CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-702

CHEMISTRY REVIEW(S)

JAN 19 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75702 APPLICANT: Bausch and Lomb Pharmaceuticals
DRUG PRODUCT: Cromolyn Sodium Nasal Solution, USP

The deficiencies presented below represent MAJOR deficiencies.

A. Chemistry Deficiencies:

1. -

size. Please submit complete batch records,

-

2.

product at release (

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)

... proposing based on results

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ages

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... reported). You should submit an updated report of results revised as indicated above.

Page(s) 2

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1/19/01

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please submit any additional stability data generated on the stability lots since the last submission.

2. Labeling deficiencies, if any, will also need to be addressed in your response.

Sincerely yours,

Paul Shrewsbury for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW NO. 2 2. ANDA # 75-702

3. NAME AND ADDRESS OF APPLICANT
Bausch and Lomb Pharmaceuticals
8500 Hidden River Parkway
Tampa, FL 33637

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Nasalcrom (Cromolyn Sodium Nasal Solution, USP).
Innovator Company: marketed by Pharmacia & Upjohn Consumer Healthcare
Patent Expiration Date: Bausch and Lomb Pharmaceuticals, Inc. has certified that, in its opinion and to the best of its knowledge, there are no unexpired patents submitted to the FDA in reference to the listed drug cited in this application.
Exclusivity: Bausch and Lomb Pharmaceuticals, Inc., has indicated that, in their opinion and to the best of their knowledge, the reference listed drug product, NasalCrom® Cromolyn Sodium Nasal Solution, USP, is subject to an exclusivity determination which expires January 3, 2000. This certification is in accordance with the Statement of Exclusivity required under Section 505(j)(2)(A)(viii) of the Act.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Cromolyn Sodium Nasal Solution, USP. The drug product is a Nasal Spray in a mechanical pump spray bottle, which delivers 5.2 mg of Cromolyn Sodium per actuation.

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

9. AMENDMENTS AND OTHER DATES:

Submission date	Submission type
09/13/99	**Original ANDA Submission**
9/14/99	Bio Information
9/14/99	MV Packages
10/13/99	Electronic Submission
10/14/99	Gratuitous Amendment (minor corrections)
10/21/99	Packaging Information
10/25/99	New Correspondence
10/25/99	Information Update N/C
10/29/99	EER
10/29/99	Acceptable for Filing
12/16/99	Labeling Review
3/16/00	Bio Deficiencies
3/16/00	CMC Review #1; N/A
4/28/00	Bioequivalence Amendment
6/1/00	Bio "No Further Questions"
5/26/00	New Correspondence
*6/19/00	ANDA Original Amendment (New Fill Size; bottle)
7/12/00	Bio "No Further Questions"
*6/26/00	ANDA Original Amendment (Response to N/A CMC Deficiencies)

XXXX - FDA Correspondences
* - Subject of the current review

10. **PHARMACOLOGICAL CATEGORY**
Anti-inflammatory

11. **Rx or OTC**
Rx

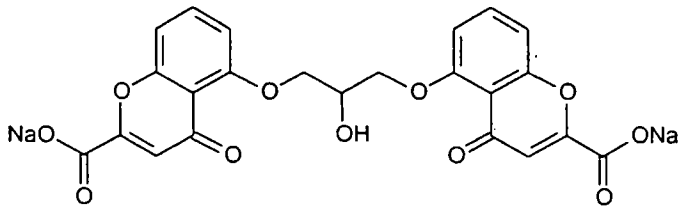
12. **RELATED IND/NDA/DMF(s)**

DMF #	Type	DMF holder	
		(XC22225)	

13. **DOSAGE FORM:** Nasal Spray

14. **POTENCY:** 40 mg/mL; 5.2 mg/actuation; 13 mL and 26 mL bottle

15. **CHEMICAL NAME AND STRUCTURE**
Cromolyn Sodium. 4*H*-1-Benzopyran-2-carboxylic acid, 5,5′-[(2-hydroy-1,3-propanediyl)bis(oxy)]bis[4,-oxo-, disodium salt]. $C_{23}H_{14}Na_2O_{11}$. 512.34. 15826-37-6. Anti-asthmatic (prophylactic).



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:** Refer to Item #38.

18. **CONCLUSIONS AND RECOMMENDATIONS:** N/A MAJOR Amendment

19. **REVIEWER:** Kenneth J. Furnkranz
DATE COMPLETED: 12/14/00
DATE REVISED: 1/4/01

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Chem Rev 2

12/14/00

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75702 APPLICANT: Bausch and Lomb Pharmaceuticals
DRUG PRODUCT: Cromolyn Sodium Nasal Solution, USP

The deficiencies presented below represent MAJOR deficiencies.

A. Chemistry Deficiencies:

1.

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2. Regarding Droplet Size testing of the drug product at release and on stability, you have revised the specifications for Droplet Size, however, there is no rationale for the established acceptance criteria. You should submit your reasons for establishing the specifications you are proposing based on results of Droplet Size evaluation of the exhibit batches).

   Also, Droplet Size results were reported in percentages (% less than 10 um, and percentages for D_{10}, D_{50} and D_{90}). D_{10}, D_{50} and D_{90} results should be reported as a size (in um).

   Finally, stability study results were reported only as % less than 10 um (no D_{10}, D_{50} and D_{90} results have been reported). You should submit an updated report of results revised as indicated above.

