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**Re: Citizen's Petition to Remove False and Deceptive Labeling for
Transderm Scōp®**

Pharmacia Consumer Healthcare, a division of Pharmacia & Upjohn

Company (hereinafter referred to as "Pharmacia"),¹ hereby petitions the Food and Drug Administration ("FDA") to order Novartis Consumer Health, Inc. (hereinafter referred to as "Novartis") to revise labeling for its prescription motion sickness product Transderm Scōp®, so as to remove certain false or misleading statements comparing Transderm

¹ Pharmacia markets a number of over-the-counter medications, including Dramamine Original Formula, as well as prescription medications. Dramamine Original Formula contains the active ingredient dimenhydrinate. Dramamine is also sold in another formulation, Dramamine Less Drowsy Formula, which contains meclizine hydrochloride as the active ingredient.

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Scōp with oral dimenhydrinate (the active ingredient in Dramamine® Original Formula) from the Transderm Scōp physician package insert. The labeling statements at issue in this Citizen's Petition are used by Novartis to support, and to claim FDA approval for, a major nation-wide direct-to-consumer advertising campaign centered around the claim that Transderm Scōp is "clinically proven to be more effective than Dramamine."

Pharmacia believes that that claim is both unsubstantiated and false.

Specifically, Novartis' physician package insert for Transderm Scōp (attached hereto as Exhibit 1), in a section entitled "*Clinical Results*," purports to summarize the results of certain clinical studies testing the efficacy of Transderm Scōp in reducing the incidence of motion-induced nausea and vomiting. As part of that summary, the physician package inserts states that Transderm Scōp "provided significantly greater protection [from motion-induced nausea and vomiting] than that obtained with oral dimenhydrinate."

Pharmacia believes that this language should be deleted for the following reasons, as described herein: First, the superior protection claim is not substantiated, but in fact is contradicted by available clinical studies. The comparison between Transderm Scōp and dimenhydrinate is false. Transderm Scōp did not provide significantly greater protection than oral dimenhydrinate. Second, the *Clinical Results* summary even references a comprehensive review article which explicitly states that there is no proven difference in efficacy between Transderm Scōp and dimenhydrinate. See, S.P. Clissold and R.C.Heel, "Transdermal Hyoscine (Scopolamine) A Preliminary Review of its Pharmacodynamic Properties and Therapeutic Efficacy," *Drugs*, 29; 189-207 (1985)

(referenced as note 3 in the physician package insert and attached hereto as Exhibit 2).

The reference to the Clissold article renders the physician package insert internally inconsistent and confusing. Third, at the time of product approval Novartis' partner ALZA obtained FDA approval of its packaging by disputing FDA's assertion that the *Clinical Results* paragraph was "primarily promotional" and arguing instead that the purpose of the paragraph was to "provide the physician with clinical perspective in using the material." (See below.) FDA's approval of the insert was clearly never intended to be an approval of a promotional campaign. Yet that approval is being used by Novartis as support for a nation-wide direct-to-consumer advertising campaign alleging clinically proven superiority.

On April 21, 2000, Pharmacia filed a complaint against Novartis before the National Advertising Division of the Council of Better Business Bureaus (hereinafter referred to as "NAD")². The challenge sought a recommendation from the NAD that the Novartis advertising campaign should be changed because its proven superiority claim was not substantiated. Novartis opposed the challenge by claiming that FDA had approved its advertising claims and asserting that the NAD should defer to that FDA approval. Specifically, Novartis stated that FDA had "scrutinized and approved the package labeling and inserts containing the claims in question" and that FDA's Division of Drug Marketing, Advertising and Communications ("DDMAC") "had studied and

² A copy of Pharmacia's complaint to NAD is attached hereto as Exhibit 3.

approved” previous ads making similar claims of superiority.³ The NAD, in a recommendation dated October 30, 2000, agreed with Pharmacia that the claim was not substantiated and recommended that it be discontinued. *See* NAD Recommendation, *Novartis Consumer Health, Inc.*, dated 10/30/00, at pp. 18-19 (attached hereto as Exhibit 5). Novartis appealed this decision to the National Advertising Review Board, where it again contended that FDA has approved its claims and that the NARB must defer to that approval.⁴

This Citizen’s Petition will demonstrate the following:

- The statement in the physician package insert that “Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate” is false. The statement is not substantiated by the studies that ALZA submitted to FDA, is contradicted by the very language of the publications of those studies (which were authored by ALZA employees) and is refuted by the review article which the physician package insert cites and which is thereby incorporated into the physician package insert by reference.
- As all clinical studies comparing Transderm Scōp with Dramamine demonstrated no significant difference in efficacy between the two drugs, the

³ *See*, letter from Novartis’ counsel dated May 26, 2000, to Chrysse Spathas, NAD, attached hereto as Exhibit 4 at p.1.

