CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73045

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 9

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT
ALPharma (previously known as A.L. Laboratories)
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Name of the previous applicant/owner of the ANDA:
Generics (U.K) Ltd.
England
(Ownership transferred per OGD's letter dated 5-29-92)

4. BASIS OF SUBMISSION
Expiration of the patent covering the listed drug product, Ventolin Inhalation Aerosol.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Albuterol Inhalation Aerosol

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-28-88
Amendment: 3-6-89
ONC (Bio Data): 5-16-89
ONC (Bio Data): 6-23-89
Amendment: 8-28-89 (To submit response to NA letter dated 6-26-89.
ONC (Bio data): 3-23-90
ONC: 6-18-90
Amendment: 4-30-90
Amendment: 7-5-90 (To submit response to NA letter dated 6-26-89 and 4-23-90)
Amendment: 11-19-90 (labeling)
ONC: 11-21-90
ONC: 1-2-91 (Clinical)
Amendment: 4-26-91 (labeling)
ONC: 5-7-92
NC: 7-26-93
Major Amendment: 2-4-94 (To submit response to NA letter dated 7-21-91).
Major Amendment: 12-2-94 (Response to NA letter dated 8-11-94)
Amendment: 1-27-95
ONC: 6-12-95 (BIO)
ONC: 6-22-95 (BIO)

Major Amendment: 8-1-95 (Response to NA letter dated 5-26-95)
Minor Amendment: 2-23-96 (Response to NA letter dated 1-29-96)
3-27-96 MV Information
4-1-96 PAI Information
Minor Amendment: 5-1-96 (Response to NA letter dated 4-18-96)
ONC: 8-1-96 (Response to 7-18-96 bio letter)
Telephone amendment: 8-22-96 (submitted as a results of telecon dated 8-22-96)
8-30-96: Transfer of ownership
Telephone amendment: 9-5-96 (Response to Fax dated 8-23-96 regarding MV)
9-11-96: Big Data
9-20-96:Labeling
Telephone amendment: 9-30-96 (Response to Fax dated 9-25-96 regarding MV)
Amendment (Bio): 10-8-96 (Response to bio letter dated 9-3-96)
* Amendment (Bio): 5-23-97 (Response to bio letter dated 5-12-97)
* Amendment: 5-27-97 (Response to NA Chemistry letter dated 5-20-97)
* Telephone amendment: 7-17-97

FDA:
Acknowledgement Letter: 1-13-89
Bio NA letter: 9-19-89
NA letter (chemistry & Labeling): 6-26-89 (Reviewer - F. Fang for CR # 1)
NA letter (Chemistry & labeling): 4-23-90 (Reviewer - J.T. Piechocki for CR # 2)
Information letter (Labeling): 9-25-90
NA letter (Chemistry & Labeling): 7-12-91
Acknowledgement letter for ownership change: 5-29-92
NA letter: 8-11-94 (CR # 4)
NA letter: 5-26-95 (CR # 5)
NA letter: 1-29-96 (CR # 6)
NA letter: 4-8-96 (CR # 7)
Deficiency letter: 7-18-96 (Bio)
Deficiency letter: 9-3-96 (Bio)
FAX: 8-23-96 (MV comments)
FAX: 9-23-96 (MV Comments)
Deficiency letter (BIO): 5-12-97
NA Letter (Chemistry): 5-20-97

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF ..CCL Industries..manufacturer drug Product
DMF

DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Inhalation Aerosol

14. POTENCY
0.09 mg/Actuation

15. CHEMICAL NAME AND STRUCTURE
Satisfactory per CR # 1

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Referenced DMF is adequate per last review completed by M. Shaikh review dated 10-15-96. No new amendment is submitted after this review.
The supporting DMFs became per review completed by this reviewer on 10-15-96 after review of 9-13-96 amendment. Remains adequate per review completed by this reviewer on 7-10-97 after review of 2-25-97 annual update.
2. Release and stability specifications for the finished drug product remains acceptable.
3. 24 months' stability data for exhibit batch (lot # 6403 submitted in this amendment is adequate to grant the 2 years of expiration dating period.
4. ALPharma's amendment dated 5-27-97 is acceptable from chemistry point of view.
5. EER submitted on 1-3-96 by this reviewer became acceptable on 5-29-96. A follow-up EER need to be submitted
6. MV conducted by DDA, St. Louis, MO is Acceptable.
7. FPL - acceptable per labeling review conducted on 10-8-96 by C. Holquist.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER update.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
7-17-97

cc: ANDA 73-045
DUP File
Division File
Field Copy

7/28/97

Endorsements:
HFD-623/M.Shaikh/7-17-97 /S/
HFD-623/M.Smela/7-18-97 /S/ 7/29/97
x\new\firmsam\alpharma\ltrs&rev\73045rev.9
F/T by: bc/7-21-97