Page(s) 2

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11/18/91

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please submit any additional stability data generated on the stability lots since the last submission.

2. Labeling deficiencies, if any, will also need to be addressed in your response.

Sincerely yours,

Paul Schwarz for 1/18/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 16 2006

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75702 APPLICANT: Bausch and Lomb Pharmaceuticals
DRUG PRODUCT: Cromolyn Sodium Nasal Solution, USP

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please revise your specifications for each unknown impurity in the drug substance to be . The current specification of analyze and report" is not acceptable.

2. The established bioburden specifications for the drug substance appear too wide. Please tighten or justify.

3. Please add a test and limit for Heavy Metals to the drug substance specification.

4. Regarding the tests and specifications for the drug product release:

   a. Specifications for Total Aerobic Count, Total Yeasts and Mold, and Individual Indicator Pathogens should be indicated on the Test and Specification Sheet. In addition, please add P. Cepacia as one of the individual indicator pathogens.

   b. Droplet Size limits for the Nasal Spray should include a minimum of three specifications .

   c. Please include the USP test (TLC) for related substances in addition to your est.

   d. Please utilize the APHA color test, or correlate the APHA color with the BP test.

   e. The Total Related Substances limit in the test should be tightened.

f. A Test and Specification for Fill Volume should be established.

g. The Mean Spray Weight specifications appear excessively broad. There should also be a specification for individual spray weight, in addition to the mean spray weight.

h. Regarding the Quantity Delivered per Spray; if the drug product fails the 2nd tier test, then the batch will fail. There should be no provision for 3rd tier testing.

i. An additional test and specification for Quantity Delivered per Spray through container life should be performed to demonstrate that the spray pump delivers the appropriate dose at the end of container life (200 actuations).

j. Allowance of Preservative Effectiveness testing to override the preservative content failure at release is not appropriate. There should be no significant loss of either

during processing. The lower assay limit for both of these components should be

5. The Marketed Drug Product Stability Protocol should be revised to reflect the following:

a. All tests should be performed at the 24 month time point, since a tentative 24 month expiration dating period is proposed.

b. Please perform post-approval studies on the first 3 batches in both the inverted and upright positions (annual testing of upright samples is acceptable). Elimination of upright testing through a supplement to the ANDA may be appropriate after the first 3 batches are evaluated.

c. Specifications for Total Aerobic Count, Total Yeasts and Mold, and Individual Indicator Pathogens should be indicated on the Test and Specification Sheet. In addition, please add P. Cepacia as one of the individual indicator pathogens.

d. Droplet Size limits for the Nasal Spray should include a minimum of three specifications (e 30).

e. Please utilize the APHA color test, or correlate the APHA color with the BP test.

f. The Total Related Substances limit in the test should be tightened.

g. The Mean Spray Weight specifications appear excessively broad. There should also be a specification for individual spray weight, in addition to the mean spray weight.

h. Regarding the Quantity Delivered per Spray; if the drug product fails the 2nd tier test, then the batch fails. There should be no provision for 3rd tier testing.

i. An additional test and specification for Quantity Delivered per Spray through container life on stability should be performed to demonstrate that the pump spray delivers the appropriate dose at the end of container life (200 actuations) on aged drug product.

6. Please provide revised drug substance acceptance specifications and drug product release and stability specifications considering the above deficiencies. Please also provide new Certificates of Analysis for the drug substance and drug product demonstrating compliance with the revised specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

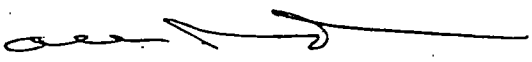
1. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

2. Please provide additional long-term stability data if available.

3. Your response must also address the labeling deficiencies.

4. Your bioequivalence information is pending review.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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7/12/00	Bio - No Further Questions
6/26/00	ANDA Original Amendment (Response to N/A CMC Deficiencies)
1/19/01	CMC Review #2; N/A MAJOR
*3/13/01	Withdrawal of the 6/19/00 ANDA Amendment
*3/29/01	ANDA Amendment (MAJOR)
*4/6/01	Request MINOR Amendment status of the 3/29/01 Amendment
*5/1/01	Telephone Amendment (Chemistry)

SHADED ITEMS - FDA Correspondences
* - Subject of the current review

10. **PHARMACOLOGICAL CATEGORY**
Anti-inflammatory

11. **Rx or OTC**
Rx

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

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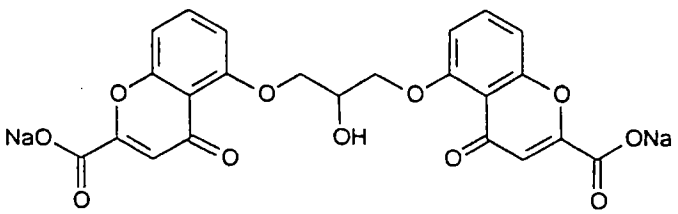

16. **RECORDS AND REPORTS: N/A**

17. **COMMENTS:** NA
- Labeling is satisfactory as per A. Payne on 5/7/01.
- Bioequivalence was found satisfactory for the 26 mL size on 5/31/00.
- Inspections are satisfactory as of 12/1/99 as per S. Ferguson of HFD-322.

18. **CONCLUSIONS AND RECOMMENDATIONS: Approve**

19. **REVIEWER:** Kenneth J. Furnkranz
DATE COMPLETED: 4/20/01
DATE REVISED: 4/23/01, 5/7/01

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chem Rev 3
4/20/01