DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Mr. Michael Law
Chattem Inc.
1715 West 38th Street
Chattanooga, Tenessee, 37409

6120 '00 OCT 10 A9:44

OCT - 3 2000

Re: Docket No. 78N-0301 comments No. CP, AMD2, RPT, AMD6, C86, C92, AMD7, C94, RPT2, SUP4, SUP5, CP10, CP11, and CP12

Dear Mr. Law:

It is our understanding that Chattem Inc. has acquired Thompson Medical Company, Inc. and its line of products. One of these products is Aspercreme, which contains the ingredient trolamine salicylate. Thompson Medical Company Inc. submitted information on this ingredient for agency review. Our letter of response was returned by the post office.

Accordingly, we are forwarding our letter in response to citizen petitions (CP) and data submitted by Thompson Medical Company, Inc. The petitions and comments are filed under Docket No. 78N-0301 (the rulemaking to establish a monograph for OTC external analgesic drug products) in the Dockets Management Branch. Please contact Elizabeth F. Yuan, R.Ph., Regulatory Project Manager, at 301-827-2222 if you have any questions.

Sincerely yours,

Charles J. Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center of Drug Evaluation and Research

Enclosure

78N-0301

AET 88

CC:

HFA-305/ dockets management branch Docket No. 78N-0301
HFD-560/Ganley/Katz/Rachanow/Lipnicki/Mokhtari/Yuan

Drafted by E. Yuan 9-21-00

Revised by G. Rachanow 9-24-00

Concurred by C. Ganley 9-25-00

Finalized by E. Yuan 10-2-00

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 18 2000

Dana Quinn Rothacker, Ph.D.
Thompson Medical Company, Inc.
222 Lakeview Ave., 17th Floor
West Palm Beach, Florida 33401-6112

Re: Docket No. 78N-0301
Comments No. CP, AMD2, RPT, AMD6, C86, C92, AMD7, C94, RPT2, SUP4, SUP5, CP10, CP11, and CP12

Dear Dr. Rothacker:

This letter responds to a citizen petition (CP) and data submitted by Thompson Medical Company, Inc. on November 24, 1981, and additional comments to support the petition submitted on April 28, 1982 (AMD2), November 12, 1982 (RPT), June 16, 1983 (AMD6), February 8, 1984 (C86), November 28, 1984 (C92), February 5, 1985 (AMD7), October 24, 1985 (C94), October 16, 1985 (RPT2), February 28, 1986 (SUP4), April 22, 1986 (SUP5), December 27, 1993 (CP10), April 15, 1994 (CP11), and July 12, 1995 (CP12). The petitions and comments are filed under Docket No. 78N-0301 in the Dockets Management Branch.

The four citizen petitions (CP, CP10, CP11, and CP12) requested that the agency reopen the administrative record for the rulemaking for over-the-counter (OTC) external analgesic drug products to consider data to support 10 percent trolamine salicylate as an effective topical analgesic for temporary relief of minor aches and pains of muscles and joints associated with arthritis, simple backache, strains, and sprains. The CP and other supplemental information were submitted in response to the agency's letter of June 19, 1981 (LET004) containing comments on your company's February 26, 1980 (C0007) comments to the December 4, 1979 advance notice of proposed rulemaking for OTC external analgesic drug products (44 FR 59768). According to the June 19, 1981 letter, the agency determined that the data were inadequate to support the effectiveness of 10% trolamine salicylate as a topical analgesic. The agency discussed the information in the June 19, 1981 letter in the tentative final monograph for OTC external analgesic drug products (February 8, 1983, 48 FR 5852 at 5855).

The Division of OTC Drug Products (the "Division") has reviewed the data and other information submitted through 1995 and has determined that they are inadequate to support the effectiveness of 10 percent trolamine salicylate as an OTC topical analgesic drug product and that the petitions should be denied. The Division has the following specific comments, which address only data in studies related to the effectiveness of trolamine salicylate as a topical analgesic. The consumer or health-care professional's testimonials, surveys, market data, etc., lack the sufficient detail that permit scientific evaluation and are not considered adequate to establish effectiveness. (See 21 CFR 330.10(a)(4)(ii).)

78N-0301

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Comments on Data in CP

1. Included with the petition were studies by Altschuler and Golden, Patel, Chapelle, Rabinowitz, St. Thomas Institute, and Hill Top Research Institute. These studies were previously evaluated by FDA in our letter of June 19, 1981 (LET004) and were not found to support the effectiveness of trolamine salicylate as a topical analgesic for musculoskeletal pain due to arthritic conditions. For additional comments on these studies, see I.B. and II.B, C & D. below.

2. The petition was divided into three parts: I. Rationales of Efficacy, II. Clinical Trials, and III. Market and Consumer Experiences.

I. CP - Rationales of Efficacy

A. A study by Rabinowitz et al. was described as an illustration of the action of trolamine salicylate and compared the amount of salicylate delivered to the site of pain by (a) orally ingested aspirin and (b) topically applied trolamine salicylate, in dogs and humans. The authors concluded that significant tissue and intra-articular salicylate levels can be achieved with topical trolamine salicylate.

