rochester, N.Y. Facility as Packaging Site
Approval of Brand Name Equasym™ ER Tablet

Dear Sir or Madam:

Reference is made to our pending application for Methylphenidate Hydrochloride Extended-Release Tablet USP, 10 mg submitted April 10, 1998, and to the Agency facsimile of October 22, 1998 which provided comments on the application from the Division of Chemistry II, the Division of Labeling and Program Support and the Division of Bioequivalence.

This submission provides a complete response to the Agency's October 22, 1998 facsimile.

It also provides for an alternate finished product packaging site at the Medeva facility located at 755 Jefferson Road, Rochester, N.Y. This facility currently packages and performs stability testing for the marketed 20 mg extended-release strength of methylphenidate hydrochloride under the approved ANDA 89-601. The Rochester facility also manufactures, packages and performs stability testing for the 5 mg, 10 mg, and 20 mg immediate release methylphenidate hydrochloride tablets under the approved ANDA(s) 86-429, 85-799 and 86-428 respectively.

The container that will be used to transport the bulk tablets will be the same double, low density polyethylene bag that comes into direct contact with the tablets at the manufacturing site. To

offer protection during shipping, bags will be placed inside 5 gallon, high density polyethylene pails with lids having a tamper evident seal. Specifications for both are provided in Tab 1.

Additionally, Medeva intends to market this product with a brand name and therefore requests FDA approval of the proprietary name Equasym ™ ER Tablets. Consequently, the enclosed package circular and immediate container label have been revised not only to address those comments conveyed in the October 22, 1998 facsimile, but also to include the Equasym ™ ER Tablet name where appropriate. Following Agency approval, Medeva plans to distribute both the 10 mg extended-release strength which is the topic of this application, and the already approved and marketed 20 mg extended-release strength with this brand name. Therefore, the attached package circular includes both strengths in the How Supplied section. Medeva will also submit a labeling supplement to ANDA 89-601 for Methylphenidate Hydrochloride Extended-Release Tablets, 20 mg to provide for use of the brand name for that strength product.

For ease in review, comments from the **DIVISION OF CHEMISTRY II** are reproduced below in **bold** type, followed by the Medeva reply. (Please note that page 4 of this letter and Tab 5 of this amendment addresses comments in the October 22, 1998 facsimile from the **DIVISION OF LABELING SUPPORT** and the **DIVISION OF BIOEQUIVALENCE**.)

1. Please submit a certificate of analysis for the finished product, lot no. H561W01 for which you have submitted an executed batch record.

The certificate of analysis for this lot was provided in the original application on page 4075 within Volume 1.13 but is reproduced in this amendment for ease in review (Tab 2).

2. Your stability report sheet(s) should be revised to identify the test date(s) along with each designated test interval.

The stability data sheets have been revised accordingly. An updated stability report which now reports eighteen months data at 25°C/60%RH is provided (Tab 3).

3. Please commit to perform assay for production batches as a routine in-process test until you have accumulated sufficient data and a supplemental application for discontinuation is approved.

Medeva commits to the above.

4. Your total degradants/impurities limit of NMT % is too high. The data you have submitted show less that % in three months. Therefore, we recommend that the total

degradants/impurities limit be lowered. We also recommend that you submit three months of accelerated stability data comparing the innovator's product with your product.

At the November 5, 1998 teleconference between Medeva and the Reviewing Chemist, it was agreed that tightening the total degradants limit to NMT _ % would obviate the recommendation to generate and submit accelerated stability data on the innovator's product. Medeva has therefore tightened the specifications for total degradants, erythro isomer and ritalinic acid accordingly to NMT %, NMT % and NMT % respectively (Tab 4). Please note that in the case of erythro isomer and ritalinic acid, these limits are actually lower than the compendial limits allowed for the active pharmaceutical ingredient which are 1.0% and 0.6% respectively.

5. Drug Master File is currently deficient and the DMF holder has been advised of the deficiencies. A satisfactory resolution of the DMF deficiencies is required by the holder prior to the approval of the application.

A response to the DMF deficiencies was made on December 18, 1998 by Medeva Pharmaceuticals, California, with a courtesy copy of the response provided to Raymond Brown, the Chemistry Reviewer for this application.

6. It is observed that kg of product is used for bulk shipment. Please advise.

This is correct as this statement appears on the bulk packaging record provided on page 3668 of the original application. These tablets were placed into 3 separate bulk boxes as described in the labeling record provided on pages 3686 - 3689 of the application and shipped from the site of manufacture to the site of stability testing where they were entered into a bulk stability program to determine bulk tablet hold time. Stability data were provided in the stability report within Volume 13 of the original application and is provided again for reference purposes within the updated stability report described in item 2 above.