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Addendum to Chemist's Review # 9:

ANDA 73-045 (Albuterol Inhalation Aerosol)

1. Chemistry Issues were previously closed per Review # 9 for this ANDA and it became approval.

2. The approval package is reviewed by Dr. Allen Rudman and found it deficient based on QA review for the ANDAs approved for Albuterol MDI. Based on this, Dr. Rudman call the firm on 8-1-97 to amend the ANDA as follows:

   1. Inclusion of an for the release of the drug product in addition to ID test.

   2. Reduction of the Unit Spray Content test limits from %.

   ALPharma submitted a telephone amendment on 8-6-97. ALPharma commits to revise its drug product release specifications to include an identification test. ALPharma also commits to tighten the drug product release and stability specifications for the Unit Spray Content from % of label claim to % of the label claim. ALPharma commits that they will submit revised specifications and ID test method post-approval of this ANDA.

   In this telephone amendment, ALPharma als listed address of facility used for microbiological testing of the drug substance and drug product as follows:

   (DMF)

   In original submission, ALPharma listed this facility located at above address with same DMF number for conducting microbiological testing of drug substance and drug product as This reviewer considers this as a name change of the facility.

   ALPharma listed address of CCL Pharmaceuticals for the manufacturing, packaging, release and stability testing of the drug product. There is no change in address of the facility.

Conclusion: ANDA remains approvable.

c.c: ANDA 73-045
Division File
FIELD COPY

Endorsements:

HFD-625/M.Shaikh/ /S/ 8/7/97
HFD-625/M.Smela/

x:\new\firmsam\alpharma\ltrs&rev\73045rv9.ad1

/S/ 8/7/97

1. CHEMISTRY REVIEW NO. 8

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT
ALPharma (previously known as A.L. Laboratories)
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Name of the previous applicant/owner of the ANDA:
Generics (U.K) Ltd.
England
(Ownership transferred per OGD's letter dated 5-29-92)

4. BASIS OF SUBMISSION
Expiration of the patent covering the listed drug product, Ventolin Inhalation Aerosol.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Albuterol Inhalation Aerosol

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-28-88
Amendment: 3-6-89
ONC (Bio Data): 5-16-89
ONC (Bio Data): 6-23-89
Amendment: 8-28-89 (To submit response to NA letter dated 6-26-89.
ONC (Bio data): 3-23-90
ONC: 6-18-90
Amendment: 4-30-90
Amendment: 7-5-90 (To submit response to NA letter dated 6-26-89 and 4-23-90)
Amendment: 11-19-90 (labeling)
ONC: 11-21-90
ONC: 1-2-91 (Clinical)
Amendment: 4-26-91 (labeling)
ONC: 5-7-92
NC: 7-26-93
Major Amendment: 2-4-94 (To submit response to NA letter dated 7-21-91).
Major Amendment: 12-2-94 (Response to NA letter dated 8-11-94)
Amendment: 1-27-95
ONC: 6-12-95 (BIO)
ONC: 6-22-95 (BIO)

Major Amendment: 8-1-95 (Response to NA letter dated 5-26-95)
Minor Amendment: 2-23-96 (Response to NA letter dated 1-29-96)
* 3-27-96 MV Information
* 4-1-96 PAI Information
* Minor Amendment: 5-1-96 (Response to NA letter dated 4-18-96)
* ONC: 8-1-96 (Response to 7-18-96 bio letter)
* Telephone amendment: 8-22-96 (submitted as a results of telecon dated 8-22-96)
*8-30-96 Transfer of ownership
* Telephone amendment: 9-5-96 (Response to Fax dated 8-23-96 regarding MV)
*9-11-96 Big Data
*9-20-96 Labeling
* Telephone amendment: 9-30-96 (Response to Fax dated 9-25-96 regarding MV)
* Amendment (Bio): 10-8-96 (Response to bio letter dated 9-3-96)