⁴ A copy of Novartis’ appeal letter is attached hereto as Exhibit 6.

representation of “significantly greater protection” than dimenhydrinate, as recited in the physician package insert, is plainly false.

- ALZA’s statistical reanalysis, submitted to FDA in 1979, constituted an inappropriate data-pooling that was not in accordance with current FDA statistical standards. Contrary to Novartis’ assertions, ALZA’s three small and inconclusive comparative studies simply cannot be pooled together to produce significant results favoring Transderm Scōp.
- Significantly, ALZA’s patient package insert, which was approved by the FDA at the same time as the physician package insert, did not contain any claim of superiority for Transderm Scōp over dimenhydrinate.
- Finally, before receiving FDA approval for its physician package insert, Novartis represented to FDA that its proposed insert language was intended simply to give to doctors a “clinical perspective in using” Transderm Scōp. (Exhibit 4 at p. 9.) Novartis is misusing its insert language to allege that, by approving the insert, FDA has approved the direct-to-consumer promotional claims alleging superior efficacy.

Action Requested

Pharmacia urges FDA to order modification of the Transderm Scōp physician package insert by deleting the sentence in the “*Clinical Results*” section that reads: “Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.” Such a modification is necessary to avoid misleading physicians,

who rely on the physician package insert, and to avoid misleading consumers, who are exposed to direct-to-consumer advertising claims, which Novartis contends are based upon the physician package insert language.

Statement of Grounds

Background

A. The Original ALZA Submissions in Support of the Physician Package Insert

To support its New Drug Application in 1976, ALZA submitted three efficacy studies performed at sea, two of which compared Transderm Scōp with dimenhydrinate. See FDA Summary Basis for Approval ("SBA") at 6-9 (attached hereto as Exhibit 7). The ALZA studies are published by ALZA researchers in Price, et al., "Transdermal Scopolamine in the prevention of motion sickness at sea," *Clinical Pharmacology and Therapeutics*, 29:414-419 (1981) (attached hereto as Exhibit 8). Another comparative study, performed not at sea, but in a motion simulator machine, was submitted as "supportive" of the application. See SBA at 8-9. This study was published in McCauley, et al., Effect of Transdermally Administered Scōpolamine in Preventing Motion Sickness, *Aviation, Space, and Environmental Medicine*, 50 (11): 1108-1111 (1979) (Exhibit 9).

As part of its New Drug Application, in 1976, ALZA proposed the following language for its physician package insert:

Clinical Results: With the 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. The Transderm-V system provided

significantly greater protection than that obtained with oral dimenhydrinate.

See Exhibit 10 hereto.

FDA did not initially approve this proposed insert statement, but requested instead that the paragraph be deleted and that a patient package insert also be provided. In 1976 FDA's Dr. Margaret A. Milliken, the Medical Officer assigned to review NDA 17-874 (ALZA's application for approval of Transderm Scōp), completed her Medical Officer's Review. A copy is attached as Exhibit 11. Dr. Milliken requested a number of changes in the physician package insert, including a request that the section on "*Clinical Results*" should be omitted because it was "primarily promotional." (*Id.* at p. 11.) She also requested that a brochure for patients be submitted. (*Id.* at p.12.) In response to Dr. Milliken's recommendation that the language be removed from the insert because it was primarily promotional, ALZA argued to FDA that the *Clinical Results* language proposed for the physician's package insert was instead intended to "provide the physician with clinical perspective in using the material."⁵ ALZA also submitted a data reanalysis combining the results from its small comparative studies and apparently arguing that the combined data reached the level of significance. Finally, in response to FDA's request, ALZA submitted a patient brochure, which contained no comparative statements regarding dimenhydrinate.

⁵ See Exhibit 4 at page 9.