7. We acknowledge that the USP specification for content uniformity is 85.0 - 115.0%. However, for in-process we recommend a specification of %. Please revise accordingly and resubmit.

It was agreed in the October 29, 1998 telephone conversation with the Reviewing Chemist that Medeva would accept the tighter specification and that OGD would accept second level testing with an RSD of % for in-process testing. The product specification has been revised accordingly and is provided in Tab 4.

Specific comments from the **DIVISION OF LABELING AND PROGRAM SUPPORT** are addressed in Tab 5 of this amendment. A copy of the revised draft labeling and a side-by side annotated comparison of the proposed labeling with the labeling submitted April 10 & 24, 1998 is included. Four copies of the draft labeling are provided in the FDA archival copy of this submission.

As noted above, Medeva requests approval of the brand name Equasym ™ ER Tablets for use with both the 10 mg and 20 mg extended-release formulations of methylphenidate hydrochloride tablets and intends to use the attached circular with both products. For ease of review, changes made per the Division's facsimile of October 22, 1998 are highlighted in pink whereas changes made to incorporate the proprietary name are highlighted in yellow.

The **DIVISION OF BIOEQUIVALENCE** recommended specific dissolution testing for this product within the October 22, 1998 facsimile which were not consistent with the USP conditions, test intervals or specifications submitted in the application. Following an October 26, 1998 telephone conversation with the Division, the dissolution criteria per <724> as defined in the USP were subsequently accepted by the Division.

We look forward to an expeditious review and approval of this application including approval of the proposed brand name under this application as well as ANDA 89-601.

We also certify that a true copy of this amendment is being sent to the home offices of the manufacturing and testing Medeva site (Los Angeles District Office) and of the packaging and and testing Medeva site (Buffalo District Office.)

Should you have any comments or questions regarding this amendment, please contact the undersigned at (716) 274-5826 or Monroe I. Klein, Ph.D., Executive Vice President Regulatory Affairs at (610) 341-9280.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Director Regulatory Affairs

FDA FIELD COPIES: Los Angeles District Office, Buffalo District Office
DESK COPY LETTER: Kassandra Sherrod, Project Manager, OGD

Medeva

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5346
Fax: (716) 272-3952

Regulatory Affairs

Certified 078/99

NEW CORRESP
NC

July 19, 1999

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-6000
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 89-601
Methylphenidate Hydrochloride Extended-Release Tablets, USP (20 mg)

ANDA 40-306
Methylphenidate Hydrochloride Extended-Release Tablets, USP (10 mg)

Labeling Amendment

Dear Sir or Madam:

Reference is made to the applications referenced above, and to the following submissions:

ANDA 40-306, March 1, 1999, Minor amendment to pending application
ANDA 40-306, May 20, 1999, Labeling amendment with proposed brandnames
ANDA 40-306, June 16, 1999, Labeling amendment with proposed brandnames

ANDA 89-601, March 18, 1999, Labeling Supplement
ANDA 89-601, May 20,1999, Labeling amendment with proposed brandnames
ANDA 89-601, June 16, 1999, Labeling amendment with proposed brandnames

Reference is also made to a May 27, 1999 telephone communication between Mark Anderson, Project Manager, OGD, and Norma Cappetti, Director Regulatory Affairs, Medeva, in which

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 22 1999
OGD

7-26-99

Medeva was informed that the pending application for ANDA 40-306 was approvable with the exception of the labeling.

In addition, reference is made telephone communications on July 15 & 16, 1999 between James Morrison, CDER Ombudsman, and the undersigned, and on July 16, 1999 between Dr. Daniel Boring, Chairman, CDER Labeling & Nomenclature Committee (LNC), and the undersigned. During these conversations it was agreed that Medeva would submit three names for review by the LNC, and that these names would be reviewed prior to the LNC's scheduled July meeting.

Therefore, Medeva is submitting the following names for consideration:

Metadate™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Amilert™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Evanax™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Upon acceptance of a proposed brandname, Medeva will submit revised draft labeling to the above applications incorporating one of the acceptable product names.

If you have any questions regarding this supplement, please contact R. Andrew Morgan, R.Ph., Director, Regulatory Affairs at (716) 274-5821, or the undersigned at (716) 274-5346.