Dog Study (CP)

Five beagle dogs received a capsule of 500 mg ^{14}C-aspirin by mouth. A second group of five dogs received 10 gm of trolamine salicylate cream containing ^{14}C-salicylate of the same total equimolecular amount and radioactivity as the aspirin capsule. Blood and urine samples were taken from the anesthetized dogs after 30 and 60 minutes and tissue samples after 1 hour.

The blood level of ^{14}C-salicylate at 30 and 60 minutes was 10 to 100 times lower after topical trolamine salicylate than after an equimolecular quantity of oral aspirin. There was a higher concentration of salicylate in skin, ligament, tendon, cartilage, fasica and fat pad after topical application than after the oral aspirin, suggesting that the topical trolamine salicylate was primarily absorbed by direct penetration. Adjacent muscle tissue showed an average of 20 times greater salicylate concentrations than from oral aspirin. Equal salicylate concentrations were noted in bone, synovial fluid, and synovium.

Comments (Dog Study)

1. Details have not been provided as to how tissue samples were collected. Also, procedures were not described for avoiding contamination of the skin from other tissues (i.e., was a bone saw used) or for the type and size of equipment used to homogenize the dog femur samples.

2. Inadequate controls were used. Because of the unique tissue distribution reported, certain additional procedures should have been added. For example, it is known that massage and exercise can increase the blood flow to muscles. Also, the shaving process itself may cause similar increases in blood flow. Therefore, similar shaving and massage techniques should be employed in topically treated animals.

Human Study (CP)

The purpose of the study was to examine the local, articular, and systemic absorption of oral aspirin and topical trolamine salicylate using radioisotope techniques. Six male subjects (55 to 62 years of age), with seropositive adult onset rheumatoid arthritis having active synovitis knee with recurrent effusions requiring frequent aspiration, were studied. Each subject received a 500 mg capsule of ^{14}C-labeled trolamine salicylate cream, which was gently massaged into the skin of one knee over a surface of 25-30 cm.

Because trolamine ^{14}C-salicylate was found in the synovial fluid it was concluded that it was percutaneously absorbed through the skin, and concentrations continued to increase at 2 hours. The synovial fluid ^{14}C-salicylate concentrations at 1 and 2 hours after cream treatment were about 60 percent of those at 1 and 2 hours after aspirin treatment. Blood ^{14}C-salicylate concentrations remained low after cream treatment and were four to eight times lower than observed with the aspirin treatment. No treatment-related adverse effects were reported. The study authors concluded that the low blood concentrations and the significant synovial fluid salicylate concentrations, following cream treatment, supported direct percutaneous transynovial penetration of trolamine salicylate cream.

Comments (Human Study)

1. The detailed protocol for the study, which included the design and conduct of the study, was not submitted for review. The exact treatment administration times, conditions (food vs. fasting for capsule treatment, etc.), sampling procedures, and techniques of collecting blood and synovial fluid were not presented. Additionally, details of urine sampling collection intervals were not provided. With topical application, the higher salicylate level detected in the synovial fluid may actually be a reflection of drug being pushed by the needle from the skin and not a reflection of what penetrates or is absorbed through the skin.

2. The design of the study was not balanced with regard to the sequence of the capsule and cream treatment administration. A balanced design in this regard should have been employed to determine if the treatment sequence may have created differences in the results. Due to study design, it would not be possible to assess treatment or sequence interactions.

3. The study called for salicylate-stabilized subjects to abstain from salicylate intake for at least 6 hours prior to treatment administration. The study should have required negligible patient salicylate levels. To achieve this, a salicylate washout period of much greater than 6 hours would have been necessary. Existing salicylate concentrations in the subjects would not be expected to affect absorption of the ^{14}C-salicylate treatments. However, it is possible, depending upon existing salicylate concentration at the time of treatment administration, that blood clearance and urinary excretion could be different for each subject due to saturable elimination processes.

4. Because the study was to compare the bioavailability of equimolar salicylate doses applied topically and taken orally, the trolamine ^{14}C-salicylate 10 percent cream should have been prepared using the Aspercreme vehicle without the existing unlabeled drug being present.

5. The labeled trolamine salicylate for topical application was prepared by mixing 10 percent trolamine salicylate (Aspercreme, Thompson Medical Co.) with trolamine ^{14}C-salicylate. If a 10 percent trolamine ^{14}C-salicylate labeled cream was prepared as stated, the actual concentration of total trolamine salicylate (labeled and unlabeled) would have been approximately 20 percent. This 20 percent concentration represents almost double the concentration (of the applied dose) of the marketed product and may alter the absorption rate (i.e., amount/time) of the labeled and unlabeled trolamine salicylate.

