CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40306

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA 40-306 - **DRUG PRODUCT:** Methylphenidate Hydrochloride Extended-Release USP

FIRM: Medeva Pharmaceuticals, Inc. **DOSAGE FORM:** Tablet

STRENGTHS: 10 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable -
See **ESTABLISHMENT EVALUATION REPORT** dated 12/15/98.

BIO INFORMATION: Acceptable -
See bio review, dated 12/7/98.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

STABILITY: Satisfactory -
Accelerated (40°C/75% RH) stability data are provided for batch no. H561W01, tested initially, 1, 2 and 3 month test intervals in the upright position. Controlled room temperature (25°C/60%RH) stability data are also provided, tested at 3, 6, 9 and 12 month test intervals. An expiration-dating period of 24 months has been granted.

LABELING: Satisfactory -
See Review of Professional Labeling dated 8/25/99.

STERILIZATION VALIDATION: N/A -

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory -
Bio batch lot no. H561W01 actual yield ( )tablets. Bulk substance manufacturer Medeva Pharmaceuticals CA, Inc., lot no. H810T01 used. DMF ( ) found **ADEQUATE**, dated 4/99.

SIZE OF STABILITY BATCHES - Satisfactory -
Executed Batch Manufacturing Documents are provided for lot no. H561W01, which consist of ( ) tablets. The batch was manufactured using production equipment under production conditions.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Yes!

The proposed master production batch size is ( )tablets.

RECOMMENDATION:

APPROVE

/S/

Raymond Brown

9/29/99
Date

/S/ 10/12/99

cc: HFD-645/RBrown/9/29/99
HFD-645/BArnwine/9/29/99

/S/ 10/4/99

F/T by pah/9/29/99
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1. CHEMISTRY REVIEW NO. 1

2. ANDA 40-306

3. NAME AND ADDRESS OF APPLICANT
Medeva Pharmaceuticals Manufacturing Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710

4. LEGAL BASIS FOR SUBMISSION
The legal basis for this ANDA for Methylphenidate Hydrochloride Tablets (20 mg) is **RITALIN®-SR** (NDA 18-029) manufactured by Ciba-Geigy (Novartis). Copies of the relevant pages of the 17th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations are provided.

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Methylphenidate Hydrochloride Extended-release Tablets

7. PROPRIETARY NAME
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR: Original ANDA

9. AMENDMENTS AND OTHER DATES:

Firm		FDA	
Orig. submission	4/10/98	CSO review	4/30/98
New correspondence	4/24/98	Acknowledgment letter	5/5/98
		Methods validation	7/7/98

This review covers submissions dated 4/10 and 4/24/98.

10. PHARMACOLOGICAL CATEGORY
Attention Deficit Disorders, Narcolepsy

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
DMF #

13. DOSAGE FORM

Tablet (Oral)

14. POTENCY

10 mg

15. CHEMICAL NAME AND STRUCTURE

Methyl α-phenyl-2-piperidineacetate hydrochloride.

$C_{14}H_{19}NO_2.HCl$ Molecular weight: 269.77

CAS Registry Number: 298-59-9

16. RECORDS AND REPORTS N/A

17. COMMENTS

a. Application contains MINOR deficiencies
b. Labeling review pending
c. Bio review completed.
d. Drug substance and drug product are compendial items
e. DMF under found inadequate
f. Establishment Evaluation Request submitted, dated 4/13/98.

18. CONCLUSIONS AND RECOMMENDATIONS

NOT APPROVABLE

19. REVIEWER: Raymond Brown

DATE COMPLETED: September 22, 1998

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Chem Review #1

38. Chemistry comments to be Provided to the Applicant

ANDA: 40-306

APPLICANT: Medeva Pharmaeuticals Manufacturing, Inc.

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

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

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

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

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.

4. Your total degradants/impurities limit of NMT % is too high. The data you have submitted show less than % 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.

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

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

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.

Sincerely yours,

/S/ 10/21/98

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO. **2**

2. ANDA **40-306**

3. NAME AND ADDRESS OF APPLICANT
Medeva Pharmaceuticals
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710

4. LEGAL BASIS FOR SUBMISSION
The legal basis for this ANDA for Methylphenidate Hydrochloride Tablets (20 mg) is **RITALIN®-SR** (NDA 18-029) manufactured by Ciba-Geigy (Novartis). Copies of the relevant pages of the 17th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations are provided.