Sincerely,

Cheryl Rini

Cheryl A. Rini, R.N.
Senior Manager, Regulatory Affairs

cc: (Facsimile copy)

Dr. Daniel Boring, Chairman, CDER Labeling & Nomenclature Committee
Charles Hoppes, Team Leader, Label Review, Office of Generic Drugs
Koung Lee, Label Review, Office of Generic Drugs

Medeva

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5346
Fax: (716) 272-3952

Regulatory Affairs

Certified 061/99

June 16, 1999

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-6000
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 89-601
Methylphenidate Hydrochloride Extended-Release Tablets, USP (20 mg)

ANDA 40-306
Methylphenidate Hydrochloride Extended-Release Tablets, USP (10 mg)

Labeling Amendment

Dear Sir or Madam:

Reference is made to the applications referenced above, and to the following submissions:

ANDA 40-306, March 1, 1999, Minor amendment to pending application
ANDA 40-306, May 20, 1999, Labeling amendment with proposed brandnames

ANDA 89-601, March 18, 1999, Labeling Supplement
ANDA 89-601, May 20,1999, Labeling amendment with proposed brandnames

Reference is also made to a May 27, 1999 telephone communication between Mark Anderson, Project Manager, OGD, and Norma Cappetti, Director Regulatory Affairs, Medeva, in which Medeva was informed that the pending application for ANDA 40-306 was approvable with the exception of the labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 17 1999
OGD

In addition, reference is made to a June 10, 1999 facsimile communication from the Division in which Medeva was informed that our proposed proprietary names included in the above submissions were found to be unacceptable by the CDER Labeling and Nomenclature Committee.

Therefore, Medeva is submitting the following names for consideration:

Attensil™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Amilert™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Evanax™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Levex™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Metadate™ Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Metafin™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Metain™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Mirivar™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Modilex™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Sérelon™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Zephrene™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Medeva requests that the Division consider the above proposed names and requests that these names be forwarded as soon as possible for review at the June 22 meeting of CDER's Labeling and Nomenclature Committee. Upon acceptance, Medeva will submit revised draft labeling to the above applications incorporating one of the acceptable product names. Medeva intends to use the other acceptable names for other products in the near future.

If you have any questions regarding this supplement, please contact R. Andrew Morgan, R.Ph., Director, Regulatory Affairs at (716) 274-5821, or the undersigned at (716) 274-5346.

Sincerely,

Cheryl Rini

Cheryl A. Rini, R.N.
Senior Manager, Regulatory Affairs

cc: Charles Hoppes, Team Leader, Label Review
Office of Generic Drugs

Medeva

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5346
Fax: (716) 272-3952

Regulatory Affairs

Certified 052/99

NEW CORRESP
NC

May 20, 1999

G Hoppes
See Review Signed
6/10/99

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-6000
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 89-601
Methylphenidate Hydrochloride Extended-Release Tablets, USP (20 mg)

ANDA 40-306
Methylphenidate Hydrochloride Extended-Release Tablets, USP (10 mg)

Labeling Amendment

Dear Sir or Madam:

Reference is made to the applications referenced above, and to the following submissions:

ANDA 40-306, March 1, 1999, Minor Amendment to Pending Application
ANDA 89-601, March 18, 1999, Labeling Supplement

Included in these submissions was draft labeling proposing the brandname of "Equasym™ ER" for these products. Reference is also made to conversations with Charles Hoppes, Team Leader, Label Review, Office of Generic Drugs (OGD), and Cheryl Rini, Senior Manager, Regulatory Affairs, Medeva Pharmaceuticals, on April 5 and April 29, 1999, and between Koung Lee, Label Reviewer, OGD, and Cheryl Rini on May 11 and May 13, 1999. During these conversations Medeva was informed that our proposed brandname of "Equasym™ ER" had been reviewed by the FDA's Labeling and Nomenclature Committee and was found to be unacceptable.

Therefore, Medeva is submitting the following names for consideration. We have listed these in order of preference:

Zyteran™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Ecuvin™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Equazin™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Equazym™ ER Tablets
(methylphenidate hydrochloride extended-release tablets, USP)

Medeva requests that the Division accept/approve more than one of the above product names. Upon acceptance, Medeva will submit revised draft labeling to the above applications incorporating one of the acceptable product names. Medeva intends to use the other acceptable product names in the near future.

If you have any questions regarding this supplement, please contact the Cheryl Rini, Senior Manager, Regulatory Affairs at (716) 274-5346, or the undersigned at (716) 274-5821.

Sincerely,

Mary Evelyn Towne for

R. Andrew Morgan, R.Ph.
Director, Regulatory Affairs

cc: Charles Hoppes, Team Leader, Label Review
Office of Generic Drugs

Medeva

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5346
Fax: (716) 272-3952

Regulatory Affairs

Certified 095/99

NDA ORIG AMENDMENT
N/AF

August 13, 1999

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 40-306
Methylphenidate Hydrochloride Extended-Release Tablets, USP (10 mg)

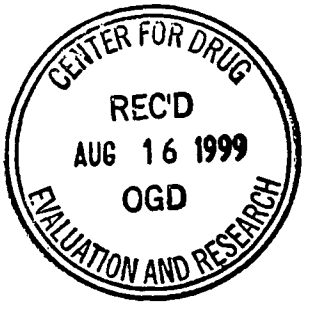
ANDA 89-601
Methylphenidate Hydrochloride Extended-Release Tablets, USP (20 mg)