6. The application of the cream treatment was incomplete because 20% remained on the gloves. Thus, only 8 of the 10 grams were delivered to the epidermal application area. A correction factor of 80 percent was incorporated into the calculation of equivalent capsule and cream ^{14}C-salicylate dosage. This procedure may have resulted in a larger ^{14}C-salicylate dose being applied to the skin than was present in the capsule. A better approach would have been to make a weight determination of cream remaining on the application glove and then make an appropriate determination of the actual dose of cream delivered to the skin.

7. The report indicated that only four of the six subjects had biologic fluid samples collected and analyzed for ^{14}C-salicylate at 2 hours after treatment administration. It is not clear why four subjects were chosen for sampling, and if the same four were sampled in both periods.

8. The exact formulations and lot identification were not submitted for the capsule and cream preparations used in the tracer study for the commercial Aspercreme formulations.

9. The submission did not include the radionuclide tracer methodology utilized in the analysis of the collected human biologic fluids. Further, validation data pertaining to linearity, reproducibility, accuracy, and sensitivity of the analysis were not submitted. Without this information, the study could not be adequately evaluated.

10. The study concluded that the low labeled salicylate blood levels as compared to the labeled salicylate synovial fluid levels support the contention of direct percutaneous/transynovial absorption after topical treatment. Additional information about the assay is needed to support this conclusion.

11. The conclusion that the labeled oral aspirin was well-absorbed into the blood and synovial fluid was not supported by the study results. The design of the study did not allow for serial blood and synovial fluid sampling over time to characterize the extent and rate of absorption (i.e., AUC, Cmax, Tmax) of labeled salicylate into the blood and synovial fluid after either the topical or oral treatments. Also the lack of serial sampling did not allow for determination of clearance of the labeled salicylate (or metabolites) from the blood or synovial fluids. Additionally, urine excretion of tracer could not be used as a measure of comparative bioavailability for clearance as the serial incremental urine collections, which would have allowed for incremental and total urinary tracer elimination determination, were not achieved.

Recommendations

Because of the aforementioned design deficiencies, we find that the tracer comparative bioavailability study (Rabinowitz et al.) does not support the conclusion of direct percutaneous/transynovial penetration of the trolamine salicylate component of the Aspercreme product into the synovium after topical administration. Therefore, the study does not support the product claim of "activity through absorption" or of the dosage recommendation to "massage into painful areas until thoroughly absorbed."

A claim of direct penetration of Aspercreme (trolamine salicylate) into underlying tissues after topical administration requires an acceptable comparative study which adequately characterizes the absorption, distribution, and elimination of molar equivalents of topical and oral salicylate treatments. The Division will review and provide comments on a protocol, if submitted, for such a study.

B. A rabbit study from the St. Thomas Institute compared topical trolamine salicylate applied to rabbit skin with orally ingested aspirin. The study reported trolamine salicylate's ability to penetrate through the rabbit's skin to the underlying muscle and give a higher concentration than the oral aspirin in the underlying muscle.

Only two animals were used and only two time points were studied. Further, muscle/serum ratios were not consistent with what is known about the distribution of such compounds.

C. A bioavailability study from Hill Top Institute was represented as additional data on the absorption and penetrability of trolamine salicylate and the recovery of topically applied salicylate from blood and urine samples.

This study previously had been submitted and evaluated by the agency in our letter of June 19, 1981 (LET004). We have no additional comments.

D. A pilot study by Zurier was submitted in which mononuclear cells from three healthy subjects were isolated and assayed for prostaglandin E levels. Trolamine salicylate was reported to inhibit prostaglandin production by the cells.

The methodology of the study was not provided in any detail. Therefore, the Division is unable to use these in vitro experiments on mononuclear cells from normal subjects to support the clinical effectiveness of topical trolamine salicylate for relief of arthritic pain.

E. The petition referred to studies by Higgs, Kantor, Vane, and Weissman to support a causal relationship between prostaglandin and the inflammatory process. These studies were not provided.

II. CP - Clinical Trials

A. The Golden study was evaluated in our letter of June 19, 1981. Tabulations not previously submitted were included in the CP. The additional data tabulations, however, do not correct two basic problems: (1) the power of the study to detect clinically important differences, and (2) the flaw of not having a placebo group (i.e., a group receiving placebo aspirin and a group receiving placebo trolamine salicylate).

B. The Golden and Altschuler study was a double-blind comparison of the effect of a single dose of trolamine salicylate and placebo in alleviating pain related to musculoskeletal symptoms.

In answer to our comments in the June 19, 1981 letter on the combining of data from two investigators, your company stated that the findings of both investigators were pooled in one report because the study was conceived and implemented as a single multisite investigation. In answer to our comment regarding the non-availability of complete data on pain relief at specific time points and patient subgroups, your company responded that the "hundred of statistically analyzed comparisons between trolamine salicylate and placebo in the Golden-Altschuler data clearly documented trolamine salicylate superiority to placebo in relief of pain." However, upon review of the data provided, despite the trends favoring Aspercreme, there was no significant difference between Aspercreme and placebo.