Two years later, FDA issued its approval letter, stating that the draft labeling was acceptable. The current physician package insert contains the following paragraph:

Clinical Results: In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. [Ftnte.: Clissold, S.P. et al: "Transdermal Hyoscine (Scopolamine), A Preliminary Review of its Pharmacodynamic Properties and Therapeutic Efficacy", *Drugs*, 29: 189-207 (1985).] Transderm Scop provided significantly greater protection than that obtained with oral dimenhydrinate.⁶

See Exhibit 1

B. Novartis' Advertising Campaign Based Upon the Physician Package Insert

As noted above, Novartis has embarked on an extensive national direct-to-consumer advertising campaign claiming that Transderm Scōp is clinically proven to be more effective than Dramamine. The campaign includes a full-page advertisement in Newsweek and other general circulation periodicals (Exhibit 12) and an extensive website advertisement (Exhibit 13). Despite the NAD decision, Novartis continues its

⁶ The Clissold, *et al.*, review article summarizes all studies comparing TransdermScōp with Dramamine and concludes that the studies show no statistically significant difference in efficacy between Transderm Scōp and Dramamine. See Exhibit 2. Thus, if any physician to whom the physician package insert is directed reviews the referenced article, he or she will learn that, in contrast to the language of the "*Clinical Results*" section, in fact Transderm Scōp did not provide "significantly greater protection" than did oral dimenhydrinate. Doctors or consumers reading only the physician package insert, and not the referenced article, will not learn that the studies failed to show a difference.

advertising claims to this day. Attached as Exhibit 14 is an advertisement in the current issue of the *Ladies Home Journal* (March 2001).

Among Novartis' comparative claims is the claim that Transderm Scop is clinically proven to be more effective than Dramamine at preventing motion sickness. When Pharmacia has asked the basis for this advertising claim, Novartis simply referred to the "FDA-approved" physician package insert. Thus its counsel stated:

"This claim is supported by the FDA-approved package insert for Transderm Scop, which describes the results of certain clinical studies, and concludes that 'Transderm Scop provided significantly greater protection than that obtained with oral dimenhydrinate.' See Package Insert (attached), and studies cited therein. Accordingly there can be no doubt that this claim is substantiated."

(Exhibit 15, May 27, 1999 letter from Barry Rosenfeld, counsel to Novartis, responding to a letter from Roberta Jacobs-Meadway, counsel to Pharmacia.)

Argument

I. False Claims on a Product Label Render the Product Misbranded.

False claims on a product label render the product misbranded. FDA regulations explicitly provide:

"Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug or a device or a food or cosmetic."

21 C.F.R. § 201.6(a). Misbranding of a drug in interstate commerce is a prohibited act.

21 U.S.C. § 321(a) & (b). FDA may compel a drug manufacturer to modify labeling that causes the drug to be misbranded.

In order to protect public health, the Act's misbranding provisions have been broadly construed. A demonstration that *any* labeling representation is either false or misleading has been held sufficient to establish misbranding. *See, e.g., United States v. Sene X Eleemosynary Corp., Inc.*, 479 F. Supp. 970, 980 (S.D. Fla. 1979)(drug was misbranded for failure to bear adequate directions for use). As the Supreme Court has stated, "[t]he high purpose of the Act [is] to protect consumers who under present conditions are largely unable to protect themselves in this field." *Kohler v. U.S.*, 335 U.S. 345, 349, 69 S. Ct. 106, 109 (1948).

II. The Sentence in the *Clinical Results* Summary that Compares Transderm Scōp with Oral Dimenhydrinate Is False.

The clinical studies described in the *Clinical Results* section fail to demonstrate superior efficacy for Transderm Scōp when compared with Dramamine. Consequently the claim in Novartis' package insert that clinical studies showed "significantly greater protection" is simply false, rendering the product misbranded under 21 C.F.R. § 201.6(a) and making Novartis' ad campaign claims equally false.

A. Available studies do not prove superior efficacy for Transderm Scōp.

None of the studies submitted to FDA by ALZA and referenced in the FDA Summary Basis of Approval for Transderm Scōp supports the package insert statement that Transderm Scōp "provided significantly greater protection" when compared to dymenhydrinate. As noted above, the SBA includes data submitted by ALZA from two clinical studies performed at sea comparing a transdermal hyoscine

product with an oral dimenhydrinate product. One other comparative study was conducted in a motion simulator and submitted as "supportive" data. Each of these studies failed to demonstrate that Transderm Scōp provided greater protection when compared with oral dimenhydrinate.