Labeling Amendment – Final Printed Labeling

Dear Sir or Madam:

Reference is made to the applications referenced above, and to the following communications:

ANDA 40-306:
April 10, 1998, submission of ANDA
October 22, 1998, Division's facsimile with comments on application
March 1, 1999, Minor amendment to pending application
May 20, 1999, Labeling amendment (revised labeling including brandname for extended-release methylphenidate tablets)
June 10, 1999, Division's facsimile with comments regarding labeling
June 16, 1999, Labeling amendment with proposed brandnames
July 19, 1999, Labeling amendment with proposed brandnames



ANDA 89-601:
March 18, 1999, Labeling Supplement (revised labeling including brandname for extended-release methylphenidate tablets)
May 20,1999, Labeling amendment with proposed brandnames
June 16, 1999, Labeling amendment with proposed brandnames
July 19, 1999, Labeling amendment with proposed brandnames

In addition, reference is made to the following telephone communications:

May 27, 1999 – Between Mark Anderson, Project Manager, OGD, and the undersigned, in which Medeva was informed that the pending application for ANDA 40-306 was approvable with the exception of labeling.

July 26, 1999 – Between Koung Lee, Label Review, OGD, and Cheryl Rini, Senior Manager, Medeva Regulatory Affairs, in which Medeva was informed that our proposed brandname of "Metadate™ ER Tablets," submitted for consideration on July 19, 1999, was found to be acceptable by the Division and CDER's Labeling and Nomenclature Committee.

The purpose of this communication is to submit final printed labeling to the above applications which incorporates the brandname "Metadate™ ER Tablets" and contains revisions to the labeling as requested in the Division's facsimile communication of June 10, 1999 for ANDA 40-306. For ease in review, comments from the Division of Labeling and Program Support are reproduced below in bold type, followed by Medeva's reply.

Comments from Division's June 10, 1999 facsimile communication:

1. General – Your proposed proprietary names, Equasym ER, Zyteran ER, Ecuvin, ER, Equazin ER, and Equazym ER Tablets, were found to be unacceptable by the CDER Labeling and Nomenclature Committee because they look like and/or sound like names of other products that are currently on the market.

Medeva was informed on July 26, 1999 that our proposed brandname of "Metadate™ ER Tablets" (submitted for consideration on July 19, 1999) was found to be acceptable by CDER's Labeling and Nomenclature Committee. Our labeling has been revised accordingly; final printed labeling is enclosed.

2. Container – 100s

a. Your container labels are difficult to read. Revise your container label to increase readability.

Draft immediate container label samples included with previous submissions (3/1/99 for ANDA 40-306, and 3/18/99 for ANDA 89-601) were actually copies from an office color printer, therefore resolution was not as clear as with final printed labeling. Final printed labels are included with this submission in which the print is clear and readable. We have also changed the color of the label from red with white print to dark blue with white print. This has also greatly improved the clarity and readability of the print.

b. Relocate "Rx only" to appear on the principal display panel.

This was done as requested.

3. Insert

a. Description – The second sentence of the first paragraph should be revised to read "... is available as extended-release tablets of 10 and 20 mg for ..."

This sentence was revised as requested.

b. Precautions (Carcinogenesis/Mutagenesis) – Separate the last three sentences from the first paragraph to form a new paragraph.

This was done as requested.

Medeva has revised the labeling as requested, and is submitted final printed labeling to both ANDA 40-306 and ANDA 89-601. Twelve (12) copies are included in the archival copies of this submission and one copy is included with each review copy. To facilitate review, and in accordance with 21 CFR §314.94(a)(8)(iv), we have provided a side-by-side comparison of our final printed labeling with the last submitted labeling. All differences are annotated and explained.

Please note that Medeva requests that the OGD approve the labeling for both of these ANDAs as we would like to market both the 10 mg *and* 20 mg methylphenidate HCl extended-release tablets as "Metadate™ ER Tablets" upon approval of the enclosed labeling (immediate container labels and package circular).

If you have any questions regarding this supplement, please contact Cheryl Rini, Senior Manager, Regulatory Affairs at (716) 274-5346, or the undersigned at (716) 274-5826.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Director, Regulatory Affairs

cc: Mark Anderson, Project Manager, OGD (cover letter only)
Robert L. West, M.S., R.Ph., Director, Division of Labeling and Program Support, OGD
Charles Hoppes, Team Leader, Division of Labeling and Program Support, OGD
Koung Lee, Label Review, Division of Labeling and Program Support, OGD

Medeva

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5716
Fax: (716) 272-3952

Regulatory Affairs

Certified 120/99

ORIG AMENDMENT

September 23, 1999

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 40-306
Metadate™ ER Tablets, 10 mg
(methylphenidate hydrochloride extended-release tablets, USP)

Amendment to a Pending Application
Revised Sentence to March 1, 1999 Amendment

Dear Sir or Madam:

Reference is made to our pending application for Metadate™ ER Tablets, 10 mg (methylphenidate hydrochloride extended-release tablets, USP), submitted April 10, 1998. Reference is also made to a telephone conversation between the undersigned and Dr. Raymond Brown, Chemistry Reviewer, OGD on September 23, 1999. In that conversation, Dr. Brown requested confirmation that there was an error on page 3 of the cover letter of the March 1, 1999 amendment and, if confirmed, that a corrected sentence be provided by facsimile as well as by mail.