C. The Patel study was a double-blind investigation of trolamine salicylate involving 50 subjects experiencing a considerable range of symptoms. Eighty-four percent reported improvement.

No new information was provided on the Patel study. Professor Patel's letter lacked detailed description of the study methodology. The case report forms submitted do not show evidence that there was a control group or even a control period of any kind.

D. The Chappelle study was a double-blind investigation of trolamine salicylate's effectiveness for relieving pain and/or trauma in muscles and ligaments in 23 subjects. The study concluded that trolamine salicylate was very effective for conditions such as lumbago, stiff neck, chronic skeletal pain, knee ligament problems, and tendon symptoms.

Our comments pertaining to the Patel study (see II.C. above) also apply to the Chappelle study.

E. Howell conducted a single-blind study of 42 subjects with pain associated with either chronic rheumatoid arthritis or osteoarthritis. Subjects received a placebo cream for 4 weeks then a cream containing 10 percent diethylamine salicylate. Another study with the same subjects compared the salicylate cream with ephedrine and adrenaline creams ($p < .001$).

This study is not relevant because trolamine salicylate was not the drug studied.

Addenda to CP

A. **AMD002** consisted of a report of consumer responses concerning Aspercreme (trolamine salicylate) and a published reprint of the Rabinowitz et al. study (submitted twice previously). The published version of the Rabinowitz et al. canine and human penetration studies contained no additional data to the previously submitted versions. The study was fatally flawed in its design. The statistical analysis was deficient because it was not adequately powered and failed to specify analysis a priori.

B. **RPT** consisted of the Iber-Shamszad study, a double-blind, placebo-controlled study that compared pain relief observed during 1 week of treatment with trolamine salicylate (Aspercreme) applied 4 times daily, compared with 325 mg aspirin given 4 times a day, in 50 subjects with arthritis having moderate to severe pain. Subjects were evaluated twice by the investigator. Trolamine salicylate was reported to be as good as, if not better than aspirin, in the relief of pain; 24 percent of the subjects on trolamine salicylate reported relief within 15 to 20 minutes after the first application compared with 8 percent of the subjects on aspirin. More frequent adverse effects were reported with aspirin than with trolamine salicylate. The global evaluation by the investigator of the total response to the treatment, including the daily decrease in pain reported by the subjects was as follows: For trolamine salicylate, 12 percent excellent,

52 percent good to better, and 76 percent fair; for aspirin, 8 percent excellent, 44 percent good to better, and 68 percent fair.

Our tabulation of the data in the Iber-Shamszad study showed that 41 of the 50 subjects were concomitantly taking 11 nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin during the study (one patient taking 2 NSAIDs concurrently), which may have influenced the results. Further, the results were not found to be statistically significant for any of the variables assessed.

C. **C86** was a partial resubmission of the Rabinowitz et al., Ibex and Shamszad, and Golden studies (see previous comments). The submission also included an article by Guy and Maibach that contained no new or independent data. The article was based on the published studies by Rabinowitz, Baldwin, and Golden. The remaining material was comprised of surveys and testimonials, which do not contain the scientific data to establish drug effectiveness.

D. **C92** contains studies by Rabinowitz, Baldwin, et al. and published reports of Guy and Maibach, Vane, Lim, et.al., Kantor, Zurier, and Arek. Dr. Rabinowitz explained a method used to eliminate any possible contamination with salicylate ointment residue of the biopsy needle. The method was proposed as an addendum to his earlier study and in response to the agency's question raised at an April 25, 1983 feedback meeting, regarding the probable availability of trolamine salicylate due to contamination in the tissues from the injection needle.

As previously discussed, we have two primary concerns with the Rabinowitz study:
(1) penetration - because of possible carriage of the drug into joint space from the needle going through the external cream, and (2) measure of pain relief - whether it is due to the drug or mechanical manipulation (massage).

The Baldwin et al. study is similar to the Rabinowitz et al. study. Using ^{14}C-labeled trolamine salicylate, absorption into the underlying skeletal muscle of a pig was measured at 0.5 and 2 hours. As with the Rabinowitz et al. study, the Baldwin et al. study has methodological problems because of extensive tissue manipulation.

The published reports by Guy and Maibach, Vane, Lim, et.al., Kantor, Zurier, and Arek have not been reviewed separately in greater detail because, based on our preliminary review, they were determined not to contain human, animal, or in vitro data relevant to the claims being pursued for trolamine salicylate. The Iber and Shamszad report has already been discussed in this letter.

E. **AMD7** is a published absorption study in human and canine knee joints by Rabinowitz and Baker and is similar to the first Rabinowitz et al. study. The purpose of this report was to determine the effects of sex, the concentration of the active ingredient with ointment, and the absorption pattern of each of the two components of trolamine salicylate salt on tissue salicylate levels. In addition, tissue salicylate concentrations were determined by

autoradiographic techniques. Human studies were designed to confirm or reject previous work and to determine whether prolonged bed rest affected transdermal absorption

Our comments regarding this study were included under CP above, comments A-D.