FDA:
Acknowledgement Letter: 1-13-89
Bio NA letter: 9-19-89
NA letter (chemistry & Labeling): 6-26-89 (Reviewer - F. Fang for CR # 1)
NA letter (Chemistry & labeling): 4-23-90 (Reviewer - J.T. Piechocki for CR # 2)
Information letter (Labeling): 9-25-90
NA letter (Chemistry & Labeling): 7-12-91
Acknowledgement letter for ownership change: 5-29-92
NA letter: 8-11-94 (CR # 4)
NA letter: 5-26-95 (CR # 5)
NA letter: 1-29-96 (CR # 6)
NA letter: 4-8-96 (CR # 7)
Deficiency letter: 7-18-96 (Bio)
Deficiency letter: 9-3-96 (Bio)
FAX: 8-23-96 (MV comments)
FAX: 9-23-96 (MV Comments)

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF ..CCL Industries..manufacturer drug Product
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM

14. POTENCY

Inhalation Aerosol 0.09 mg/Actuation

15. CHEMICAL NAME AND STRUCTURE
Satisfactory per CR # 1

16. RECORDS AND REPORTS
N/A

17. COMMENTS
1. Referenced DMF [ ] became adequate per Richard Lostritto's review/letter dated 7-31-96 and then remains adequate per M. Shaikh's review completed on 8-15-96 and 10-15-96 after review of July 31, 1996 update to the DMF and 9-11-96 amendment. The supporting DMFs [ ] became per Lostritto's review/letter dated 7-31-96. DMF remains adequate per review completed by this reviewer on 10-15-96 after review of 9-13-96 amendment.
2. Albuterol drug substance specifications meet USP/BP/EP requirements.
3. The firm has committed to adopt CDER's current requirements regarding CFC-11 and CFC-12 per 1-29-96 letter.
4. Release specification for the finished drug product are acceptable.
5. 24 months' stability data for exhibit batch (lot # 6403 submitted in this amendment is adequate to grant the 2 years of expiration dating period.
6. Follow-up EER submitted on 1-3-96 by this reviewer is acceptable since 5-29-96.
7. MV conducted by DDA, St. Louis, MO is Acceptable.
8. FPL - acceptable per labeling review conducted on 10-8-96 by C. Holquist.
9. As a results of review of BIO amendments dated 6-12-95, 6-22-95 and 8-1-96, a bio deficiency letter was issued on 9-3-96. All of the comments cited in this bio letter are bio issues. ALPharma responded to this letter on 10-8-96 which is pending review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable bio status. Chemistry is closed.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 10-15-96

cc: ANDA 73-045
DUP File
Division File
Field Copy

Endorsements:
HFD-623/MShaikh/10-15-96
HFD-623/MSmela/10-16-96

/S/ 10/17/96
/S/ 10/17/96

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Manufacturing Controls

Addendum to Chemist's Review # 8:

ANDA 73-045 (Albuterol Inhalation Aerosol)

1. Chemistry Issues were previously closed per Review # 8 for this ANDA and it became approval pending acceptable bio status.

2. Bio status: The Division of Bioequivalence (DBE) issued a letter to the firm on 5-12-97 citing bio deficiencies after writing two reviews both dated 4-29-97 as a results of review of 9-9-96, 8-1-96, 10-8-96, 11-15-96, 1-6-97 and 1-22-97 amendments. Based on this bio deficiency letter, a NA letter is being issued to the firm.