This amendment provides the following corrected sentence:

- "Please note that in the case of erythro isomer, this limit is actually lower than the compendial limit allowed for the active pharmaceutical ingredient which is 1.0%."

The sentence being replaced was worded:

- "Please note that in the case of erythro isomer and ritalinic acid, these limits are actually lower than the compendial limits allowed for the active pharmaceutical ingredient which are 1.0% and 0.6% respectively."

We also certify that a true copy of this amendment is being sent to the FDA home offices of the manufacturing and testing Medeva site (Los Angeles District Office) and of the packaging and testing Medeva site (Buffalo District Office.)

If you have any questions regarding this submission, please contact the undersigned at (716) 274-5826.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Director, Regulatory Affairs

FDA FIELD COPIES: Los Angeles District Office, Buffalo District Office
DESK COPY LETTER: Kassandra Sherrod, Project Manager, OGD

Medeva

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5716
Fax: (716) 272-3952

Regulatory Affairs

Certified 112/99

September 7, 1999

ANDA ORIG AMENDMENT
N/AM

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 40-306
Metadate™ ER Tablets, 10 mg
(methylphenidate hydrochloride extended-release tablets, USP)

Amendment to a Pending Application
Revised Post-Approval Stability Protocol

Dear Sir or Madam:

Reference is made to our pending application for Metadate™ ER Tablets, 10 mg (methylphenidate hydrochloride extended-release tablets, USP), submitted April 10, 1998. Reference is also made to a telephone conversation between the undersigned and Dr. Raymond Brown, Chemistry Reviewer, OGD on August 31, 1999. In that conversation, Dr. Brown requested that our commitment to place the first three commercial production batches into the post-approval stability program, as noted on page 3910 of the original ANDA, be directly incorporated into the Post-Approval Stability Protocol.

This amendment provides a revised Post-Approval Stability Protocol in response to Dr. Brown's request. Our commitment to place the first three commercial production batches into the post-approval stability program, in addition to annual batches thereafter, has been incorporated under the "Number of Lots" section.

In addition, the following changes have been made in the protocol:

Under "Objective," it is now noted that product may be packaged at either the California or Rochester, NY Medeva site, in accordance with our amendment of March 1, 1999.

Under "Storage Conditions and Test Intervals: Accelerated Lots," for the 30°C/60% RH storage condition, the 3 month interval is now asterisked to note that testing at that condition will only be done if significant change is observed from the 40°C/75% RH testing. An asterisk at the 3 month interval was inadvertently left off the initial protocol and is consistent with the ICH stability guideline.

Under "Control Tests," the specifications for total degradants, α-phenyl-2-piperidineacetic acid hydrochloride (ritalinic acid), and erythro isomer have been updated in accordance with our amendment of March 1, 1999.

The revised Post-Approval Stability Protocol, Protocol #561990004, is provided under **Tab 1.**

We also certify that a true copy of this amendment is being sent to the FDA home offices of the manufacturing and testing Medeva site (Los Angeles District Office) and of the packaging and testing Medeva site (Buffalo District Office.)

If you have any questions regarding this submission, please contact Norma J. Cappetti, Director, Regulatory Affairs at (716) 274-5826, or the undersigned at (716) 274-5716.

Sincerely,

Donald J. Handley
Manager, Regulatory Affairs

FDA FIELD COPIES: Los Angeles District Office, Buffalo District Office
DESK COPY-LETTER: Kassandra Sherrod, Project Manager, OGD

Medeva

NEW CORRESP

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5346
Fax: (716) 272-3952

Regulatory Affairs

Certified 106/99

August 26, 1999

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 40-306
Metadate™ ER Tablets, 10 mg
(methylphenidate hydrochloride extended-release tablets, USP)

ANDA 89-601
Metadate™ ER Tablets, 20 mg
(methylphenidate hydrochloride extended-release tablets, USP)

General Correspondence

Dear Sir or Madam:

Reference is made to the applications referenced above and to the following communications:

