CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-463/S-002

CORRESPONDENCE

FOOD AND DRUG ADMINISTRATION
DIVISION OF OVER-THE-COUNTER DRUG PRODUCTS
DOCUMENT CONTROL ROOM HFD-560
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: February 9, 2001

TO:

Name: Ray Dann
Phone No. 908-306-8317
Fax No. 908-306-8713
Location : Pharmacia & Upjohn

FROM:

Name: Babette Merritt
Phone No.: 301-827-2301
Fax No.: 301-827-2315
Location: 9201 Corporate Blvd.
Rockville, MD 20850

Comments/Message:

This telefacsimile is to confirm our telephone conversation today, February 8, 2001 at approximately 2:15 p.m. discussing your labeling submissions of November 22, 2000 and December 14, 2000 for NasalCrom, NDA 20-463 supplement 002. The participants were as follows: Marina Chang, Cazemiro Martin and Babette Merritt from the Division of Over-The-Counter Drug Products Division/Center for Drug Evaluation; and Ray Dann from Pharmacia-Upjohn. In this conversation, we recommended that the following changes be made to this labeling:

1. The carton labeling should be revised as follows:

   a. PDP: Either remove the emphasis (i.e., bolding) of the word "*allergy*" or bold the entire phrase *"Prevents and Relieves nasal allergy symptoms:"* to avoid consumer misunderstanding.

   b. Drug Facts panel: Under the warning subheading " Stop use and ask a doctor if", revise the bulleted statement "your symptoms worsen or you have new symptoms" to read as two separate bulleted statements (i.e., "[bullet] your symptoms worsen" and "[bullet] you have new symptoms") under this subheading.

2. The 6.0 and 6.35 pt. leading (13 mL and 26 mL package, respectively as indicated in attachment 1 of the your submission dated 11/22/00 (amendment number 6 to NDA supplement S-002), is not consistent with the leading required as set forth in 21 CFR 201.66(d)(3). We recommend that you revise the specifications for the leading as set forth in 21 CFR 201.66 (d)(3).

3. Additional directions should be provided under the heading "SPRAY PUMP DIRECTIONS" that assists the healthcare provider when inserting the nozzle of the product into the nostril of a very young child. In addition, as part of the directions, a statement needs to be included that instructs the healthcare provider to sue caution to prevent injury to a very young child when inserting the nozzle in the child's nostril. These directions should also state that this product should only be administered to a very young child by a healthcare provider; not by the child him/herself.

4. We recommend that at the time of the next printing or within 180 days, whichever comes first, further revise the labeling as follows:

Carton right side-panel:

(i) Under the paragraph *"Nasal Allergy Symptom Prevention,"* delete the last 3 words *"with regular use"* and replaced with the phrase *" as long as you continue to use NasalCrom as directed"* to avoid consumer misunderstanding.

(ii) Under the paragraph *"Works only in your nose"*, insert the word *"nasal"* after the word *"where"* in the phrase *"where allergens attack"* for clarity.

(iii) Under the heading *"Safe,"* (a) delete the bulleted statement *"Does not contain corticosteroids, antihistamines, or decongestants"* to avoid misunderstanding that such ingredients are unsafe when used appropriately; and (b) replace the word *"through"* with the word *"throughout"* in the 6" bulleted statement to provide clarity.

Package insert:

(i) In the first paragraph under the heading *"WHAT MAKES NASALCROM UNIQUE?"*. insert the word "nasal" before the word *"allergies"* and insert the words *"nasal allergy"* before the word *"symptoms"* to provide further clarification. In addition, replace the phrase *"with regular use"* with *"as long as you continue to use NasalCrom as directed"* to specify the frequency of use and therefore, avoid consumer misunderstanding.

(ii) Under the subheading *"Safe,"* replace the word *"through"* with the word *"throughout"* in the 6th bulleted statement to provide clarity.

Please revise the labeling as discussed in our teleconference dated February 8, 2001 and submit draft labeling for our review and comment.

Thank you.