3. The EER and Labeling both are currently satisfactory.

Conclusion: ANDA became not-approvable. A NA letter with MINOR amendment is being issued to the firm based on bio letters issued on 5-12-97 to the firm.

c.c: ANDA 73-045
Division File
FIELD COPY

Endorsements:

HFD-625/M.Shaikh/5/14/97
HFD-625/M.Smela/5/15/97

/S/ 5/15/97

/S/ 5/15/97

1. CHEMISTRY REVIEW NO. 7

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT
A.L. Laboratories
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Name of the previous applicant/owner of the ANDA:
Generics (U.K) Ltd.
England
(Ownership transferred per OGD's letter dated 5-29-92)

4. BASIS OF SUBMISSION
Expiration of the patent covering the listed drug product, Ventolin Inhalation Aerosol.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Albuterol Inhalation Aerosol

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-23-88
Amendment: 3-6-89
ONC (Bio Data): 5-16-89
ONC (Bio Data): 6-23-89
Amendment: 8-28-89 (To submit response to NA letter dated 6-26-89.
ONC (Bio data): 3-23-90
ONC: 6-18-90
Amendment: 4-30-90
Amendment: 7-5-90 (To submit response to NA letter dated 6-26-89 and 4-23-90)
Amendment: 11-19-90 (labeling)
ONC: 11-21-90
ONC: 1-2-91 (Clinical)
Amendment: 4-26-91 (labeling)
ONC: 5-7-92
NC: 7-26-93
Major Amendment: 2-4-94 (To submit response to NA letter dated 7-21-91).
Major Amendment: 12-2-94 (Response to NA letter dated 8-11-94)
Amendment: 1-27-95
Major Amendment: 8-1-95 (Response to NA letter dated 5-26-95)

* Minor Amendment: 2-23-96 (Response to NA letter dated 1-29-96)

FDA:
Acknowledgement Letter: 1-13-89
Bio NA letter: 9-19-89
NA letter (chemistry & Labeling): 6-26-89 (Reviewer - F. Fang for CR # 1)
NA letter (Chemistry & labeling): 4-23-90 (Reviewer - J.T. Piechocki for CR # 2)
Information letter (Labeling): 9-25-90
NA letter (Chemistry & Labeling): 7-12-91
Acknowledgement letter for ownership change: 5-29-92
NA letter: 8-11-94
NA letter: 5-26-95
NA letter: 1-29-96

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF ,CCL Industries..manufacturer drug Product
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Inhalation Aerosol

14. POTENCY
0.09 mg/Actuation

15. CHEMICAL NAME AND STRUCTURE
Satisfactory per CR # 1

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A. General Comments:
1. Referenced DMF remains inadequate per Richard Lostritto's review/letter dated 3-11-96. The supporting DMFs remained deficient per Lostritto's review/letter dated 3-11-96.
2. CDER's current requirements regarding CFC-11 and CFC-12 imposed on the firm. The firm has committed to establish the current specs. in this amendment.
3. BIO Study data is under review.
4. Release specification for the finished drug product remains acceptable.
5. 24 stability data for exhibit batch (lot # 6403 submitted in this amendment is adequate to grant the 2 years of expiration dating period.

6. Complete MV package is being sent on 4-1-96 to DDA, St.Louis, MI per their request along with review.
7. A follow-up EER submitted on 1-3-96 by this reviewer is pending.

B. Comments need to be included in NA letter:

1. DMF [ ] remains deficient.
2. In-vivo bio data submitted on June 12, 1995 is under review.
3. A satisfactory cGMP status of all the facilities is required prior to approval.

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approved. A NA letter with minor amendment along with bio comment is being sent to the applicant including all the deficiencies listed in sections # 17(B).

19. REVIEWER: Mujahid L. Shaikh — DATE COMPLETED: 4-1-96

cc: ANDA 73-045
DUP File
Division File
Field Copy

Endorsements:

HFD-623/MShaikh/4-1-96 /S/ 4/4/96
HFD-623/MSmela/ /S/ 4/4/96

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1. CHEMISTRY REVIEW NO. 6

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT
A.L. Laboratories
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Name of the previous applicant/owner of the ANDA:
Generics (U.K) Ltd.
England
(Ownership transferred per OGD's letter dated 5-29-92)

4. BASIS OF SUBMISSION
Expiration of the patent covering the listed drug product, Ventolin Inhalation Aerosol.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Albuterol Inhalation Aerosol