ANDA 40-306:
April 10, 1998, submission of ANDA
October 22, 1998, Division's facsimile with comments on application
March 1, 1999, Minor amendment to pending application
May 20, 1999, Labeling amendment (revised labeling including brandname for extended-release methylphenidate tablets)
June 10, 1999, Division's facsimile with comments regarding labeling
June 16, 1999, Labeling amendment with proposed brandnames
July 19, 1999, Labeling amendment with proposed brandnames
August 13, 1999, Labeling amendment with final printed labeling

ANDA 89-601:
March 18, 1999, Labeling Supplement (revised labeling including brandname for extended-release methylphenidate tablets)
May 20,1999, Labeling amendment with proposed brandnames
June 16, 1999, Labeling amendment with proposed brandnames
July 19, 1999, Labeling amendment with proposed brandnames
August 13, 1999, Labeling amendment with final printed labeling

In addition, reference is made to a telephone communication on August 26, 1999 between Koung Lee, Label Review, Division of Labeling and Program Support, Office of Generic Drugs (OGD), and the undersigned. During the aforementioned conversation Mr. Lee stated that the OGD was requesting that Medeva increase the prominence of the appearance of the established name (methylphenidate hydrochloride) in the product labeling submitted as the last requirement for ANDA approval. Mr. Lee further stated that to facilitate product approval, a post-approval commitment from Medeva regarding this would be acceptable to OGD.

This is to confirm that Medeva commits via this correspondence to OGD's request to revise the labeling as a post approval commitment. Specifically, upon approval of ANDA 40-306 and the labeling supplement under ANDA 89-601, Medeva will revise the product labeling to increase the prominence of "methylphenidate hydrochloride" in the established name at the next printing due by October 31, 1999.

If you have any questions regarding this supplement, please contact either R. Andrew Morgan, R.Ph., Director, Regulatory Affairs at (716) 274-5821, or the undersigned (716) 274-5346.

Sincerely,

Cheryl Rini

Cheryl Rini, R.N.
Senior Manager, Regulatory Affairs

cc: Facsimile Copies:
Mark Anderson, Project Manager, OGD
Robert L.West, M.S., R.Ph., Director, Division of Labeling and Program Support
Charles Hoppes, Team Leader, Division of Labeling and Program Support, OGD
Koung Lee, Label Review, Division of Labeling and Program Support, OGD

Medeva

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Regulatory Affairs

Certified 127/99

October 7, 1999

NDA ORIG AMENDMENT
N/A

Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 40-306
Metadate™ ER Tablets, 10 mg
(methylphenidate hydrochloride extended-release tablets, USP)

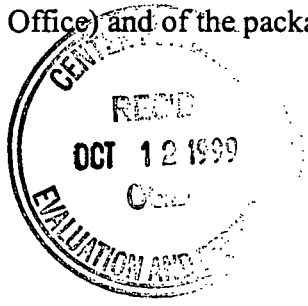
Amendment to a Pending Application
Commitment Regarding Stability Tables

Dear Sir or Madam:

Reference is made to our pending application for Metadate™ ER Tablets, 10 mg (methylphenidate hydrochloride extended-release tablets, USP), submitted April 10, 1998. Reference is also made to a telephone conversation between the undersigned and Ms. Kassandra Sherrod, Product Manager, OGD, on October 7, 1999. In that conversation, Ms. Sherrod requested that Medeva provide a written commitment that future stability tables will specify the number of tablets per bottle.

Medeva commits to this request. The words "Package Size: 100's" will appear on future stability tables for each lot. This communication is provided by facsimile as well as by mail.

We also certify that a true copy of this amendment is being sent to the FDA home offices of the manufacturing and testing Medeva site (Los Angeles District Office) and of the packaging and testing Medeva site (Buffalo District Office.)



If you have any questions regarding this submission, please contact the undersigned at (716) 274-5826.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Director, Regulatory Affairs

FDA FIELD COPIES: Los Angeles District Office, Buffalo District Office
DESK COPY LETTER: Kassandra Sherrod, Project Manager, OGD

MEDEVA
PHARMACEUTICALS

Medeva Pharmaceuticals Mfg., Inc.
755 Jefferson Road
Post Office Box 1710
Rochester, New York 14603

Telephone: (716) 475-9000
Fax: (716) 272-3952

505(j)(2)(A) OK
5/1/98
Gregory S. Davis

Certified 031/98

April 10, 1998

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

RE: Original Abbreviated New Drug Application (ANDA)
Methylphenidate Hydrochloride Extended-Release Tablet USP, 10 mg

Dear Sir or Madam:

In accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act and pursuant to 21 CFR § 314.94, Medeva Pharmaceuticals is submitting, in duplicate, an original ANDA for the above referenced product. This application consists of 13 volumes.

