

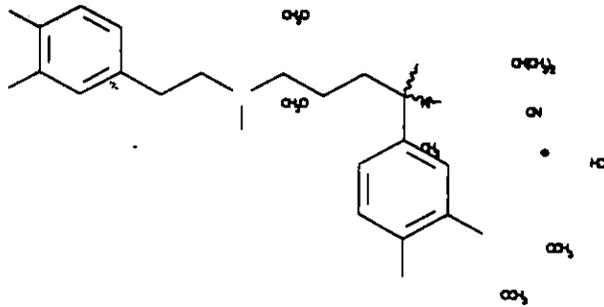
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-072

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.
4
2. ANDA #
75-072
3. NAME AND ADDRESS OF APPLICANT
Duramed Pharmaceuticals, Inc.
Cincinnati, OH
4. LEGAL BASIS FOR SUBMISSION
Section 505(j)
5. SUPPLEMENT(s)
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Verapamil HCl ER Tablets, USP
8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A
9. AMENDMENTS AND OTHER DATES:
- | <u>Duramed</u> | <u>FDA</u> |
|-----------------------------------|---|
| 2/10/97 (Original Filing) | 3/31/97 (Refuse to File) |
| 4/4/97 (Dissolution data) | 4/7/97 (Acknowledgement) |
| 4/10/97 (BIO) | 5/8/97 (Refuse to File Correction) |
| 6/3/97 per MIS | |
| 6/13/97 (BIO) | 8/20/97 NA FAX |
| | 8/18/97 BIO NA Letter |
| 10/24/97 | |
| 11/24/97 | 5/13/98 NA FAX |
| 12/10/97 (BIO) | 4/7/98 BIO NA FAX |
| 12/17/97 (BIO) | |
| 6/19/98 | 4/6/99 NA FAX |
| 6/25/98 (BIO) | 10/26/98 BIO NA FAX |
| 1/13/99 (BIO) | 4/6/99 BIO (Part of 4/6/99, Chem. NA FAX) |
| 4/12/99 (Subject of this review.) | |
10. PHARMACOLOGICAL CATEGORY
Antihypertensive
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
ER Film-coated Tablets
14. POTENCY
120 mg, 240 mg
15. CHEMICAL NAME AND STRUCTURE
Benzeneactonitrile, α -[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]]-3,4-dimethoxy- α -(1-methylethyl)-, monohydrochloride, (\pm)-

C₂₇H₃₈N₂O₄.HCl; M.W. = 491.07



16. RECORDS AND REPORTS
N/A

17. COMMENTS

Our **3/31/97**, Refuse to File letter informed Duramed that complete comparative dissolution data had not been submitted.

The applicant responded in a FAX and follow-up letter dated **4/4/97**, with the dissolution data.

Our letter dated **4/7/97**, acknowledged receipt of the ANDA, and declared that the DATE ACCEPTABLE FOR FILING WAS **4/4/97**.

The firm's correspondence dated **4/10/97**, contained a copy of the diskette for the bio study of the 120 mg dosage strength.

Our letter dated **5/8/97**, corrected the "Refuse to File" letter dated **3/31/97**, and our letter dated **4/7/97**, acknowledging receipt of the application. According to this letter, the date of receipt of the ANDA was **2/10/97**.

The results of an *in vivo* bioequivalence studies for the 2 dosage strengths are found in volumes 1.1 through 1.30 on pp. **01-0057 ff.**

Proposed labels/labeling are in vol 1.1 on pp. **01-0008 ff.**; revised FP labels are in the **6/19/98**, amendment; FP insert labeling is in the **4/12/99**, amendment.

The firm's **10/24/97**, amendment addresses the Chemistry and Label/Labeling deficiencies in our FAX dated **8/20/97**.

The firm's **11/24/97**, amendment addresses comment 5. of our FAX dated **8/20/97**.

The applicant's **6/19/98**, amendment addresses the Chemistry and Label/Labeling deficiencies in our FAX dated **5/13/98**. Additionally, the applicant has withdrawn the 180 mg dosage strength from the application based upon outstanding BIO issues that have not been resolved.

Duramed/Verapamil Hydrochloride ER Tablets

The comment #'s in our FAX dated 4/6/99, and the applicant's responses (4/12/99, amendment) are cited in the appropriate sections (i.e., items 20. thru 37.) of this review.

4/12/99, amendment: Please provide any additional data for ongoing stability studies for the exhibit batches if available.

