CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-361

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 40-361

3. NAME AND ADDRESS OF APPLICANT
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
Pomona, NY 10970-0519

4. BASIS OF SUBMISSION
Reference Listed drug product: Dextrostat[R]
Tablets by Shire Richwood approved in NDA #84-051.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug. There is no marketing exclusivity for this drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Dextroamphetamine Sulfate Tablets, USP

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-18-99
Acknowledgement: 3-16-99
Major amendment: 7-29-99
Amendment Response: 4-5-00
Major deficiency letter: 8-31-00
Reclassification to minor request: 9-7-00
Minor amendment response: 10-9-00
Minor deficiency letter: 11-22-00
Amendment Response: 12-15-00

10. PHARMACOLOGICAL CATEGORY
For treatment of Narcolepsy and ADS

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg and 10 mg

15. CHEMICAL NAME AND STRUCTURE

See labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - All chemistry issues have been resolved.
Bioequivalence - Bioequivalence acceptable on 4/2/99 by M. Makary.
Labeling - Satisfactory dated 8/16/00.
EER - ~~Withhold~~ ok. 1/19/01

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable, ~~pending satisfactory EER~~. OK 1/15/01 1/24/01

19. REVIEWER: Karen A. Bernard, Ph.D.

DATE COMPLETED: 1-12-01

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

Chem Rev 4
9/12/01

NOV 22 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-361 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Please be aware that this application cannot be approved until deficiencies regarding DMF have been addressed satisfactorily by the DMF holder.

2. We acknowledge that you have lowered your impurity specification limits on release and stability for the drug product. We however believe that the limits you propose are still not justified by the data you have provided. You are requested to further lower these limits to be more in line with the actual data.

Sincerely yours,

for Vilayat Sayed

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

AUG 3 1 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-361 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

The deficiencies presented below represent MAJOR deficiencies.

Deficiencies:

1. Regarding your request seeking approval for an alternate drug substance supplier in your April 5, 2000 amendment, we have the following comments:

   a. Although you are proposing as an alternate supplier for Dextroamphetamine Sulfate, USP, and you have listed DMF on your 356h form, you did not submit a Letter of Authorization to the Agency from to review the DMF. You should be aware that the Agency does not have the authority to review this drug master file in the context of your ANDA without this letter. Please provide this information to the ANDA and be aware that at that time the DMF will be reviewed.

   b. You have has also stated that due to an unforeseen manufacturing site disaster, the current vendor is no longer able to supply Barr with Dextroamphetamine Sulfate, USP raw material. If this statement is correct as written, you should withdraw as a drug substance supplier.

2. Although, you have revised your Impurities testing specifications for the drug substance as requested, it is recommended that you lower your limits for knowns and unknowns be more in line with the actual data.

3. Although you have provided stability data for lots #309529001 and #309539001 manufactured using the material, you did not provide the executed manufacturing and packaging records for these lots. This information should be submitted in support of the new drug substance supplier you are proposing. In addition, all batch reconciliation data, yields, deviation reports, in-process specs, etc. should be submitted to the application. We also request that you provide dissolution data on 12 tablets for review by the Division of Bioequivalence.

4. We note that you are withdrawing all previously proposed packaging configurations for both strengths of this product except the 100 fill bottle with screw cap. Please clarify if you are intending to market the bulk package.

5. Based on the release and stability data provided for the new lots of drug product manufactured using the Johnson Matthey material, it appears that the impurity levels proposed for release and stability are too high and should be lowered to be more in line with the actual data (known, unknown and total impurities).

Sincerely yours,

for

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

JUL 29 1999

Chemistry Comments to be Provided to the Applicant

ANDA: 40-361 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Dextroamphetamine Sulfate Tablets USP, 5 mg and 10 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. You should include the designation in your Components and Composition statement for Calcium Sulfate.

2. It is unclear why the quantitative list of components for the 5 mg tablet lists 4 significant figures (5.000 mg) for the amount of Dextroamphetamine Sulfate, USP and for the 10 mg tablet a value of 10.00 (3 significant figures are reported).

3. Please clarify if you utilize USP Dextroamphetamine Sulfate material as a reference standard for the testing of the active raw material.

4. We recommend that you revise your testing specifications for the active drug substance to include testing for the 2 process impurities identified by the drug substance manufacturer

). We note that you utilize this method in your finished product testing protocol.

5. Your raw materials testing for Magnesium Stearate, does not appear to meet current compendia. See USP 23. Supp. 10.

6. We note that the exhibit batches were manufactured over the course of several days. In accordance with 21 CFR, you are requested to clarify if you have established any time limits on production with regard to storage or holding of intermediates during each of the major steps of manufacture.

7. The exhibit batch sizes for both the 5 mg and 10 mg strengths were for tablets. The Master batch records you submitted were also for a batch size of ablets for each strength. Please clarify that your maximum proposed batch size for each strength is tablets.

8. You are requested to supply a complete list of **all** in-process testing with specifications that you intend to perform during the manufacture of all future batches of Dextroamphetamine Sulfate Tablets. Although you have included guidelines for tabletting, in accordance with 21 CFR 211.110, valid in-process specifications for such characteristics shall be consistent with drug product final specifications.

Examination and testing of samples shall assure that the drug product and in-process material conform to specifications. You are requested to establish and submit future in-process testing with reasonable specifications. Use of guidelines only is unacceptable.

9. You are also requested to commit to perform routine in-process blend homogeneity testing on future manufacturing batches of the drug product. It is recommended that the acceptance criteria for blend uniformity analysis be established at (mean value) with an RSD of In addition you should outline the number of samples and what the sample size will be for this testing. It is recommended that the sample size of the blend should be greater than three times the weight of an individual dose.

10. Please clarify why the finished product COA for the 5 mg strength (lot #8R95204) does not appear to be included with any testing results. Refer to page 15-00048. A COA for the 10 mg strength (lot #8R95305) is included on page 15-00051 with full testing results. Testing results for lot # 8R95204 should be submitted to the Agency.

11. It is noted that the release specifications for the tablets include a specification for Water as, (where indicated). Please clarify if you intend to perform routine testing for Water on release and during stability for the tablets.

12. You are also requested to comment if you have detected any other impurities other than the 2 identifiable process impurities. We recommend that you include a specification for Single Unknown and Total Impurities (Known and Unknown).

13. Although you have included a testing summary of stability data for exhibit lots (#8R95204 and #8R95305), you should submit the authentic stability report forms with the actual testing dates.

B. In addition to the deficiencies listed above, please note and acknowledge the following:

You are requested to provide a list of excipient functionalities for each of the inactives used in the tablet formulation.

Sincerely yours,

Libya K. Sayoc

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