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-23-88
Amendment: 3-6-89
ONC (Bio Data): 5-16-89
ONC (Bio Data): 6-23-89
Amendment: 8-28-89 (To submit response to NA letter dated 6-26-89.
ONC (Bio data): 3-23-90
ONC: 6-18-90
Amendment: 4-30-90
Amendment: 7-5-90 (To submit response to NA letter dated 6-26-89 and 4-23-90)
Amendment: 11-19-90 (labeling)
ONC: 11-21-90
ONC: 1-2-91 (Clinical)
Amendment: 4-26-91 (labeling)
ONC: 5-7-92
NC: 7-26-93
Major Amendment: 2-4-94 (To submit response to NA letter dated 7-21-91).
Major Amendment: 12-2-94 (Response to NA letter dated 8-11-94)
Amendment: 1-27-95
* Major Amendment: 8-1-95 (Response to NA letter dated 5-26-95)

FDA:
Acknowledgement Letter: 1-13-89
Bio NA letter: 9-19-89
NA letter (chemistry & Labeling): 6-26-89 (Reviewer - F. Fang for CR # 1)
NA letter (Chemistry & labeling): 4-23-90 (Reviewer - J.T. Piechocki for CR # 2)
Information letter (Labeling): 9-25-90
NA letter (Chemistry & Labeling): 7-12-91
Acknowledgement letter for ownership change: 5-29-92
NA letter: 8-11-94
NA letter: 5-26-95

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF CCL Industries..manufacturer drug Product
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Inhalation Aerosol

14. POTENCY
0.09 mg/Actuation

15. CHEMICAL NAME AND STRUCTURE
Satisfactory per CR # 1

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A. General Comments:
1. Referenced DMF remains inadequate per S. Brown's review/letter dated 11-22-95 because supporting DMFs remained deficient per S. Brown's review/letter dated 11-21-95.
2. Labeling became acceptable completed on 10-27-95 y C. Zimmermann.
3. CDER's current requirements regarding CFC-11 and CFC-12 are being imposed on the firm.
4. BIO Study data is under review.
5. Release specification for the finished drug product remains acceptable.
6. Pre-approval and post-approval stability testing protocol and specification remains acceptable. Stability data is adequate to grant the 2 years of expiration dating period per CR # 5.
7. A sample pick up request is being to made to for MV.

8. A follow-up EER is being requested by this reviewer.
B. Comments need to be included in NA letter:

1. DMF [ ] remains deficient.
2. Revision of CFC-11 and CFC-12 specification per CEDER'S current requirements is requested.
3. MV is being requested.
4. In-vivo bio data submitted on June 12, 1995 is under review.
5. A satisfactory cGMP status of all the facilities is required prior to approval.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with minor amendment along with bio comment is being sent to the applicant including all the deficiencies listed in sections # 17(B).

19. REVIEWER: DATE COMPLETED:
Mujahid L. Shaikh 12-20-95

cc: ANDA 73-045
ANDA 73-045/DUP/Division File
Field Copy

Endorsements:

/S/ 1/17/96

HFD-623/MShaikh/12/20/95
HFD-623/SSherken for MSmela/1/3/96 /S/ 1/17/96

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1. CHEMISTRY REVIEW NO. 5

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT
A.L. Laboratories
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Name of the previous applicant/owner of the ANDA:
Generics (U.K) Ltd.
England
(Ownership transferred per OGD's letter dated 5-29-92)

4. BASIS OF SUBMISSION
Expiration of the patent covering the listed drug product, Ventolin Inhalation Aerosol.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Albuterol Inhalation Aerosol

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-23-88
Amendment: 3-6-89
ONC (Bio Data): 5-16-89
ONC (Bio Data): 6-23-89
Amendment: 8-28-89 (To submit response to NA letter dated 6-26-89.
ONC (Bio data): 3-23-90
ONC: 6-18-90
Amendment: 4-30-90
Amendment: 7-5-90 (To submit response to NA letter dated 6-26-89 and 4-23-90)
Amendment: 11-19-90 (labeling)
ONC: 11-21-90
ONC: 1-2-91 (Clinical)
Amendment: 4-26-91 (labeling)
ONC: 5-7-92
NC: 7-26-93
Major Amendment: 2-4-94 (To submit response to NA letter dated 7-21-91).
* Major Amendment: 12-2-94 (Response to NA letter dated 8-11-94)
* Amendment: 1-27-95