Applicant's response: Updated stability data have been provided. Twenty-four mos. data for lot # 960702S of the 120 mg strength in 100's and 500's have been provided; 36 mos. data for lot # 950301 of the 240 mg strength in 100's and 500's have been previously submitted.

The data are within specs.

Significant CGMP deficiencies for

. have prompted a "withhold" approval for this ANDA. A Memorandum dated 10/20/97, from J. Singer of Investigations & Preapproval Compliance Br/DMPQ (HFD-324) recommends to Withhold Approval of this ANDA due to significant CGMP deficiencies for Consumer Product Testing Co., located at 70 New Dutch Lane, Fairfield, NJ. See item 33. review.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend Approval w/satisfactory labeling review and EER. Alternatively, recommend to the applicant the withdrawal of the facility with CGMP deficiencies, and to provide the name/address of a new facility w/o CGMP problems at which the same tests can be performed.

19. REVIEWER:

Robert C. Permisohn

/S/

DATE COMPLETED:

4/20/99

4/18/99

Page(s)

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Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

*Security Review # 4
5/10/99*

Duramed/Verapamil Hydrochloride ER Tablets

AADA/ANDA: 75-072 APPLICANT: Duramed, Inc.DRUG PRODUCT: Verapamil HCl Extended-release Tablets, 120 mg
and 240 mg.

The deficiencies presented below represent FACSIMILE deficiencies.

The cited comment numbers are derived from the facsimile dated May 13, 1998, to you.

Chemistry Deficiencies:

1. Regarding comment 2.d., the in-process controls differ from those declared in the response to comment 6.a. of the October 24, 1997, amendment. Please provide justification for deletion of the tests for bulk density, tapped density, and particle size distribution on the lubricated granules.
2. Regarding comment 3., there still is not any specific identification test that will be performed on the packaged products. The packaged product is regarded as the finished product. The description test for these products may serve as adequate for this purpose. The test may be performed at the time that tablet count of each market package is determined throughout the packaging operations. Please submit revised specifications for the packaged products.
3. Please provide any additional data for ongoing stability studies for the exhibit batches if available.

Sincerely yours,

/s/

Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO.

3

2. ANDA #

~~75-072~~

3. NAME AND ADDRESS OF APPLICANT

Duramed Pharmaceuticals, Inc.
Cincinnati, OH

4. LEGAL BASIS FOR SUBMISSION

Section 505(j)

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Verapamil HCl ER Tablets, USP

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

N/A

9. AMENDMENTS AND OTHER DATES:

Duramed
2/10/97 (Original Filing)
4/4/97 (Dissolution data)
4/10/97 (BIO)
6/3/97 per MIS
6/13/97 (BIO)

10/24/97
11/24/97
12/10/97 (BIO)
12/17/97 (BIO)
6/19/98 (Subject of this review)
6/25/98 (BIO)
1/13/99 (BIO)

FDA
3/31/97 (Refuse to File)
4/7/97 (Acknowledgement)
5/8/97 (Refuse to File Correction)

8/20/97 NA FAX
8/18/97 BIO NA Letter

5/13/98 NA FAX
4/7/98 BIO NA FAX

10/26/98 BIO NA FAX

10. PHARMACOLOGICAL CATEGORY

Antihypertensive

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

ER Film-coated Tablets

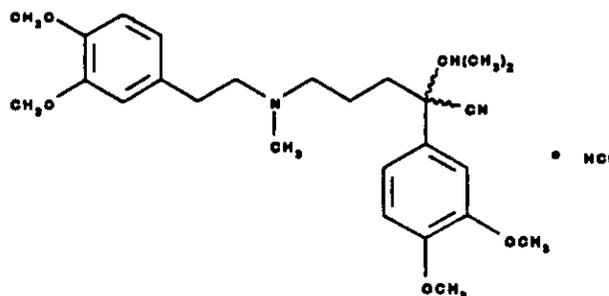
14. POTENCY

120 mg, 180 mg, 240 mg

15. CHEMICAL NAME AND STRUCTURE

Benzeneacetonitrile, α -[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]]-3,4-dimethoxy- α -(1-methylethyl)-, monohydrochloride, (\pm)-

C₂₇H₃₈N₂O₄.HCl; M.W. = 491.07



16. RECORDS AND REPORTS

N/A

17. COMMENTS

Our 3/31/97, Refuse to File letter informed Duramed that complete comparative dissolution data had not been submitted.

