# Meeting Minutes
# Public Feedback Meeting



**Date / Time:** May 1, 2001 / 2:30 pm

**Location:** Conference Room S400
9201 Corporate Blvd., Rockville, MD

**Docket:** 78N-0301

**Topic:** Trolamine Salicylate as an External Analgesic

**Sponsor:** Chattem, Inc.
1715 West 38th Street
Chattanooga, TN 37409

**Meeting Chair:** Charles Ganley, M.D.

**Meeting Recorder:** Walter Ellenberg, Ph.D.

Charles Ganley M.D.
Walt Ellenberg Ph.D.

**Protocol No.:** CHA-TEA01-01

**Attendees:**

**Food and Drug Administration**
Jonca Bull, M.D., Deputy Office Director, Office of Drug Evaluation V
Charles Ganley, M.D., Director, DOTCDP
Linda Katz, M.D., Deputy Director, DOTCDP
Andrea Leonard-Segal, M.D., Medical Officer, DOTCDP
Gerald Rachanow, J.D., Regulatory Counsel, DOTCDP
John Lipnicki, Team Leader, DOTCDP
Nahid Mokhtari, Ph.D., IDS Reviewer, DOTCDP
Walt Ellenberg, Ph.D., Regulatory Project Manager, DOTCDP
Dan Keravich, Regulatory Project Manager, DOTCDP
Larry Goldkind, M.D., Medical Reviewer, DAAODP
Joseph Stauffer, D.O., Medical Reviewer, DAAODP
Christina Fang, M.D., Medical Reviewer, DAAODP
Joel Schiffenbaner, M.D., Medical Reviewer, DAAODP
Jyoti Zalkikan, Ph.D., Statistician, DAAODP
Barbara Gould, Regulatory Project Manager, DAAODP

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**Chattem, Inc.**
Alec Taylor, President, Chattem Inc.
William J. Durkin, MS, Manager of Product Safety, Chattem, Inc.
Blair Ramey, Director of Marketing, Chattem, Inc.
Michael Law, Ph.D., Regulatory Affairs Manager, Chattem, Inc.
Elaine Morefield, Vice President-Research and Development, Chattem, Inc.
Darcee Strube, Vice President, Clinical Research Operations, Clinical Research/Chattem, Inc.
J. Richard Tout, Ph.D., Statistical Consultant, Rutgers University/Chattem, Inc.
Alan Minsk, J.D., Regulatory Counsel, Arnall-Golden-Gregory, LLP

**Other Attendees:**

Lorna Totman, Ph.D., Director of Scientific Affairs, Consumer Healthcare Products Association
Susan Sutter, Senior Editor, "The Tan Sheet"
Steven Kishter, M.D., D.D.S., Associate Director of Clinical Research, Whitehall-Robbins
Angela Brown, Pharm. D., Manager, Novartis Consumer Health, Inc.
Cynthia Psaras, Ph.D., Associate Director, Novartis Consumer Health, Inc.

**Protocol / Title:** A Randomized, Double-Blind, Parallel, Design, Vehicle Controlled Study Evaluating the Efficacy of a Topically Applied Cream Containing 10% Trolamine Salicylate in the Relief of Pain and Discomfort of Osteoarthitis of the Knee.

**Meeting Objectives**:

1. Review the protocol submitted on February 16, 2001, filed March 8, 2001, comment no. PR 4 in docket no. 78N-0301, for its acceptance as a well-designed study to demonstrate that 10% trolamine salicylate is an effective ingredient in an over-the-counter (OTC) external analgesic drug product for temporary relief of minor aches and pains of muscles and joints associated with arthritis, simple backache, strains, and sprains.

2. Discuss the usefulness of this model in future studies to demonstrate the effectiveness of ingredients in an OTC external analgesic drug product for temporary relief of minor aches and pains of muscles and joints associated with arthritis, simple backache, strains, and sprains.

**General Comments on Trolamine Salicylate Development**

The Agency provided the following comments: It does not consider osteoarthritis (OA) to be an OTC indication. (The sponsor was informed that if it wishes to label the product

for the treatment of OA, then it should consider a New Drug Application (NDA) route for approval as a prescription product.) One properly designed and powered OA protocol may be sufficient to determine if the product is effective for the temporary treatment of minor aches and pains of arthritis, but will be insufficient to support the indication for minor aches and pains of muscles, simple backaches, strains, and sprains. Thus, we recommend two efficacy trials, one for the temporary relief of minor aches and pains of arthritis claim, and one for the muscle pain claim.