APPEARS THIS WAY
ON ORIGINAL

PHARMACIA & UPJOHN COMPANY

Pharmacia & Upjohn Consumer Healthcare
100 Route 206 North, Peapack, NJ 07977
Office of:
Raymond E. Dann, Ph.D.
Director, Regulatory Affairs
Telephone No: (908) 306-8317
Telefax No: (908) 306-8713

June 27, 2000

Dr. Charles J Ganley
Division of OTC Drug Products (HFD-560)
Attn: Document Control Room
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NasalCrom® Nasal Solution
NDA 20-463
Response to FDA Requests in the June 27, 2000 Teleconference Regarding NDA Supplement S-002 "Pediatric Study Reports - Pediatric Exclusivity Determination Requested"

Dear Sir/Madam,

As agreed upon in the June 27, 2000 Teleconference between FDA and Pharmacia & Upjohn (P&U), we are providing written confirmation of our response to the following 4 items addressed during the teleconference:

1. Drug Facts Labeling:

[redacted]

2. Package Insert, Carton Side Panel, and Immediate Container Labeling:

[redacted]

Package Insert: [redacted]

P&U Response: We agree to these changes

3. Principle Display Panel (PDP)– Allergy Prevention Descriptor

FDA Request: The agency has proposed the descriptor, "Nasal Allergy Symptom Prevention", to replace the sponsor's currently used term, "Allergy Prevention", below the statement of identity.

P&U Response: We need to have the opportunity to conduct consumer testing on the comprehension of this term vs other options.

4. Justification of the Children's NasalCrom product: [redacted]

P&U Response: We need more time to fully understand the impact of this request.

Because of the need to further evaluate points #3 and #4 above, we strongly urge the agency to issue an "approvable" letter instead of an "approval" letter. We would agree to a time limit of 60 days for responding to you on these points such that a final approval would not be significantly delayed.

If you have any questions or comments regarding this submission, please contact Toni Ann Dudor at (908) 306-8259 or Ray Dann at (908) 306-8317.

Sincerely,

Raymond E. Dann, Ph.D.
Director, Regulatory Affairs

PHARMACIA & UPJOHN COMPANY

Pharmacia and Upjohn Consumer Healthcare
100 Route 206 North, Peapack, NJ 07977
Office of:
Toni Ann Dudor, Senior Regulatory Manager
Regulatory Affairs

Telephone No: (908) 306-8259
Telefax No: (908) 306-8713

June 26, 2000

Dr. Charles J Ganley
Division of OTC Drug Products (HFD-560)
Attn: Document Control Room
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NasalCrom® Nasal Solution
NDA 20-463
General Correspondence to NDA Supplement S-002 entitled
"Pediatric Study Reports - Pediatric Exclusivity Determination Requested"

Dear Sir/Madam,

This submission provides for our response to the FDA prototype labeling for NasalCrom® Nasal Solution provided in the FDA telefaxes dated June 14, 2000 and June 22, 2000.

We propose the following revisions to the FDA prototype labeling for NasalCrom® Nasal Solution:

DRUG FACTS LABELING:

Below are three additional warnings proposed by FDA and how they appear in Drug Facts labeling:

Warnings

[redacted]

We propose that the above warning statements be consolidated and relocated directly under the heading "Warnings", subheading "Allergy alert:" as provided for in 21 CFR 201.66(c)(5)(ii)(A). The revised warning would read as follows:

> **Warnings**
>
> **Allergy alert:** if shortness of breath, wheezing, chest tightness, hives, or swelling of the mouth or throat occurs while using this product, stop use and ask a doctor. You may be allergic to NasalCrom and require further medical attention. Do not use NasalCrom if you are allergic to any of its ingredients.

The proposed revisions to the Drug Facts labeling are provided in **Attachment 1**. The original FDA prototype labeling appears first, and the sponsor revised labeling appears last. The sponsor revisions are formatted in *italics* for convenience in FDA review. The final printed labeling text will be formatted using the permitted font sizes and types outlined in 21CFR 201.66(d).

PACKAGE INSERT TEXT:

A summary of the proposed revisions is as follows:

[redacted]

CARTON LABEL TEXT:

A summary of the proposed revisions is as follows:

IMMEDIATE CONTAINER LABEL TEXT:

There are no other revisions to the immediate container label text proposed by the FDA.

The proposed immediate container label is provided in **Attachment 4**. The original FDA prototype labeling appears first, and the sponsor revised labeling follows. The sponsor revisions are formatted in *italics* for convenience in FDA review. The final printed labeling will contain regular font style text.

CARTON PRINCIPLE DISPLAY PANEL (PDP):

FDA has communicated that the phrase "Allergy Prevention" on the NasalCrom® principal display panel (PDP) implies an allergy "cure" and has requested we revise our PDP to communicate the concept of "nasal allergy symptom prevention". As requested, we have revised the principal display panel (PDP) to remove the phrase "ALLERGY PREVENTION". We have replaced this phrase with the proposed text "ALLERGY". In addition, we have modified the "Prevents and Relieves" phrase on the PDP to read "Prevents and Relieves Nasal Allergy Symptoms". We believe this properly communicates the use of NasalCrom for "nasal allergy symptom prevention", rather than "allergy prevention" or "cure".