F. **C94** contained a summary of previously submitted data, reports and copies of three published studies (two previously submitted studies and a new study by Politino et al.). Modified labeling for Aspercreme was also included.

The Politino study was a double-blind, randomized, placebo-controlled, single center, two-observer, 7-day trial comparing 10 percent trolamine salicylate cream with a placebo cream in subjects who had participated in vigorous sports-related activity, such as running, bicycling, dancing, etc., which induced muscle and/or joint soreness. Ninety volunteers (18 to 60 years of age) with moderate to severe discomfort were enrolled in the study.

Subjects provided daily assessment of pain level: pain relief, activity level of treatment, and overall evaluation of pain relief. Trolamine salicylate treatment was reported to be more effective than placebo treatment for alleviating delayed-onset arthralgia/myalgia. These differences were reported as statistically significant ($p = 0.05$) in favoring trolamine salicylate for observer global evaluation and total drug effect on study days five through seven. Thirty-nine percent of the trolamine salicylate group said they received good-to-excellent relief from their muscle pain; whereas this was reported by only 20 percent of the placebo group. Forty-eight percent indicated that the placebo gave poor results as compared to 23 percent of the trolamine salicylate group.

Comments (Politino et al. study)

Although the approach taken in the study has promise as a model for OTC analgesia studies, there were some deficiencies in the design and execution of the study, which prevented it from providing substantial evidence of effectiveness. Also, to assess the accuracy of the model, a positive as well as a placebo control is preferable. In most successful mild to moderate pain models it has been necessary to demonstrate both the integrity of the study, i.e., a significant difference between a known active control and placebo, as well as the effectiveness of the test drug, i.e., a difference between the test drug and placebo and no difference between the test drug and the positive control. Full FDA statistical review was not conducted for the reasons discussed below.

1. Blinding - It was not stated when and by whom the tubes were checked, and when or whether the investigators were made aware of the test results.

2. Randomization - The randomization schedule was unbalanced. Subjects had been involved in widely different athletic events (marathon dances, 3-5 K runs, superstar competition, etc.). It would have been better to have randomization and stratification by the type of athletic event.

3. Placebo - The apparent mix-up in the treatment dispensed to the subject who developed a rash calls into question the assignment of other subjects in the study. The "rash subject" whose code was broken was listed in the final report as being in the placebo group; however, this individual had actually received study drug.

4. Investigators - Curriculum vitae for the investigators were not provided.

5. Conditions Treated - The model could be improved by looking at subjects with muscle "injury" separately from those with joint "injury" or ligament "injury." Combining subjects with different kinds of injury decreases the ability to find true differences.

6. Entrance Criteria - Inclusion criteria were not listed while the exclusion criteria were listed. It was stated in the report that "no more than 12 hours elapsed after exercise until the first application." Both the protocol and report of results did not permit any other treatment 3 hours prior to or 4 hours post-cream application. The clinical results forms did not document that these conditions were met. In some cases it was not clear when the exercise occurred in relation to the symptoms.

7. Patient Instructions - The subjects in this trial were not uniformly reporting the pain relief on their daily evaluation cards. This discrepancy weakens the study and invalidated the use of the three repeat measures (activity, pain level, and pain relief) on the daily evaluation cards.

8. Medication Usage - The protocol and published study differed as to how often the cream was to be used. The actual use was not recorded on any of the record forms.

9. Guidelines - The trial might have been improved if there were guidelines regarding the handling of pain less than moderate at the time of enrollment. The criteria for daily overall evaluation by the subject and global evaluation by the investigator should have been defined.

10. Statistical Testing - Proposed statistical evaluations were not adequately explained in the protocol, report, or published study. Variables should be designated as primary and as secondary. It would be necessary for the majority of the primary efficacy variables to show a difference favoring active treatment ($p < 0.05$) for the results to be considered as providing substantial evidence of efficacy. The secondary variables should be analyzed and would be expected to be consistent with the primary efficacy variables.

11. Tabulations - Without tabulations of the data it was very difficult to cross check and spot check to verify the results. At a minimum, the data should be tabulated with a clear description of what algorithms were used in assigning data to days.

12. Missing Data - There are illegible and missing data on the subjects' daily evaluation cards, which need to be verified. An intent-to-treat analysis should have been performed, with the last observation carried forward. If this was not done, the investigator should describe the methodology used to assess missing data.

G. **RPT2** contained a preliminary report of a clinical trial by Dr. A. S. Dana, a statistical report by Dr. D. J. Clyde, and a consumer survey by Monroe Mendelsohn Research, Inc. (requested by the Pfizer Company). The study was a double-blind, placebo-controlled, crossover comparison of orally-ingested aspirin and topically applied trolamine salicylate cream to test the effectiveness for temporarily relieving the minor aches and pains of arthritis. The parameters evaluated were: reduction in pain intensity and amount of pain relief. Although 60 subjects were to participate in the study, the submitted statistical data were based on interim data from the first 23 participants. The study subsequently was discontinued. The results of the statistical analysis indicated that individuals in both the salicylate cream treatment group and the aspirin tablet treatment group had greater pain relief than observed in the placebo treatment group, but the difference did not reach the 0.05 level of statistical significance.