The sponsor should provide absorption studies that evaluate the maximum systemic concentration of trolamine salicylate that is achieved through absorption under the condition of proposed maximum use.

1. It is unclear if the concentrations of absorbed product, especially under conditions of chronic, maximum use, would be enough to cause salicylate toxicity (particularly with someone who uses the product in combination with oral aspirin).
2. As this is a salicylate, the agency has concerns about the possibility of occurrence of Reye's syndrome in the vulnerable population of teenagers and children (i.e., if used to relieve aches and pains from the flu).

**Comments on the Trolamine Salicylate Protocol**

1. The principal investigator should be a physician able to diagnose OA as the cause of the pain the subject is experiencing (For example, the investigator should be someone with training enough to know that OA does not always cause pain and that someone with radiographic changes of OA might in fact be having pain from a nonarthritic cause.)
   The principal investigator and his/her qualifications are not clearly stated.
2. There should be a sufficient sample size to adequately power the study.
3. The inclusion criteria should be people with <u>any</u> functional capacity classification (the OTC marketplace for a product like this would probably attract people with all degrees of OA). The sponsor should consider opening the study to those who experience moderate pain levels. By limiting the study to those individuals who experience only mild pain, the ability to demonstrate product efficacy may be compromised.
4. The agency recommends that the sponsor conduct two efficacy trials. One addressing the claim of temporary relief of minor aches and pains of arthritis, and one which addresses the claim for muscle pain. These studies would support each other. If one study fails, neither claim may be supported.
5. The protocol did not clearly address the use of rescue medication during the washout period. The sponsor should adequately address issues regarding the washout period and specify which medication would be utilized (if any). Moreover, the rescue medication should not be permitted within 12 hours of assessment to prevent confounding the results of the study.
6. The protocol needs to clearly address the amount of product to be applied to the affected area (e.g., knee). The protocol also needs to define the maximum use

condition (the quantity of product that can be applied safely, the size of the treatment area, and the number of treatment areas that can be treated at once or in one day).

7. If the product is supposed to provide acute relief, the protocol should establish efficacy for the acute pain relief endpoint. The efficacy endpoint should be at least within the first 24 hours, and perhaps within an hour of using the first dose. The study duration (21 days) is acceptable for efficacy. The agency encourages the sponsor to extend the trial to 6 months by adding an open label portion. The information gathered from the 6-month extension would be beneficial in providing actual use and safety data for the product. It is suspected that, if the product is efficacious, people will use it on a chronic basis.
8. The use of patient diaries was also encouraged for the studies.
9. The physician global assessment is unnecessary. If this product were to be OTC, the subject's global assessment would provide better information.

10. Exclusion Criteria

- All types of inflammatory arthritis should be excluded.
- The study should include a population that requires chronic daily therapy with a nonsteroidal anti inflammatory drug (NSAID) and/or analgesic, because this population is likely to try topical therapy as an adjunct to their systemic medication. The sponsor should consider stratifying the study – one group on stable dose chronic NSAID Rx and one group with intermittent NSAID use that have washed out prior to entry.
- Individuals who have taken an oral NSAID or analgesic within a minimum of one week from baseline assessments should be excluded from the study. Forty-eight hours may be insufficient time to overcome the NSAID effects.
- Patients with liver disease should be excluded if the sponsor chooses to use acetaminophen as the rescue medication.
- Subjects with inflamed skin on the knee should be excluded.

11. History Forms

- The statement addressing the date of onset of OA in the subject history form may not be useful as most individuals cannot identify this date.

12. Statistical Power

- The agency stated that it was essential that the studies incorporate enough subjects to allow detection of potentially small efficacy differences in treatment populations. When a single study is used to support a claim, the results should be convincing. (See: Providing Clinical Evidence of Effectiveness for Human Drug Biological Products Guidance)

- In addition, the protocol needs to properly describe the process of randomization to allow for validation during the review process.

- If the sponsor has more than one primary efficacy endpoint (relief within 24 hours and relief at 21 days), $\alpha$ should be adjusted for multiple endpoints.

13. The agency further stressed the importance for conducting multi-center studies for each of the suggested protocols (arthritis pain and muscle aches and pain).

    At the close of the meeting, the agency invited the sponsor to submit the revised protocol(s) for comment before beginning the studies.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: June 15, 2001

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 78N-0301

TO: Dockets Management Branch, HFA-305

[X] The attached material should be placed on public display under the above referenced Docket No.

[ ] This material should be cross-referenced to Comment No. _____

Charles J. Ganley, M.D.

Attachment

Minutes of Meeting
May 1, 2001
Trolamine Salicylate
as an External Analgesics