A copy of the revised PDP is provided in **Attachment 5.**

In the FDA teleconferences dated May 16, 2000 and June 20, 2000, FDA has questioned the justification for having a separate product labeled "Children's NasalCrom" and a separate product labeled "NasalCrom" when both products are identical in formulation and strength. FDA has stated that children's medications are labeled as such as they typically differ in formulation (chewable, flavored for children, etc) or are a lower dose/strength than the adult version.

NasalCrom is not typical of other medications because product does NOT require a change in formulation in order for children to use the product. NasalCrom is a topical nasal spray and its administration in children does not depend on ability to swallow a tablet or capsule or a better tasting formula. NasalCrom is also not typical of other medications because it has been demonstrated as being safe and effective in children as young as 2 years of age, at the SAME strength and dose as that demonstrated to be safe and effective in adults. Therefore, NasalCrom does NOT require a reduction in dose or strength in order for children to use the product.

Because NasalCrom is a nasal spray, the "product" actually incorporates two elements: the nasal solution + the spray pump. What justifies a separate Children's NasalCrom product is the children's grip that is provided in the Children's NasalCrom package that is NOT provided in the regular NasalCrom package. The fact that the children's grip is attached to the pump by the consumer, and not pre-assembled, hardly makes Children's NasalCrom identical to regular NasalCrom. When the consumer slides the grip over the nozzle and snaps the grip into place, the spray pump becomes a unique children's spray pump, which differs from the adult pump. The grip on the container makes the spray pump easier to handle and use by children who are able to self-administer the product. When the children's grip and spray pump snaps together, this combination forms the children's spray pump and therefore, makes Children's NasalCrom a true children's product.

In our view, nothing in the Children's NasalCrom labeling or packaging expresses or implies that the drug formulation is different from that of regular NasalCrom. Rather, the Children's NasalCrom packages merely convey to the consumers that if they are buying the product for a child's use, they should buy the package with the children's grip.

We look forward to your comments on our proposed labeling. If you have any questions or comments regarding this submission, please contact Toni Ann Dudor at (908) 306-8259 or Ray Dann at (908) 306-8317.

Sincerely,

Toni Ann Dudor
Senior Regulatory Manager

Suppl amen
S-002 Bm
ORIGINAL

PHARMACIA & UPJOHN COMPANY

Pharmacia and Upjohn Consumer Healthcare
100 Route 206 North, Peapack, NJ 07977
Office of:
Toni Ann Dudor, Senior Regulatory Manager
Regulatory Affairs

Telephone No: (908) 306-8259
Telefax No: (908) 306-8713

October 27, 1999

Dr. Charles J Ganley
Food and Drug Administration
Division of OTC Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Attn: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

RE: NasalCrom™ Nasal Solution
NDA 20-463
Amendment No. 1 to NDA Supplement S-002 entitled "Pediatric Study Reports - Pediatric Exclusivity Determination Requested"

Dear Dr. Ganley,

This Amendment provides for the submission of the following information requested by FDA during the October 15, 1999 teleconference between Babette Merritt, Marina Chang, Linda Hu (FDA) and Pharmacia & Upjohn in support of the August 19, 1999 NDA Supplement (S-002) entitled "Submission Of Pediatric Study Reports – Pediatric Exclusivity Determination Requested":

- Item 1 Index
- Literature Review and Analysis
- Listing of Spontaneous Adverse Events (January 1, 1997 thru October 3, 1999)

The requested information in this Amendment is provided in 2 Volumes and is presented as follows:

Item 1: Index ..... Volume 1

Item 9: Safety Update - Section A: Literature Review & Analysis ..... Volume 1
- Section B: Spontaneous Adverse Events ..... Volume 2

Item 13: Patent Information ..... Volume 2

Item 14: Patent Certification ..... Volume 2

Item 16: Debarment Certification ..... Volume 2

If you have any questions or comments regarding this submission, please contact Toni Ann Dudor at (908) 306-8259 or Ray Dann at 908-306-8317.

Sincerely,

Toni Ann Dudor
Senior Regulatory Manager

cc: full copies sent under separate cover to:
Babette Merritt (HFD-560)
Marina Chang (HFD-560)
Linda Hu (HFD-560)

MEMORANDUM OF TELECONFERENCE

June 27, 2000

Corporate Building, Room S251

11:30 a.m.