The applicant responded in a FAX and follow-up letter dated 4/4/97, with the dissolution data.

Our letter dated 4/7/97, acknowledged receipt of the ANDA, and declared that the DATE ACCEPTABLE FOR FILING WAS 4/4/97.

The firm's correspondence dated 4/10/97, contained a copy of the diskette for the bio study the 120 mg dosage strength.

Our letter dated 5/8/97, corrected the "Refuse to File" letter dated 3/31/97, and our letter dated 4/7/97, acknowledging receipt of the application. According to this letter, the date of receipt of the ANDA was 2/10/97.

The results of an *in vivo* bioequivalence studies for the 2 dosage strengths are found in volumes 1.1 through 1.30 on pp. 01-0057 ff.

Proposed labels/labeling are in vol 1.1 on pp. 01-0008 ff.

The firm's 10/24/97, amendment addresses the Chemistry and Label/Labeling deficiencies in our FAX dated 8/20/97.

The firm's 11/24/97, amendment addresses comment 5. of our FAX dated 8/20/97.

The applicant's 6/19/98, amendment addresses the Chemistry and Label/Labeling deficiencies in our FAX dated 5/13/98. Additionally, the applicant has withdrawn the 180 mg dosage strength from the application based upon outstanding BIO issues that have not been resolved.

Duramed/Verapamil Hydrochloride ER Tablets

The comment #'s in our FAX dated 5/13/98, and the applicant's responses are cited in the appropriate sections (i.e., items 20. thru 37.) of this review. Outstanding issues will be presented in item 38. of this review; these will be FAXed (or otherwise transmitted) to the applicant as is appropriate.

In addition to responding to the deficiencies presented in the FAX dated 5/13/98, the firm was asked to note and acknowledge the following comments in their response:

Comment 1. Your response to the Division of Bioequivalence deficiency letter dated August 18, 1997, is under review. You will be notified in a separate letter of any deficiencies in the Bioequivalence portion of your application. The dissolution method and specifications will be set by the Division of Bioequivalence.

Applicant's response: We are in receipt of the facsimile deficiency letter dated 4/7/98, from the DOB. As part of the response, we will withdraw the 180 mg strength from the ANDA. We acknowledge the issues in the 2nd and 3rd sentences of this comment.

Subsequent to this response, the applicant has provided DOB related material in the 6/25/98, and 1/13/99, submissions.

Comment 2. Regarding comments 4.j. and 4.k., the analogy between the loss on drying (LOD) of the unlubricated granulation and the maximum contribution to LOD based upon their vendors' specifications may not be justified. Since it is a wet granulation process, an increase in the LOD for any one or more of the ingredients may not be predicted. This is supported by the diversity of the LOD results of the unlubricated granulation that are tabulated on page 46 of the October 24, 1997, amendment.

Applicant's response: We agree that for a wet granulation process, an increase in the LOD for one or more of the ingredients may not be predicted. The LOD will be factored into yield calculations. The Master Batch Manufacturing Record has been revised accordingly.

Comment 3. The evaluation of compliance of all firms involved in the manufacture and testing of this drug product with the current good manufacturing practices (CGMP) regulations had been undertaken by our Office of Compliance. As a result of the evaluation, significant CGMP deficiencies were noted. A satisfactory evaluation is required prior to approval of this application.

Applicant's response: Acknowledged. Consumer Product Testing Co. has responded to the FDA comments and believes they are in compliance.

Duramed/Verapamil Hydrochloride ER Tablets

Comment 4. Please provide any additional data for ongoing stability studies for the exhibit batches if available.

Applicant's response: Updated stability data have been provided. Eighteen mos. data for lot # 960702S of the 120 mg strength in 100's and 500's, 36 mos. data for lot # 950301 of the 240 mg strength in 100's and 500's have been included.

The data are within specs.

Significant CGMP deficiencies for

prompted a "withhold" approval for this ANDA. A Memorandum dated 10/20/97, from J. Singer of Investigations & Preapproval Compliance Br/DMPQ (HFD-324) recommends to Withhold Approval of this ANDA due to significant CGMP deficiencies for Consumer Product Testing Co., located at 70 New Dutch Lane, Fairfield, NJ. See item 33. review.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

Robert C. Permisohn
/S/

DATE COMPLETED:

2/10/99

3/16/99

Page (s)

20

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #3

3/16/99.