Comments (RPT2)

1. This study was prematurely halted, and the results failed to demonstrate substantial evidence regarding the effectiveness of topical trolamine salicylate.

2. According to the study's statistical report, active treatment could not be distinguished from placebo treatment.

H. **SUP4** contained a synopsis of an abstract of an animal study by Dr. Vane that investigated the relationship between the anti-inflammatory activity of aspirin and salicylate through the inhibition of prostaglandin synthesis, and testimonial letters of Drs. Kantor, Vane, Beaver, and Calabro based on reviews of the studies (Politino, Iber-Shamszad, Golden/Altschuler, Pfizer, Robinowitz and Baldin studies) relating to the effectiveness of 10 percent trolamine salicylate. No new data were included in this submission.

I. **SUP5** contained no new data. The abstract of a study by J. R. Vane, an article by Guy and Maibach, and the Shamszad et al. published study have been discussed earlier in this letter.

J. **CP10** included two double-blind, placebo-controlled clinical trials (protocols 87-001 and 92-003), marketing data, and a table of previously submitted studies.

Study 87-001 entitled: "Effect of a Topical 10% Trolamine Salicylate Cream Compared with Placebo Cream on Exercise Induced Muscle Soreness."

This randomized double-blind, placebo-controlled study was conducted with 45 students, 18 to 25 years of age, to evaluate the effectiveness of a topically applied 10% trolamine salicylate cream (Aspercreme) compared with placebo cream in avoiding and/or relieving pain in subjects with induced muscular soreness associated with heavy resistance exercise of the flexor of the elbow. An evaluation of plasma creatine phosphokinase (CPK) levels before and following exercise was also included in the study to ascertain whether or not these levels are affected by topical application of a 10% trolamine salicylate cream.

The report concluded that plasma CPK was increased in both treatment groups and that there was insufficient evidence to demonstrate statistically significant differences between the treatment groups. No significant differences were reported between the two treatment groups with respect to strength assessments or arm circumference measurements.

Comments (Study 87-001)

1. The randomization scheme did not follow appropriate randomization procedure in that there was no sequential assignment of subject numbers and pre-numbered treatment packages to dispense to those who enrolled in the study. Also, the trial was inadequately powered to detect statistically significant differences.

2. The study did not demonstrate efficacy over the entire 12 days. Further, it did not demonstrate efficacy early in the development of the post-exercise pain, during Days 0, 1, and 2.

3. Only 24 subjects were exposed to Aspercreme (3 of whom did not complete the study). No safety information was provided. More carefully, properly randomized, controlled studies with larger numbers of subjects would need to be submitted to establish safety and effectiveness for this ingredient.

4. The study did not appear to follow the protocol. For example, five soreness measurements were reported instead of four as stated in the protocol.

Study 92-003 entitled: "A Double-Blind Comparison of Aspercreme vs. Placebo Cream for Relief of Pain and Stiffness in Subjects with Osteoarthritis in their Hands."

This study was a single center, randomized, double-blind, placebo-controlled crossover study of 50 subjects (males and females over the age of 18) with osteoarthritis of the hand. Each active phase of the study consisted of one application of study cream during a morning arthritis flare. Participants had three clinic visits. The two phases of the crossover were to be separated by at least 1 week. The rating was done according to a pain gradient scale and a stiffness gradient

scale. Subjects were to massage to use the study medication on a morning when they were experiencing at least moderate pain.

Pain and stiffness were considered to be primary efficacy variables. Subjective comparisons with oral analgesics and other topicals were considered secondary efficacy variables. The study results indicated that at 30 minutes there was a trend in favor of Aspercreme over placebo for pain relief and that at 45 minutes the Aspercreme was significantly better. The study concluded that Aspercreme treatment was consistently superior to placebo in reducing pain during the period of 30 to 120 minutes after application in period 1.

Comments (Study 92-003)

1. This study had serious flaws in methodology. The accuracy of a diagnosis of osteoarthritis (OA) in the subjects is questionable because the history and physical examination performed at the beginning of the study lacked any detail regarding the musculoskeletal system.

2. It is not clear how subjects were recruited to participate in the study.

3. Because OA is predominantly a condition of the middle-aged and elderly, including subjects under the age of 50 for the study leaves the diagnosis in question.

4. The baseline pain and stiffness characteristics of any of the subjects were not clearly delineated.

5. Subjects who may have been regularly taking an OTC nonsteroidal anti-inflammatory drug (NSAID) a few times per week may not have an adequate wash out period.

6. The history form the investigator completed did not ask a subject to describe his/her arthritic symptoms. Subjects should have filled out a baseline pain and stiffness form. Without this baseline information, a change of symptoms in response to study medication cannot be easily appreciated. Similarly, the physical examination form should have included specific questions about the subjects' hands.