Product: NasalCrom (cromolyn sodium)

NDA: 20-463/S-002

Applicant: Pharmacia-Upjohn

Project Manager: Babette Merritt

FDA Participants:

Division of OTC Drug Products, HFD-560

Marina Chang, R.Ph., Team Leader
Cazemiro R. Martin, Interdisciplinary Scientist
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager

Applicant Participants:

Pharmacia-Upjohn

Raymond E. Dann, Ph.D., Director, Regulatory Affairs
Toni Dudor, Senior Regulatory Manager
Ronald Transic, Clinical Section
Jim Spindlick, Clinical Section

TOPIC: Telephone discussions between the Division of Over-the-Counter Drug Products (DOTCDP) and Upjohn concerning the applicant's 6/26/00 telefacsiimile response to the Agency's proposed labeling recommendation forwarded to the applicant by telefacsimile on 6/14 and 6/22/00.

1. Allergy alert:

[redacted]

2. 21 CFR 201.66: The applicant was reminded of the requirement for labeling to comply with this cited regulation.

3. Package Insert (submitted on 6/26/00):

[redacted]

c. Fax page number 24: Under the "Nasal Allergy Symptom Prevention," insert the word "nasal" before the word "allergies."

4. Tradename:

The applicant stated that its internal staff has not come to consensus with regard to the tradename issue and is considering additional marketing survey for name recognition. However, the applicant will accept the Agency's recommended tradename (i.e., NasalCrom Nasal Allergy Symptom Prevention) to support an approval action.

5. Children's product:

The Agency stated that it does not agree with the applicant's rationale for the OTC availability of a separate Children's NasalCrom product, as stated in the 6/26/00 correspondence. Subsequently, the applicant agreed not to market two separate products, specifically, one product labeled exclusively for children and another product labeled for adults.

6. Other comments:

The Agency indicated that an approval action may be possible for this supplemental new drug application. The applicant was requested to formally respond to the issues discussed during this teleconference. If there is mutual agreement on the resolution of the outstanding issues, the Agency will send the applicant a facsimile specifying elements that need to be included in a letter of commitment.

The applicant agreed and said they will send a formal response to the Project Manager.

/S/

Babette Merritt
Project Manager
Minutes Preparer

/S/

Maria Rossana. R. Cook, M.B.A.
Supervisory Project Manager
Concurrence

JUN 26 2000

MINUTES OF A TELECONFERENCE

June 20, 2000

Corporate Building, Room S200A

10:30 a.m.

Product: NasalCrom (cromolyn sodium)

NDA: 20-463/S-002

Sponsor: Pharmacia-Upjohn

Project Manager: Babette Merritt

FDA Participants:

Division of OTC Drug Products, HFD-560

Charles Ganley, M.D., Director
Linda M. Katz, M.D., M.P.H., Deputy Director
Linda Hu, M.D., Medical Officer
Marina Chang, R.Ph., Team Leader
Cazemiro R. Martin, Interdisciplinary Scientist
Maria R. R. Cook, M.B.A., Supervisory Project Manager

Sponsor Participants:

Pharmacia-Upjohn, Regulatory Affairs

Toni Dudor, Senior Regulatory Manager
Edward M. Block, Ph.D., Clinical Trials Conduct Leader
James R. Spindler, M.D., Medical Advisor

Objective: To discuss the package insert and our concerns for the principal display panel for NasalCrom Allergy Prevention Nasal Spray and Children's NasalCrom Allergy Prevention Nasal Spray.

Discussion: The Division of Over-the-Counter Drug Products (OTC) contacted Pharmacia-Upjohn to discuss the following items in the labeling for NasalCrom:

1. Package Insert:

In response to the sponsor's submission dated June 4, 2000, the Agency does not agree that the changes in the package insert are minor editorial changes. The package insert is considered labeling and such changes as made by the sponsor require prior approval from the Agency before implementation.

A copy of the Agency's proposed labeling changes will be sent by facsimile to the sponsor on June 20, 2000.