FDA:
Acknowledgement Letter: 1-13-89
Bio NA letter: 9-19-89
NA letter (chemistry & Labeling): 6-26-89 (Reviewer - F. Fang for CR # 1)
NA letter (Chemistry & labeling): 4-23-90 (Reviewer - J.T. Piechocki for CR # 2)
Information letter (Labeling): 9-25-90
NA letter (Chemistry & Labeling): 7-12-91
Acknowledgement letter for ownership change: 5-29-92
NA letter: 8-11-94

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF .CCL Industries..manufacturer drug Product
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Inhalation Aerosol

14. POTENCY
0.09 mg/Actuation

15. CHEMICAL NAME AND STRUCTURE
Satisfactory per CR # 1

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A. General Comments:
1. Referenced DMF became unacceptable after review of July 1994 update to DMF by this reviewer. Supporting DMFs are also deficient.
2. BIO Study data is still pending to be submitted.
3. Adequate information is submitted regarding inactive ingredients per this review.
4. EER will be submitted after the bio data is submitted.
5. Adequate information is submitted regarding container/closure system. All the referenced DMF for c/c system has been found acceptable.
6. Release specification for the finished drug product are acceptable.
7. Pre-approval and post-approval stability testing protocol and specification are acceptable. Stability data is adequate to grant the 2 years of expiration dating period.
8. Adequate information is submitted regarding Environmental considerations.

B. Comments need to be included in NA letter:
1. DMF [ ] is deficient.
2. ALL must revise Post-approval Stability protocol to reflect temperature of [ ]C/ambient humidity in both upright and inverted orientations.
3. MV is being requested.
4. Labeling comments.
5. Awaiting in vivo bio data.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with major amendment is being sent to the applicant including all the deficiencies listed in sections # 17(B).

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 4-10-95

cc: ANDA 73-045
Division File
DUP File
Field Copy

Endorsements:

HFD-625/M.Shaikh/4-10-95 /S/ 5/24/95
HFD-625/M.Smela/4-26-95 /S/ 5/24/95

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1. CHEMISTRY REVIEW NO. 4

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT
A.L. Laboratories
The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, MD 21224

Name of the previous applicant/owner of the ANDA:
Generics (U.K) Ltd.
England
(Ownership transferred per OGD's letter dated 5-29-92)

4. BASIS OF SUBMISSION
Expiration of the patent covering the listed drug product, Ventolin Inhalation Aerosol.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Albuterol Inhalation Aerosol

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

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submission: 12-23-88
Amendment: 3-6-89
ONC (Bio Data): 5-16-89
ONC (Bio Data): 6-23-89
Amendment: 8-28-89 (To submit response to NA letter dated 6-26-89.
ONC (Bio data): 3-23-90
ONC: 6-18-90
Amendment: 4-30-90
Amendment: 7-5-90 (To submit response to NA letter dated 6-26-89 and 4-23-90)
Amendment: 11-19-90 (labeling)
ONC: 11-21-90
ONC: 1-2-91 (Clinical)
Amendment: 4-26-91 (labeling)
ONC: 5-7-92
*NC: 7-26-93
*Major Amendment: 2-4-94 (To submit response to NA letter dated 7-21-91).

FDA:
Acknowledgement Letter: 1-13-89
Bio NA letter: 9-19-89
NA letter (chemistry & Labeling): 6-26-89 (Reviewer - F. Fang for CR # 1)
NA letter (Chemistry & labeling): 4-23-90 (Reviewer - J.T. Piechocki for CR # 2)
Information letter (Labeling): 9-25-90
NA letter (Chemistry & Labeling): 7-12-91
Acknowledgement letter for ownership change: 5-29-92

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF .CCL Industries..manufacturer drug Product
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM
Inhalation Aerosol

14. POTENCY
0.09 mg/Actuation

15. CHEMICAL NAME AND STRUCTURE
Satisfactory per CR # 1

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A. General Comments:

1. This amendment is essentially a new ANDA based on the fact that the owner of ANDA, manufacturing site, container/closure system, new bio/stability batch is changed and new bio guideline for conducting in-vivo studies.

2. Composition remained acceptable. The drug product is formulated with _% excess of albuterol drug substance.

3. Ownership of the application is changed to A.L. Laboratories.

4. The drug product will be manufactured, packaged, labeled, quality tested and stability tested at CCL Industries, England.