We also certify that a "true" copy of the technical sections of the ANDA (without Section VI Bioavailability/Bioequivalence), is being sent to **two** FDA District Offices. The Los Angeles Office is receiving a copy since the Medeva facility in California (MD Pharmaceutical Inc.) is the manufacturer and primary test site for release of the finished product. The Buffalo District Office is receiving a copy since the Medeva facility in New York State is responsible for all stability testing of the finished product. This facility will also be functioning as an alternate test site for release of the finished product.

Please direct any written communications regarding this ANDA to me or to Robert B. Parker, Ph.D., Senior Director, Regulatory Affairs at the above address or fax number. My direct line telephone number is (716) 274-5826.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Senior Manager, Regulatory Affairs

RECEIVED
APR 13 1998
GENERIC DRUGS

FDA Field Copies: Buffalo District Office, Los Angeles District Office

TO

Medeva Pharmaceuticals CA, Inc.
3130 South Harbor Boulevard
Suite 320
Santa Ana, CA 92704
Telephone: (714) 556-3941
Fax: (714) 556-0315

October 20, 1998

Ms. Elaine C. Messa
District Director
U.S. Food and Drug Administration
19900 MacArthur Blvd., Ste. 300
Irvine, CA 92714-2445

RE: FORM FDA 483 ISSUED 10/9/98 TO GAYLE M. DEFLIN

Dear Ms. Messa:

This letter is in response to the Form FDA 483 (483) issued to Medeva Pharmaceuticals CA, Inc. at 3501 W. Garry Avenue, Santa Ana, CA 92704 on October 9, 1998.

We have reviewed each of the 483 observations in depth and have enclosed our response. Each observation is typed in bold, exactly as it appears on the 483, and is followed by our corresponding response.

Medeva Pharmaceuticals CA, Inc. remains committed to aggressively resolving these issues and assuring full compliance with applicable regulations. Upon completion of our corrective actions we will contact the District Office. We anticipate completion of all activities to be during December, 1998. At that time, we would like to discuss approval of Methylphenidate Hydrochloride Extended-Release 10 mg, USP, based upon successful completion of items noted by the Agency.

If you, or your staff, have questions or need additional information, please feel free to contact us at (714) 556-3941. Medeva Pharmaceuticals CA, Inc. is always willing to meet and further discuss any comments or suggestions you may have.

Sincerely,

Gayle M. Deflin
President

enc.
cc: Thomas Sawyer, Director, Compliance Branch - FDA
Richmond Yip, Investigator - FDA

1. **During a review of process validation records for Methylphenidate HCl tablets 20 mg. ER (Extended Release) and 10 mg. IR (Immediate Release), the following were noted:**

   a.) **The firm obtained, consistently, out-of-specification test results for the top right of the blender for two of the three lots tested, during the revalidation of the manufacturing process for 20 mg. ER tablets (report dated 10-4-98). Three samples from the top right of the blender for lot P562D05 tested 119.4, 123.8, and 116.5%; three samples from the top right of the for lot P562D07 tested %. (The firm's specification is %).**

The Methylphenidate Hydrochloride Extended Release Tablets 20 mg, USP process was successfully validated in 1994. Revalidation of this process was performed in 1998 in order to enhance the original validation. Both process validations included blend samples from the blender in addition to normal in-process blend samples taken from the drums, which contain material directly discharged from the blender. No out-of-specification (OOS) values were obtained in the 1994 process validation (4.5 g samples). During the 1998 validation, the blender yielded analytical results that were OOS for the top right location within the blender (420 mg samples). All values obtained from the drums for in-process were well within specification, ranging from % for all positions sampled for all three validation lots. All content uniformity results were also well within specification, ranging from % for all three validation lots.

Medeva's experience with performing sampling indicates that several factors could potentially contribute to the generation of apparent OOS results. The size of the sample, sampling devices used, sampling technique, and environmental conditions, could create localized demixing or desegregation of the active ingredient. Individually, or collectively, these factors may have produced the OOS test results reported. However, additional revalidation work has been planned, as noted in our validation summary. We will endeavor to identify all possible causes contributing to the OOS results from the pan blender samples. The revalidation exercise will provide us with additional information regarding the impact of the above factors and confirm actual performance of the blender in achieving a uniform blend.

   b.) **The firm obtained an out-of-specification test result for one of the three validation lots tested, Batch P530C02, during the revalidation of the manufacturing process for the 10 mg. IR tablets. Test results for the center left sampling point of the assayed %. Although the "Suspect or Out-of-Specifications Result Report Form" is missing, the firm concluded that a 250 ml volumetric flask must have been used in place of the specified 200 ml volumetric flask. In its "Process Validation Summary Report-10 mg. IR Tablets" (Protocol No. VP 98-530.6), effective date 10-4-98, the firm reported both % and % for that sampling site % is the original test result; % would be the result if the 250 ml. Volumetric flask had been used. The firm did not use either value in its calculation of the % RSD, even though it had no conclusive evidence that the result of % was in error. If that value had been included, the % RSD would be out-of-specification) rather than the reported % (in-specification).**

It is correct that the out-of-specification (OOS) test result was not used in the calculation of the RSD; however, the value was included in the validation report and an explanation for its exclusion was provided. The OOS result was investigated and its evaluation indicated an apparent laboratory error. We agree with the investigators that the OOS investigation required additional documentation, and have introduced a new investigation form which was presented to the FDA inspectors. In addition, this form is now distributed and tracked by Medeva's Quality Assurance unit which will allow for adequate control of these investigation documents.