2. Principal Display Panel (PDP):

a. Children's product:

The Agency has concerns regarding the additional product line (i.e., Children's NasalCrom Allergy Prevention). There is no difference in formulation and labeling between the "adult" and "children's" products, except for the addition of the grip device in the children's product. The sponsor should justify why a separate product name is needed for this target population.

b. Allergy prevention claim on the labeling:

This product is approved for the prevention and relief of nasal allergy symptoms. The inclusion of "Allergy Prevention" as part of the trade name on the PDP can be misinterpreted by consumers to mean that NasalCrom is a preventive medicine for all types of allergies. The Agency defers further comment on the trade name until the sponsor responds to the Agency on this issue prior to the action date (June 30, 2000).

c. Other comment:

The Agency will send the sponsor prototype for the side panels of the carton label and container label by facsimile on June 20, 2000.

d. Sponsor's question to the Agency:

The sponsor inquired about the additional warning statements (i.e., under the subheading "Stop use and ask a doctor if" the first two bulleted statements - "shortness of breath, wheezing, chest tightness", and "hives or swelling of the mouth or throat occurs").

These statements were added based on review of the safety data submitted by the sponsor and on existing foreign labeling. The Agency considers that possible allergic reactions to the product could lead to serious outcomes and should be included in the label. The sponsor agreed with the Agency recommendation.

APPEARS THIS WAY
ON ORIGINAL

/S/

Babette Merritt
Minutes Preparer

/S/

Marina Chang
Chair Concurrence

APPEARS THIS WAY
ON ORIGINAL

MINUTES OF A TELECONFERENCE

May 16, 2000

Corporate Building, Room S300

3:00 p.m.

Product: NasalCrom (cromolyn sodium)

NDA: N20-463

Sponsor: Pharmacia-Upjohn

Project Manager: Babette Merritt

FDA Participants:

Division of OTC Drug Products, HFD-560

Charles Ganley, M.D., Director
Linda M. Katz, M.D., M.P.H., Deputy Director
Linda Hu, M.D., Medical Officer
Marina Chang, R.Ph., Team Leader
Cazemiro R. Martin, Interdisciplinary Scientist
Thomas Parmelee, Pharm.D., Project Manager

Division of Pulmonary Drug Products, HFD-570

Charles E. Lee, M.D., Medical Officer
Ladan Jafari, Project Manager

Sponsor Participants:

Pharmacia-Upjohn, Regulatory Affairs

Ray Dann
Toni Dudor

Objective: To discuss and clarify naming issues of the product, NasalCrom Allergy Prevention Nasal Spray and Children's NasalCrom Allergy Prevention Nasal Spray.

Discussion: HFD-560 contacted Mr. Ray Dann and Ms. Toni Dudor at Pharmacia-Upjohn and presented the following questions concerning the name change and addition of the children's line for NasalCrom:

- The "allergy prevention" immediately following the tradename has not been approved by the Agency. When did this name change occur?
- When was the package insert changed?
- Since the package insert is part of the labeling, the sponsor was asked why they submitted these changes in the annual report.

The sponsor replied :

- The name change occurred sometime in 1998 and was submitted in the 1999 Annual Report.
- The package insert was changed at the same time and submitted in the 1999 Annual Report.
- The sponsor felt that the changes were minor editorial changes. Thus, they could be submitted in the Annual Report.

The sponsor was asked to submit a side by side comparison of the old package insert to the new package insert. The sponsor agreed.

Other questions and points of discussion:

- The children's allergy prevention product is the same as the adult product except for a handle inserted over the device. The sponsor was asked to explain how they differ, and why they should have different names?

- How long has the children's product been marketed?
- The sponsor was asked to clarify how children down to 2 years of age can self-administer this product.

The sponsor replied:

- The only difference in the children's product is that it has a hand-grip device added to the spray container.
- Parents should administer the product, not young children.
- The sponsor stated they will get back to the HFD-560 as to why the product has a different name.

HFD-560 explained to the sponsor that this product is an NDA which FDA regulates and there is approved labeling for this product. HFD-560 needs an explanation as to why there is no pre-approval for this current name change, carton and package insert labeling to the product. The sponsor's advertisements state that the product "prevents allergy." This is derived from the name of the product "allergy prevention." This statement is misleading as this product prevents and relieves nasal symptoms of hay fever and other nasal allergies. HFD-560 asked the sponsor to provide a copy of the package insert and the dates the sponsor changed the claim to allergy prevention.

Action Items: The sponsor should submit the following information to the NDA:

- Provide a side by side comparison of the approved package insert labeling with the currently marketed product package insert labeling and highlight the substitutions.

- Dates of all the labeling changes (i.e., package insert labeling, product name change and new product line).