5. Referenced DMF is acceptable for the application per Memo for record drafted by this reviewer.

6. Adequate information is submitted regarding drug substance and for all inactive ingredients.

7. Adequate information is submitted regarding other firm involved in this application.

8. Applicant withdrew reference to [Lachman Consultant Services as US Agent,] and [SuperPharm Corporation as US. Agent to this application.]

9. The drug product will be distributed through ALL's subsidiary, Barre-National Inc. MD.

10. A new exhibit batch (lot # 6403 or also called lot # 403 or 6403 is manufactured in the manufacturing facility of CCL Industries, England. Size of the exhibit batch is [ ] units.
11. Production size will be [ ] units.

12. Adequate information is submitted for labeling and packaging. CCL packaged the entire exhibit batch.
13. Adequate in-process controls.

14. Samples for MV will be requested after bio study data is submitted and found acceptable.

15. EER is submitted by this reviewer for all the facilities listed in Section # 33 on 6-6-94. The EER is recalled by √EMail dated 6/17/94 pending submission of new bio data.

B. Comments need to be included in NA letter:
All the comments listed in section # 26, 28, 29, 31, 32, 34 and 35 of this review.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approved. A NA letter with major amendment is being sent to the applicant including all the deficiencies listed in sections # 26, 28, 29, 31, 32, 34, and 35 of this review.

19. REVIEWER: Mujahid L. Shaikh
DATE COMPLETED: 6-6-94 Revised on 6-20-94

cc: ANDA 73-045
ANDA 73-045/DUP/Division File
Field Copy

Endorsements:

HFD-623/MShaikh/6/20/94
HFD-623/MSmela/6-23-94

/S/ 8/8/94
/S/ 8/10/94

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1. CHEMIST'S REVIEW NO. 3

2. ANDA # 73-045

3. NAME AND ADDRESS OF APPLICANT

Generics (UK) Limited
Herts, ENG 1TL England

c/o Lachman Consulting Services
Westbury, NY 11590

4. AF NUMBER

N/A

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Albuterol Inhalation Aerosol

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

N/A

9. AMENDMENTS AND OTHER DATES:

DOA 12/23/88; Bio NA 9/19/89; Amend 3/6/89; ONC Bio 5/16/89; NA 6/26/89-Reviewer F. Fang; Amend 8/28/89; NA 4/23/90-Reviewer J.T. Piechocki; ONC 6/18/90; Amend 3/23/90; Label Rev 9/25/90; Amend-Bio 7/5/90; Amend-Chem 7/5/90; Amend 11/19/90; Phone Conv., G Johnston - Firm 6/6/90; ONC 11/21/90.

10. PHARMACOLOGICAL CATEGORY

Bronchodilator

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF

13. DOSAGE FORM

Inhalation aerosol

14. POTENCY

0.09 mg/inhalation

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Application, except for minor problems, is very close to approval. Particle size differences using three different methods need explanation. Methods need to be validation since it is not a USP item. Bio remains a problem.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable for chemistry.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken

/S/ 7/5/91

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1. CHEMIST'S REVIEW NO. 2

2. ANDA 73-045

3. NAME AND ADDRESS OF APPLICANT
Generics (UK) Limited
Station Close, Potters Bar
Herts ENG 1TL, England

c/o Superpharm Corp.
1769 Fifth Avenue
Bayshore, NY 11706

4. AF NUMBER
Innovator:
Glaxo, Inc.'s Ventolin
Schering's Proventil
Patent 3644353 expired 2/22/89
Patent 3705233 will expire on 12/5/89 p. 4

5. SUPPLEMENT(s)
Original submission amended

6. NAME OF DRUG
Albuterol Inhalation Aerosol

8. SUPPLEMENT(s) PROVIDE(s) FOR:
Original submission amended

9. AMENDMENTS AND OTHER DATES:
Firm:

12/23/88	ANDA submission dated 12/23/88
3/6/89	Submitted newly assigned DMF numbers
5/16/89	submitted biostudy (3 way study) (In vitro comparison data submitted 12/23/88 vol. 1.3)
8/28/89	Response to our letter dated 6/26/89

FDA:

1/5/89	EIR for applicant (analytical testing), [ ] (micronization), [ ] (contract manufacturer), [ ]
1/13/89	Acknowledgement of ANDA submission
6/26/89	Deficiency letter sent, not approvable

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. HOW DISPENSED
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]

13. DOSAGE FORM
Inhalation aerosol

14. POTENCY
0.09 mg/in

15. CHEMICAL NAME AND STRUCTURE
1-(4-Hydroxy-3-hydroxymethyl-phenyl)-2-(tert-Butylamino)ethanol.

17. COMMENTS
Deficiencies identified:

1) Standard Control Procedure (new drug substance specification sheet) refers to the Laser Method SOP but does not specify which of the methods contained in SOP.MI03 to use.