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Methylphenidate Hydrochloride Extended-release Tablet USP

7. PROPRIETARY NAME
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR: Original ANDA

9. AMENDMENTS AND OTHER DATES:

Firm		**FDA**	
Orig. submission	4/10/98	CSO review	4/30/98
New correspondence	4/24/98	Acknowledgment letter	5/5/98
		Methods validation	7/7/98
New correspondence	8/3/98	Bio review	9/10/98
		Labeling	10/15/98
		Deficiency FAX	10/22/98
Amendment	3/1/99		
Amendment (labeling)	8/13/99		
Amendment (labeling)	8/26/99		
Amendment (phone)	9/23/99		
New correspondence	10/7/99		

This review covers submissions dated 3/1, 9/23 and 10/7/99.

10. PHARMACOLOGICAL CATEGORY
Attention Deficit Disorders, Narcolepsy.

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)
DMF #

13. DOSAGE FORM
Tablet (Oral)

14. POTENCY
10 mg

15. CHEMICAL NAME AND STRUCTURE
Methyl α-phenyl-2-piperidineacetate hydrochloride.

$C_{14}H_{19}NO_2.HCl$ Molecular weight: 269.77

CAS Registry Number: 298-59-9

16. RECORDS AND REPORTS N/A

17. COMMENTS
a. Application is **SATISFACTORY** for approval.
b. Labeling review found **ADEQUATE.**
c. Bio review found **ADEQUATE.**
d. Drug substance and drug product are compendial.
e. DMF found **ADEQUATE**, dated 4/99
f. Establishment Evaluation Report found **ACCEPTABLE**, dated 4/12/99.

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVE

19. REVIEWER: Raymond Brown
DATE COMPLETED: October 12, 1999

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Chem Review #2

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 40306/000**
Priority:
Org Code: **600**
Stamp: **13-APR-1998** Regulatory Due:
Action Goal:
District Goal: **13-JUN-1999**
Applicant: **MEDEVA PHARMS**
755 JEFFERSON RD
ROCHESTER, NY 146031710
Brand Name:
Established Name: **METHYLPHENIDATE HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **10MG**

FDA Contacts: **K. SHERROD (HFD-617) 301-827-5849 , Project Manager**
B. ARNWINE (HFD-645) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 15-DEC-1998 by R. WOODS (HFD-324) 301-827-0062

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **15-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **FIRM RESPONSE TO DEFIC. ADEQ**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **15-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **FIRM RESPONSE TO DEFIC. ADEQ**

Establishment: **1314625**
MEDEVA PHARMACEUTICALS MAN
755 JEFFERSON RD
ROCHESTER, NY 146031710

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **06-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

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for May 05, 1998

Application: **ANDA 40306/000**
Stamp: **13-APR-1998** Regulatory Due:
Applicant: **MEDEVA PHARMS**
755 JEFFERSON RD
ROCHESTER, NY 146031710

Priority:
Org Code: **600**
Action Goal:
District Goal: **13-JUN-1999**
Brand Name:
Established Name: **METHYLPHENIDATE HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **10MG**

FDA Contacts: **K. SHERROD** **(HFD-617)** **301-827-5849 , Project Manager**
B. ARNWINE **(HFD-645)** **301-827-5849 , Team Leader**

Overall Recommendation:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **05-MAY-1998**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **05-MAY-1998**

Establishment: **1314625**
MEDEVA PHARMACEUTICALS MAN
755 JEFFERSON RD
ROCHESTER, NY 146031710

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC**
Milestone Date: **05-MAY-1998**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

dl 10/20/99 request

ion: **ANDA 40306/000**
13-APR-1998 Regulatory Due:
nt: **MEDEVA PHARMS**
755 JEFFERSON RD
ROCHESTER, NY 146031710

Priority:
Action Goal:
Brand Name:
Established Name: **METHYLPHENIDATE HYDROCHLORIDE**
Generic Name:
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **10MG**

Org Code: **600**
District Goal: **13-JUN-1999**

Contacts: **K. SHERROD (HFD-640) 301-827-5849 , Project Manager**
B. ARNWINE (HFD-645) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 15-DEC-1998 by R. WOODS (HFD-324) 301-827-0062

Establishment:

DMF No:
AADA No:

[redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **15-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **FIRM RESPONSE TO DEFIC. ADEQ**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE MANUFACTURER

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **15-DEC-1998**
Decision: **ACCEPTABLE**
Reason: **FIRM RESPONSE TO DEFIC. ADEQ**

Establishment: **1314625**
MEDEVA PHARMACEUTICALS MA
755 JEFFERSON RD
ROCHESTER, NY 146031710

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **06-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**