APPEARS THIS WAY
ON ORIGINAL

/S/

Babette A. Merritt, Project Manager

Minutes Preparer

/S/

Cazemiro Martin, Interdisciplinary Scientist

Concurrence

APPEARS THIS WAY
ON ORIGINAL

5 Merit

RECORD OF TELEPHONE CONVERSATION
NDA NUMBER: 20-463, SE5-002 DATE: 4/6/00, 9:50 AM

INITIATED BY: APPLICANT:_____ FDA:_____X_____
NAME AND PERSON WITH WHOM CONVERSATION WAS HELD:

Toni Ann Dudor
Senior Regulatory Manager
Pharmacia and Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001-0199

(908) 901-8000

Reference: NDA 20-463, SE5-002

I called Ms. Dudor's office on 4/6/00 at 9:50 AM. I left a message on her answering machine. I asked for the following information:

Was the active drug product, (NasalCrom™ nasal spray) used in Protocol M\3235\0002 exactly the same as the currently marketed drug product.

I asked her to call me back with this information.

She returned the call at 11:15 AM on 4/6/00. She confirmed that the drug product used in Protocol M\3235\0002 was exactly the same as the currently marketed drug product.

She will submit a letter to the application documenting this information, dated 4/6/00.

Charles E. Lee, M.D.

cc:
Original NDA 20-463
HFD-570/Division File
HFD-570/Chowdhury/Acting Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Jafari/ CSO
HFD-560/Parmelee/CSO

APR 20 2000

MINUTES OF TELECONFERENCE
March 21, 2000
Corporate Building, Room S-227

NDA: 20-463 Nasalcrom

Project Manager: Tom Parmelee, Pharm.D.

FDA Participants:

Marina Chang, IDS Team Leader (HFD-560)
Cazemiro Martin, IDS (HFD-560)
Tom Parmelee, Project Manager (HFD-560)

Sponsor Participants:

Pharmacia & Upjohn

Edward M. Block, Associate Director of Clinical Research
Raymond E. Dann, Director of Regulatory Affairs
William Doskoczynski, Senior Packaging Engineer
Toni Ann Dudor, Senior Regulatory Manager
Diane Hrozencik, Senior Marketing Manager

Objective:

To discuss the status of requested information from the sponsor including literature review, ADR's, and marketing history of Nasalcrom. Also to discuss general labeling issues and drug facts format for OTC drug products.

Discussion:

The Agency representatives started the meeting by asking the sponsor representatives about the status of their pending submission of requested information contained in the December fax (see Attachment 1). The sponsor representatives replied that the literature review has been completed and they are targeting the middle of April for submission of the ADR's and marketing history of this product.

Agency representatives made general comments regarding labeling using the drug facts format. The new OTC labeling rule contained in the Final Rule published in March 1999 requires the outer carton or container for a given drug product to use the drug facts format. The Agency representatives commented that the term "Drug Facts" refers to the labeling information as outlined in 21 CFR 201.66. The expectations of this labeling and terminology would be reflective of the requirements as set forth by this regulation.

The sponsor had submitted "Drug Facts" labeling for both Nasalcrom Allergy Prevention and Children's Nasalcrom Allergy Prevention Nasal Sprays. Both products

are labeled down to 2 years of age. The sponsor representatives inquired about a possible labeling change (i.e. changing the age to 6 years of age). It was unclear which labeling the sponsor wished to change, the Children's Nasalcrom Allergy Prevention and/or the Nasalcrom Allergy Prevention which has currently approved labeling (not in "Drug Facts") for ages 6 to adult. Since the "Drug Facts" labeling does not require immediate implementation, the Agency representatives suggested waiting for the finalized review of the efficacy supplement to determine labeling changes that may be warranted based on the results of that efficacy supplement.

Finally, the agency representatives requested the sponsor submit samples of this product including the child grip used for drug delivery.

Action Items:

1) The sponsor is to submit the requested information (i.e. marketing history, ADR's, etc. as outlined in our IR sent December 21, 1999) with a target submission date of mid-April.
2) The sponsor is to submit a sample of the child grip used for drug delivery with this product.

/S/

Tom Parmelee, Pharm.D., Project Manager
Minutes Preparer
Division of OTC Drug Products (HFD-560)

/S/

Marina Chang, RPh., Chair Concurrence
Division of OTC Drug Products (HFD-560)

T. Parmelee

MINUTES OF TELECONFERENCE
February 22, 2000
Corporate Building, Room S-200A

NDA: 20-463 Nasalcrom

Project Manager: Tom Parmelee, Pharm.D.