7. Components of the placebo cream were not provided.

8. Questions about concomitant medications were answered only at the visits. Because subjects may have forgotten what they took, they should have received a diary to complete at home during the study.

9. As this was a cross-over trial, returning to baseline after period 1 is critical in order for the period 2 results to be accurately interpreted.

10. The line listings regarding continuation of other pain medications during the study are not complete so we do not have documentation that subjects discontinued them, as the study required.

11. Adverse reactions were reported with inconsistencies and without dates of occurrence. Therefore, we do not know the temporal relationship between dates the subjects actually used the study creams and when adverse events occurred.

12. Our review of the data did not demonstrate statistically significant efficacy of Aspercreme in the subjects treated.

13. That placebo applied in period 2 following Aspercreme in period 1 worked as well as the Aspercreme, suggesting that any benefit may have been psychological or related to the massage alone.

K. **CP11** - This single application study 93-003 was conducted to compare pain and stiffness relief of a topically applied 10% trolamine salicylate cream (Aspercreme) with placebo cream in subjects suffering from OA in their hands who experience characteristic pain and stiffening in the morning upon awakening. This protocol was submitted to confirm what the company regarded as positive results of study 92-003.

In this double-blind, placebo-controlled, parallel, single application study, 80 subjects over 18 years of age, with OA in their hands having moderate to severe morning stiffness, were to be randomized to treatment with active or placebo creams. As in protocol 92-003, subjects were asked to compare OTC topicals and oral analgesics with the study cream as excellent, good, average, fair, or poor. Morning pain intensity relief was the primary efficacy variable. Morning stiffness relief and subjective comparisons with oral analgesics and other topicals were considered secondary efficacy variables.

Both Aspercreme and placebo reduced pain and stiffness of the left and right hands significantly in the intent-to-treat analysis. Aspercreme was reported as superior to placebo treatment in reducing pain intensity in the left hand, right hand, mean of both hands, and the dominant hand at 45 minutes. In the right hand (the dominant hand in all but 4 subjects) the study reported significant pain intensity reduction at both 45 and 120 minutes in both the per-protocol and intent-to-treat analyses when subjects with at least mild baseline pain were considered. The study also reported that subjects in the Aspercreme treatment group who had arthritic symptoms for longer than 10 years had the greatest reduction in pain and stiffness intensity scores. Subjects that had used topical analgesics in the past had significant pain intensity relief at 45 and 120 minutes compared to subjects who did not normally use topical analgesics. This effect was greatest within the placebo group. The study reported that Aspercreme was superior to placebo treatment in reducing stiffness intensity in the right hand, both hands, and dominant hand at 45

minutes. Subjects in the placebo group that had used topical analgesics in the past had slightly greater stiffness intensity relief than did subjects who did not normally use topical analgesics.

Comments on Study Results (Protocol 93-003)

There are a number of methodology problems, consisting of the following:

1. There is no information about the baseline characteristics of the arthritis of the subjects, including the duration of the morning stiffness or pain of each subject. The study did not control the hand activities of the subjects for the 2-hour duration of the study. Activities performed could have a direct impact on symptoms. Subjects who had used Aspercreme in the past should have been excluded from the study because they had a chance of recognizing the study cream which would interfere with the blinding of the study. One study treatment is not adequate, because of the variable nature of OA symptoms to make an adequate determination as to effectiveness.

2. Among the subjects using long half-life NSAIDS, a 12-hour washout would be inadequate to get them to baseline status.

3. Although subjects were supposed to receive a baseline physical examination, Appendix l-d of the intent-to-treat subject listing indicates that only vital signs and examination of the extremities were done as part of the physical examination. A complete physical examination should have been performed in order to eliminate systemic rheumatic conditions that can cause hand pain and to appropriately diagnose OA. A complete exam would also make certain that OA subjects met the inclusion criteria of having an otherwise normal baseline physical exam. Further, the extremity examination was not diagnostic of OA as recorded for many of the subjects, especially those described as having swelling of small joints of the hands, tender and/or swollen metacarpophalangeal (MCP) joints, joint "thickening" (too general a term), and nodules (a term not generally applied to OA). The description of the hands should have used standard terminology and the diagnosis should have been focused on the proximal interphalangeal (PIP) joints and distal interphalangeal (DIP) joints. One subject was described as having thickening of the metatarsophalangeal (MTP) joints. These joints are in the feet and this subject does not belong in this study. Thirty-three of the subjects in the study were classified as having abnormal MCP joints. This joint is not a hallmark joint for OA. It is more commonly symptomatic in inflammatory conditions like rheumatoid arthritis.

4. Many of the subjects in the protocol did not have a physician make a prior diagnosis. The sole fact that many of the subjects in the study were in their 30s and 40s also makes the diagnosis of OA in those subjects suspect.