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

5/13/98
Chemistry Comments

#38

1. CHEMISTRY REVIEW NO.

2

2. ANDA #

072

3. NAME AND ADDRESS OF APPLICANT

Duramed Pharmaceuticals, Inc.
Cincinnati, OH

4. LEGAL BASIS FOR SUBMISSION

Section 505(j) RLD: Patent/Exclusivity:

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Verapamil HCl ER Tablets, USP

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

N/A

9. AMENDMENTS AND OTHER DATES:

Duramed
2/10/97 (Original Filing)
4/4/97 (Dissolution data)
4/10/97 (BIO)
6/3/97 per MIS
6/13/97 (BIO)

FDA
3/31/97 (Refuse to File)
4/7/97 (Acknowledgement)
5/8/97 (Refuse to File Correction)
8/20/97 NA FAX
8/18/97 BIO NA Letter

10/24/97 Subject of this review.
11/24/97 Subject of this review.
12/10/97 (BIO)
12/17/97 (BIO)

10. PHARMACOLOGICAL CATEGORY

Antihypertensive

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

ER Film-coated Tablets

14. POTENCY

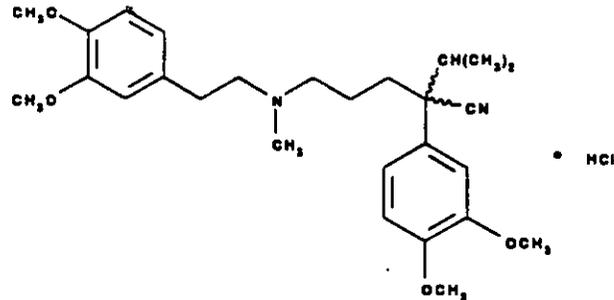
120 mg, 180 mg, 240 mg

15. CHEMICAL NAME AND STRUCTURE

Benzeneacetonitrile, α -[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]]-3,4-dimethoxy- α -(1-methylethyl)-, monohydrochloride, (\pm) -

$C_{27}H_{38}N_2O_4 \cdot HCl$; M.W. = 491.07

Duramed/Verapamil Hydrochloride ER Tablets

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Our 3/31/97, Refuse to File letter informed Duramed that complete comparative dissolution data had not been submitted.

The applicant responded in a FAX and follow-up letter dated 4/4/97, with the dissolution data.

Our letter dated 4/7/97, acknowledged receipt of the ANDA, and declared that the DATE ACCEPTABLE FOR FILING WAS 4/4/97.

The firm's correspondence dated 4/10/97, contained a copy of the diskette for the bio study the 120 mg dosage strength.

Our letter dated 5/8/97, corrected the "Refuse to File" letter dated 3/31/97, and our letter dated 4/7/97, acknowledging receipt of the application. According to this letter, the date of receipt of the ANDA was 2/10/97.

The results of an *in vivo* bioequivalence studies for the 3 dosage strengths are found in volumes 1.1 through 1.30 on pp. 01-0057 ff.

Proposed labels/labeling are in vol 1.1 on pp. 01-0008 ff.

The firm's 10/24/97, amendment addresses the Chemistry and Label/Labeling deficiencies in our FAX dated 8/20/97.

The firm's 11/24/97, amendment addresses comment 5. of our FAX dated 8/20/97.

The comment #'s in our FAX dated 8/20/97, and the applicant's responses are cited in the appropriate sections (i.e., items 20. thru 37.) of this review. Outstanding issues will be presented in item 38. of this review; these will be FAXed (or otherwise transmitted) to the applicant as is appropriate.

In addition to responding to the deficiencies presented in the FAX dated 8/20/97, the firm was asked to note and acknowledge the following comments in their response:

Duramed/Verapamil Hydrochloride ER Tablets

Comment 1. On p. 32-0405, USP 23 Supplement 5, p. 3441 is cited as the source of the monograph for the drug products; it should be p. 3741.

Applicant's response: At the time of submission of the ANDA Supplement 5 of the USP 23 was official, and the page citation was correct. We acknowledge this new information on p. 3741. However, at the time of submission, the new material on p. 3771, was first contained in the 14th IRA, PF 22 (6) which was official at that time.

Comment 2. In the event that a rework procedure is required, it has not been stated that samples of all rework batches will be placed on stability.

Applicant's response: A commitment has been made.

Comment 3. You will be notified in a separate letter of any deficiencies in the Bioequivalence portion of your application. The dissolution method and specifications will be set by the Division of Bioequivalence.