FDA Participants:

Charles Ganley, Division Director, Division of OTC Drug Products (HFD-560)
Linda Katz, Deputy Division Director (HFD-560)
Linda Hu, Medical Officer (HFD-560)
Marina Chang, IDS Team Leader (HFD-560)
Cazemiro Martin, IDS (HFD-560)
Babette Merritt, Project Manager (HFD-560)
Tom Parmelee, Project Manager (HFD-560)
Charles Lee, Medical Officer, Division of Pulmonary Drug Products (HFD-570)
Ladan Jafari, Project Manager (HFD 570)

Sponsor Participants:

Pharmacia & Upjohn

Alexei Arkhipov, Director-Global Drug Surveillance (calling from Kalamazoo)
Linda Byas, LPN, Clinical Trial Specialist (calling from Kalamazoo)
Edward M. Block, Ph.D., Associate Director-Clinical Research
Ray Dann, Ph.D., Director-Regulatory Affairs
Toni Ann Dudor, Senior Regulatory Manager

Objective:

To discuss the delayed submission of the safety profile update and marketing history information for NDA 20-463 Supplement-002, requested via telefaxes from the Agency on December 21, 1999. Also, to discuss the questions from the sponsor faxed to the Agency on February 2, 2000, and the conversion of adverse event terms utilizing a single electronic dictionary (COSTART). See attachment 1 for the agenda sent in by the sponsor.

Discussion:

Initial discussion focused on the requested information contained in the fax sent to the sponsor on 12/21/99. The sponsor representatives stated that they are planning to submit the requested marketing history information as outlined. The sponsor

representatives stated that the Nasalcrom product is manufactured by [redacted] but they hold the rights to the product line. The sponsor has requested the distribution history of this product, both in the worldwide and the U.S. markets.

Regarding the electronic databases, the sponsor representatives stated that there is no current problem with putting the terms into COSTART. The sponsor representatives stated that they had submitted a FOI request to the Agency in December 1999. The sponsor had not yet received a response from the Agency regarding this request. There are approximately 4,500 events in the MEDRA system, of which approximately 66% have been incorporated into COSTART.

The next discussion focused on the questions submitted by the sponsor as shown below:

1) Sponsor Question: Please clarify if FDA would like the information for the 2<6 year old group only, or both the 2<6 year old and older age group?

Agency Response: The Agency requests the information for both age groups.

2) Sponsor Question: Please clarify if the FDA would like the information for cromolyn sodium nasal solutions/sprays only?

Agency Response: The agency requests worldwide post-marketing adverse events for nasal solutions/sprays only.

Action Items:

1) The Agency is still targeting the June deadline to issue an action letter.
2) The sponsor is to submit all requested information in pieces as it becomes available, still targeting the June deadline.

/S/

Tom Parmelee, Pharm.D., Project Manager
Minutes Preparer
Division of OTC Drug Products (HFD-560)

/S/

Linda Hu, M.D., Chair Concurrence
Division of OTC Drug Products (HFD-560)

NASALCROM™ - NDA 20-463
AGENDA FOR FDA TELECONFERENCE ON FEBRUARY 22, 2000

Company: Pharmacia & Upjohn Consumer Healthcare (P&U)

Date, Time: Tuesday, February 22, 2000 at 3pm. At approx. 3pm, FDA will call in to P&U at the following number: 908-306-5529 (Moscow Conference Room #627 at P&U Bridgewater, NJ).

Product: NasalCrom™ (cromolyn sodium) Nasal Solution - NDA 20-463

Attendees: Alexei Arkhipov, Director-Global Drug Surveillance (calling in from Kalamazoo site)
Edward M. Block, PhD, Associate Director - Clinical Research
Linda Byas, LPN, Clinical Trial Specialist (calling in from Kalamazoo site)
Ray Dann, PhD, Director - Regulatory Affairs
Toni Ann Dudor, Senior Regulatory Manager

Topic/Issues: On 12/21/99, Pharmacia & Upjohn received a fax from the FDA requesting additional Adverse Events information in support of the NDA Supplement S-002 (submitted on 8-19-99) for NasalCrom™ Nasal Solution.

After extensive investigation and research into providing the requested information, Pharmacia and Upjohn has determined that the US OTC Experience data required by FDA is currently available both electronic and paper format. The electronic data is currently in 3 different dictionaries: UMED, MEDRA, and COSTART It has been determined that the timeline for Pharmacia &Upjohn to enter and convert this data into COSTART terms as requested by the FDA and issue a final report will be approximately 4 months. Conversion of some of the data into COSTART may be able to be accomplished by scanning the existing records (hard copy) into the database. If technical problems arise with this scanning process, the 4 month timeline may need to be extended. Other AE information will be entered and converted to COSTART within this timeframe.