In our opinion, the analytical results for the three validation batches (blender, drums, and content uniformity) strongly support a fully validated process. The evidence substantiates that this result is OOS due to determinant laboratory error. The data generated during the revalidation of the 10 mg IR tablet demonstrates that the process is acceptable. In addition, we are enhancing our analytical resources, training, and program oversight to reduce the incidences associated with laboratory error. We are committed to closely monitor and critically evaluate any suspect results, and their impact on manufacturing processes.

2. **The firm has not fully investigated out-of-specification test results, obtained on 6-16-98, for the analysis of the blend from one of the drums of lot P562H07, Methylphenidate HCl tablets, 20 mg. ER. One of the test points at the top of the drum assayed %. According to the Non Compliance Investigation Record for that lot, results of the investigation into the high results are not due until 10-16-98.**

The issues associated with the OOS blend result noted for lot P562H07 were still under investigation during the FDA inspection. A protocol outlining additional sampling to be performed to investigate lot P562H07 was issued during the inspection and provided to the FDA investigators. Medeva Quality Assurance is currently executing this protocol and evaluating probable causes for this OOS result. Our documented Non-Conformance Investigation assigned a completion date for the examination of this issue of October 16, 1998. We expect to be completed with all required actions including the additional testing per the protocol by October 23, 1998. Medeva commits to increasing the scope and timeliness of all investigations.

3. **The firm lacks adequate control over the documentation of the investigation of suspect or out-of-specification test results. For example:**

   a. **For lot P530C02, one of the process validation lots for the 10 mg. IR Methylphenidate HCl tablets, the firm could not find QCTR 98-43, the report which described the investigation into the % test result for the assay for the middle of the blender.**
   b. **For lot M562E08, 20 mg. ER Methylphenidate HCl tablets, there exist two "Suspect or Out-of-Specification Result Report" forms, each of which appears to be original.**

Prior to the FDA inspection of 10/5-9/98, a Medeva audit team performed an extensive regulatory review of Medeva Pharmaceutical CA, Inc.'s OOS investigations program. The audit documented that improvements were needed in a number of key areas including documentation and record keeping. Corrective actions such as formal training, revision of the OOS standard operating procedure (SOP), the use of controlled forms and closer program oversight have been initiated to address the issues identified internally and by FDA. During the FDA inspection, a corrective action plan was presented to the investigators. These actions will significantly improve the quality of our OOS investigations, and therefore heighten our level of cGMP compliance.

4. **The firm's sampling and testing procedure for their active pharmaceutical ingredient, Methylphenidate HCl, does not reflect the quality of the finished product produced in that, SOP QA-004, Inspection, Sampling of Raw Materials and Packaging, dated 2/23/98, requires samples taken from each drum of Methylphenidate HCl, to be composited for sampling. For example, particle size test results for drum No. 4, API Methylphenidate HCl, batch M810R05, were % above 125µ. The specification is NMT % greater than or equal to 125µ. Results for drum No. 4 were averaged with the particle size test results for the other 3 drums of this lot, yielding an average of % greater than or equal to 125µ, which meets the specification. Each individual drum may be used in the manufacture of 3 to 6.25 batches of Methylphenidate HCl finished product.**

Methylphenidate HCl, USP is dried in a fluid bed dryer in four separate parts. Each part is unloaded into separate drums. For batch release, each drum is sampled from the top, middle and bottom using a sampling thief and these samples are composited in a single container. As described in SOP QA-004, rev. 4, the results from the composite sample are used for release. Batch M810R05 was released using the results from the composite sample as per SOP QA-004. For the validation exercise associated with batch M810R05, an additional set of samples were collected from each drum, and individually analyzed.

We concur with the investigator that the analytical results from drum number four should have been further investigated and documented. SOP QA-004 will be revised to require sampling and testing of each drum of Methylphenidate HCl for particle size and LOD testing. We are aware of issues with the accurate and reproducible sampling of this active pharmaceutical ingredient for particle size testing. Prior to initiating individual drum sampling, we will need to validate our sampling, compositing, and ruffling (preparation of composite sample for particle size testing) techniques. Upon completion of this work, we will notify the agency and institute individual drum sampling. We expect this work to be completed by December, 1998.