Applicant's response: We received a deficiency letter dated 8/18/97, from the DOB.

Comment 4. The evaluation of compliance of all firms involved in the manufacture and testing of this drug product with the current good manufacturing practices regulations will be undertaken by our Office of Compliance. A satisfactory evaluation is required prior to approval of this application.

Applicant's response: We acknowledge.

However, significant CGMP deficiencies for

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ive
prompted a "withhold" approval for this ANDA. A Memorandum dated 10/20/97, from J. Singer of Investigations & Preapproval Compliance Br/DMPQ (HFD-324) recommends to Withhold Approval of this ANDA due to significant CGMP deficiencies for Consumer
ield, NJ.

See item 33. review.

Comment 5. Please provide any additional data for ongoing stability studies for the exhibit batches if available.

Applicant's response: Additional data for lot #'s 950301 (24 mos.), 960701S (12 mos.), and 960702S (12 mos.) in 100's and 500's that were stored at 28°C have been submitted.

The results of stability testing are within specs.

Anda 75-072

4

Duramed/Verapamil Hydrochloride ER Tablets

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

Robert S. Permisohn

DATE COMPLETED:

3/31/98

4/30/98

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

5/6/98
Chemistry Comments
#380

Chemistry Review # 2
4/30/98

Contain Trade Secret,
Commercial/Confidential
Information and are not
releasable.

8/20/97
Clarity Comments

#38

1. CHEMISTRY REVIEW NO.

1

2. ANDA #
75-072

3. NAME AND ADDRESS OF APPLICANT
Duramed Pharmaceuticals, Inc.
Cincinnati, OH

4. LEGAL BASIS FOR SUBMISSION
Section 505(j)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Verapamil HCl ER Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Duramed
2/10/97* (Original Filing)
4/4/97* (Dissolution data)
4/10/97* (BIO)
6/3/97 per MIS
6/13/97* (BIO)

FDA
3/31/97 (Refuse to File)
4/7/97 (Acknowledgement)
5/8/97 (Refuse to File Correction)

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
(Small pharmaceutical)

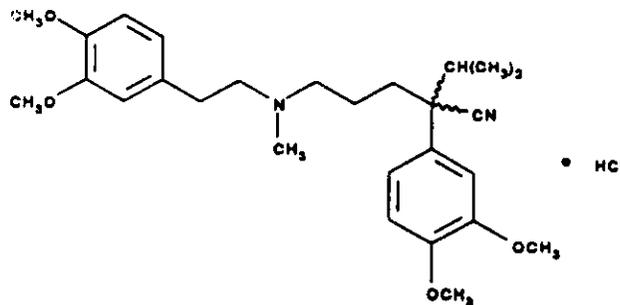
13. DOSAGE FORM
ER Film-coated Tablets

14. POTENCY
120 mg, 180 mg, 240 mg

15. CHEMICAL NAME AND STRUCTURE

Benzeneacetonitrile, α -[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy- α -(1-methylethyl)-, monohydrochloride, (\pm)-

$C_{27}H_{38}N_2O_4 \cdot HCl$; M.W. = 491.07



16. RECORDS AND REPORTS
N/A

17. COMMENTS

Our 3/31/97, Refuse to File letter informed Duramed that complete comparative dissolution data had not been submitted.

The applicant responded in a FAX and follow-up letter dated 4/4/97, with the dissolution data.

Our letter dated 4/7/97, acknowledged receipt of the ANDA, and declared that the DATE ACCEPTABLE FOR FILING WAS 4/4/97.

The firm's correspondence dated 4/10/97, contained a copy of the diskette for the bio study the 120 mg dosage strength.

Our letter dated 5/8/97, corrected the "Refuse to File" letter dated 3/31/97, and our letter dated 4/7/97, acknowledging receipt of the application. According to this letter, the date of receipt of the ANDA was 2/10/97.

The results of an *in vivo* bioequivalence studies for the 3 dosage strengths are found in volumes 1.1 through 1.30 on pp. 01-0057 ff.

Proposed labels/labeling are in vol 1.1 on pp. 01-0008 ff.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

Robert C. Permisochn

/S/

DATE COMPLETED:

7/14/97

8/1/97

Page (s)

18

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Commercial/Confidential
Information and are not
releasable.

Chemistry Review # 1

8/1/97

Page(s) 7

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Information and are not
releasable.

8/18/97

Chemistry Comments

#3P