FDA has targeted a PDUFA review timeline of 10 months for this Supplement (FDA target end review date of June 31, 2000). We are aware that our 4-month timeline will result in a submission to FDA of the requested information sometime in May 2000. This is only 1 month prior to FDA's targeted a PDUFA review timeline of June 2000. We feel there is a need to discuss this situation/timeline in detail with the FDA during this teleconference.

Question: Refer to: First item on page 2 of the 12/21/99 Fax:

The first paragraph states a request for serious worldwide post marketing adverse events and deaths for ages 2<6. The next paragraph and 3 bullets requests presentation of information for both the age groups 2<6 year old and 6 years and older age group. It is also not specified if this information is required only for nasal solutions/sprays.

Please clarify if FDA would like the information for the 2<6 year old group *only*, or for *both* the 2<6 year old and 6 years and older age group. Also, please clarify if the FDA would like the information for cromolyn sodium nasal solutions/sprays only.

MEMORANDUM

Date: October 21, 1999

To: Linda Hu, M.D., HFD-560, Medical Officer
Linda Katz, M.D., M.P.H., HFD-560, Deputy Director, DOTCDP

From: Charles E. Lee, M.D. Charles E. Lee
Medical Officer, Division of Pulmonary and Allergy Drug Products

Through: Badrul A. Chowdhury, M.D., Ph.D., Badrul A. Chowdhury 10/25/99
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

Through: Robert J. Meyer, M.D. 10/25/99
Director, Division of Pulmonary and Allergy Drug Products

Subject: Medical Officer Consultation regarding issues with SE-002 to NDA #20-463, NasalCrom™ (cromolyn sodium) nasal spray.

General Information:
NDA#: 20-463, SE5-002
Sponsor: Pharmacia & Upjohn Company
Drug Product: cromolyn sodium nasal solution, NasalCrom™
Request from: HFD-560
Materials: Request for consultation, date 10/5/99
NDA #20-463, SE5-002

Background and Comments
A protocol for a safety and tolerance study of cromolyn sodium nasal solution in children ages ≥ 2 years to < 6 years was submitted to the FDA on 8/27/98 by the Pharmacia & Upjohn Company. The FDA made a formal Written Request to the Pharmacia & Upjohn Company on 11/24/98. The terms and conditions of the original protocol were revised in the Written Request, in an amended Written Request on 1/25/99, and were finalized in a teleconference on 4/8/99. The study was to be submitted on or before 11/1/99 to qualify for pediatric exclusivity.

A pediatric study report entitled "An Evaluation of Safety and Tolerance of Cromolyn Sodium Following the Administration of Nasal Solution to Pediatric Subjects" was submitted by the sponsor on 8/19/99 in response to the Written Request. Proposed product labeling is included in this submission. This submission is the subject of this consultation.

One clinical safety and efficacy study was submitted for review. This was a multi-center, multiple dose, randomized, double-blind, placebo-controlled, parallel group study. The duration of treatment was 4 weeks. The primary endpoint of this study was subject incidence of nasal mucosa adverse events based on physician nasal exam. Secondary endpoints included subject incidence of adverse effects, changes from baseline to end of study for vital

signs and physical examination, subject global assessment of efficacy, physician global assessment of efficacy, and changes in symptoms.

The submission includes a clinical protocol, data line listings, and a study synopsis. An index, literature review, and safety update is not included with the submission, but will be submitted by the sponsor during the review period.

The clinical study results are appropriately organized, and contain the line listings required for review. Electronic data would aid the review process. A review issue may be possible confounding of efficacy results by use of rescue medication. There appear to be no issues from the safety or efficacy standpoints that would interfere with filing.

This submission appears to be adequate for review with the exception of the index, literature review, and safety update, which are due later. In our opinion this supplement would meet ordinary criteria for filing (however, our understanding of supplements submitted to meet Written Requests is that all such applications must be filed).

cc: HFD-560/Division File
HFD-570/Division File
HFD-560/Hu/Medical Officer
HFD-570/Lee/Medical Officer
HFD-570/Chowdhury/Team Leader
HFD-560/Katz/Deputy Division Director
HFD-570/Meyer/Division Director
HFD-570/Jafari/Project Manager
HFD-560/Merritt/Project Manager