5. The protocol is not clear about the time frame within which subjects were to report for visit 2 following the application and assessment of the study cream.

6. The pain and stiffness scales used in this study were identical to those of protocol 92-003 as described above.

7. Because of the methodology flaws, we do not consider this study as adequate to establish safety and effectiveness.

L. **CP12** - This single application study 94-006 was conducted in 80 individuals with confirmed OA of the hands who experienced moderate to severe pain and morning stiffness, in order to compare pain and stiffness relief between a topically applied 10% trolamine salicylate cream (Aspercreme) and a placebo cream. The purpose of the study was also to replicate the results from protocol 93-003. The company considered this a true placebo-controlled study of topical analgesic effectiveness because Aspercreme has no odor or counter-irritating properties.

The study concluded that in comparison with baseline, both Aspercreme and placebo cream reduced pain and stiffness of the left and right hands significantly in the intent-to-treat analysis and in the per-protocol analysis. This was attributed to the therapeutic effect of rubbing. The study also concluded that Aspercreme was superior to placebo in reducing pain intensity in the left hand (per protocol analysis P=0.0004; intent-to-treat analysis P=0.0004), pain of both hands (per protocol analysis P=0.0112; intent-to-treat analysis P=0.0204), and stiffness in both hands (per protocol analysis P=0.327; intent-to-treat analysis P=0.0215) at 45 minutes. Unlike previous Aspercreme study protocols (93-003 and 92-003), results for the right hand alone were not better than for the left hand, both hands, and dominant hand. The study found the superior results in this study for the left hand difficult to explain. The study found that significantly more subjects in the Aspercreme group said their study cream was average, good, or excellent compared with oral analgesics.

One subject reported moderately cold hands lasting 2.5 hours after application of the study cream. The incident resolved itself, was not treated, and was not considered serious. The investigator felt the reaction was possibly related to application of the study drug. No other adverse reactions were reported.

Comments (Protocol 94-006)

We disagree that studies 93-003 and 94-006 showed statistically significant differences between treatment groups. In study 94-006, although significant differences were found for the left hand pain scores at 45 and 120 minutes following treatment, the pain scores for the dominant pain hand at these time points did not demonstrate statistically significant differences. Also, two-sided tests of significance should have been used rather than one-sided tests and issues of multiplicity were not taken into account.

Summary Comments (Protocols 92-003, 93-003, 94-006)

1. We did not find that these studies showed a statistically significant benefit of Aspercreme. There are serious flaws of methodology in all three protocols, particularly regarding the diagnosis of OA, the absence of baseline information about severity and duration of pain and stiffness in the subjects prior to treatment, control of hand activity during the 2-hour study time, and the fact that there was only a one-time application of the medication. Considering that OA symptoms vary depending on factors like physical activity and weather, it would be difficult to get any meaningful information from a one-time cream application. Because of methodology flaws and a lack of statistical significance, the studies were not adequate to show that Aspercreme is effective for the relief of symptoms of OA of the hands.

2. These studies only offered very short-term exposure to the topical product. Since OA is a chronic condition, subjects would tend to chronically use a product that helps their symptoms. Therefore, to accurately assess efficacy and safety, OA study protocols should reflect repeated use or chronicity of use patterns.

Overall Recommendations and Conclusions

1. A future study test for percutaneous absorption and serum salicylate levels is recommended.

2. Overall, the data are not sufficient to substantiate the effectiveness of 10 percent trolamine salicylate as an external analgesic for temporary relief of minor aches and pains of muscles and joints. As noted in our comments for the earlier, individual studies, there were one or more flaws relating to the requirements for adequate, well-controlled clinical trials to test for analgesic effectiveness. The most recently submitted data in the citizen petitions (CP10, CP11, and CP12) did not support the claim for relief of morning pain and stiffness in OA of the hands, or the claim for exercise-induced muscle soreness, for the reasons discussed in the specific comments. In addition, data were not provided with these four studies to support the premise that Aspercreme does not cause gastrointestinal irritation, a rational for use of a topical salicylate offered in the introductions to the protocols.

3. Two well-controlled multi-dose studies for each indication with appropriate inclusion and exclusion criteria are needed to make an adequate determination as to the effectiveness of the product for OA and muscle soreness. In addition, appropriate documentation is required that the subjects in the OA studies indeed have OA. We recommend that you submit study protocols to Docket No. 78N-0301 for our review before conducting any further studies. Please let us know within the next 30 days whether you intend to conduct any additional clinical studies. We intend to recommend to the Commissioner that the agency deny your petitions for the foregoing reasons. Any comment you wish to make on the above information, or any additional information you wish to provide, should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch

(HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. This letter should not be considered a formal ruling on your petitions. That occurs when you are sent a response by the Associate Commissioner for Regulatory Affairs.

We hope this information will be helpful.

Sincerely yours,

Charles J. Ganley, M.D.
Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

DATE:

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.

[X] This material should be cross-referenced to Comment No. LET-87.

Charles J. Ganley, M.D.

Attachment