2) Firm has not completed one-time temperature cycling study.

3) Firm objects to having water determination as part of the STABILITY program since the container is pressurized. This is acceptable for routine stability but not the SIMULATED use study.

18. CONCLUSIONS AND RECOMMENDATIONS
A not approvable letter is to be issued detailing the deficiencies outlined above

19. REVIEWER: J. Piechocki /S/ 4/19/90 DATE COMPLETED: 3/30/90

R/D INIT. BY RPatel 4/12/90 /S/ 4/19/90
ms: 4/10/90 (4390m)

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Manufacturing Controls

1. CHEMIST'S REVIEW NO. 1

2. ANDA 73-045

3. NAME AND ADDRESS OF APPLICANT
Generics (UK) Limited
Station Close, Potters Bar
Herts ENG 1TL, England

c/o Superpharm Corp.
1769 Fifth Avenue
Bayshore, NY 11706

4. AF NUMBER
Innovatrore: Glaxo, Inc.'s Ventolin
Schering's Proventil
Patent 3644353 expired 2/22/89
Patent 3705233 will explore on 12/5/89 p. 4

5. SUPPLEMENT(s)
Original submission amended

6. NAME OF DRUG
Albuterol Inhalation Aerosol

8. SUPPLEMENT(s) PROVIDE(s) FOR:
Original submission amended

9. AMENDMENTS AND OTHER DATES:
Firm:

12/23/88	ANDA submission dated 12/23/88
3/6/89	Submitted newly assigned DMF numbers
5/16/89	submitted biostudy (3 way study) (In vitro comparison data submitted 12/23/88 vol. 1.3)

FDA:

1/5/89	EIR for applicant (analytical testing), [ ] (micronization), [ ] (contract manufacturer), [ ]
1/13/89	Acknowledgemant of ANDA submission

10. PHARMACOLOGICAL CATEGORY
Bronchodilator

11. HOW DISPENSED
Rx

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

13. DOSAGE FORM
Inhalation aerosol

14. POTENCY
0.09 mg/in

15. CHEMICAL NAME AND STRUCTURE
1-(4-Hydroxy-3-hydroxymethyl-phenyl)-2-(tert-Butylamino)ethanol.

17. COMMENTS
Deficiencies identified:

1) Composition statement - composition per aerosol can.
2) DMF[ ]and DMF[ ]deficient
3) Drug substance controls:
   a) COA fro[ ]to be revised
   b) particle size determination, upper limit of acceptance to be specified.
   c) contamination in micronization
   d) Microbial limits test

4. U S testing of finished product manufactured at foreign facilities no longer required.

5. Clarification of[ ]

6. Drug product manufacture:
   a)[ ] µm filter for trichlorofluoromethane,[ ] µm?
   b) on line filter for dichlorodifluoromethane?
   c) batch record and test data for drug product based on the drug substance from a second source.

7) Container/closure system:
   a) Components qualify for food contact surfaces
   b) Extractable studies

8) Finished product testing:
   a) 17 point document
   b) laser technique
      i) upper limit of acceptance
      ii) one additional method
      iii) amount retained on the mouthpiece

9) Stability testing:
   a) temperature cycling study
   b) testing parameters incomplete
   c) some parameters to be monitored under simulated use conditions.
   d) 18 month expiration dating

10) Bulk drug analysis

11) Finished dosage from testing

12) Sample of the container/closure system and a unit of the drug product

13) CGMP evaluation

14) Biostudy under review

15) labeling

18. CONCLUSIONS AND RECOMMENDATIONS
A not approvable letter is to be issued detailing the deficiencies outlined above

19. REVIEWER: Florence Fang
DATE COMPLETED: 6/2/89

R/D INIT. BY BTArnwine, A.S.
jth: 6/8/89 0080j

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