1. The ALZA Studies

The three comparative efficacy studies submitted by ALZA and evaluated by the SBA are as follows:

a. Trobough Study (Calm Seas). In the first study, conducted by Dr. G. Trobough, three groups were tested in a boat on calm seas. See Exhibit 7 at pp. 6-7. In Group I, a group of either 14 or 13 subjects (both numbers are used in the SBA) were exposed to Transderm Scōp 13.5 hours before motion. In Group II, 14 subjects were exposed to a capsule containing dimenhydrinate 1.5 hours before motion. In Group III, 12 subjects were exposed to placebos. Following exposure to motion, one of the subjects in Group I, two of the subjects in Group II and four of the subjects in Group III became ill. This study is discussed in Price, *et al.*, "Transdermal Scopolamine in the prevention of motion sickness at sea," *Clinical Pharmacology and Therapeutics*, 29:414-419 (1981) ("Price *et al.*") (attached as Exhibit 8). Table I in Price, *et al.*, presents the results of the Trobough study as Study 2 and the results of the Price study as Study 3 (*see below*). As Table III indicates, there is no statistically significant difference between Transderm Scōp and dimenhydrinate when the results of Studies 2 and 3 are combined (probability level = 0.30).

b. **Price Study (Rough Seas)**. In the second study, conducted by Dr. N. Price, three groups were tested in rough seas. In Group I, 12 subjects were exposed to Transderm Scōp 13.5 hours before exposure to motion. In Group II, 11 subjects were exposed to a capsule containing dimenhydrinate 1.5 hours before exposure to motion. In Group III, 13 subjects were exposed to placebos. Following exposure to motion, three of the subjects in Group I, five of the subjects in Group II, and ten of the subjects in Group III became ill. This study is also discussed in Price, *et al.*. Table I in Price, *et al.*, presents the results of the Price study as Study 3. As Table III indicates, there is no statistically significant difference between Group I and Group II when Studies 2 and 3 are combined.

c. **Jones/McCauley Study (Motion Simulator)**. A third study submitted by ALZA as "supportive" in its NDA was conducted by Dr. J.P. Jones and is described in the SBA at p. 8-9. (Exhibit 7.) The design and results of this study are the same as those of a study published by ALZA researchers in 1979, McCauley, *et al.*, "Effect of Transdermally Administered Scopolamine in Preventing Motion Sickness," *Aviation, Space, and Environmental Medicine*, 50 (11): 1108-1111 (1979) (Exhibit 9). (Dr. J.P. Jones was the consulting physician for the McCauley-published study.) This study also compared Transderm Scōp with dimenhydrinate, although it utilized a different design. The Jones/McCauley study was a double-blind cross-over study in which 32 subjects were sequentially exposed to Transderm Scōp, dimenhydrinate, and placebo prior to being exposed to motion in a motion simulator. The Transderm Scōp was administered 12 to 24 hours before exposure to motion. The dimenhydrinate was

administered 30 to 45 minutes before exposure to motion. After reviewing the results, the authors concluded that “[t]he difference in vomiting frequency between treatment with scopolamine and dimenhydrinate was not statistically significant.” (Exhibit 9 at p.1110.)

2. The Clissold Review Article

All three of these studies are discussed in the review article that is cited as a reference in the *Clinical Results* section of the physician package insert, Clissold, S.P. and R.C. Heel, “Transdermal Hyoscine (Scopolamine) A Preliminary Review of its Pharmacodynamic Properties and Therapeutic Efficacy,” *29 Drugs*: 189-207 (1985) (Exhibit 2). The Clissold reference confirms that none of the comparative studies showed any statistically significant difference between the two drugs. The Clissold review article states:

Trials comparing transdermal hyoscine with oral dimenhydrinate have failed to establish any significant differences in efficacy between the 2 drugs in small numbers of subjects, although there was always a more favorable trend towards the transdermal system.

• • •

Thus, preliminary evidence suggests transdermal hyoscine may offer an effective and conveniently administered alternative for the prevention of motion-induced nausea and vomiting in certain situations. However, the duration of its clinical effectiveness, and its relative efficacy and tolerability compared with other agents needs to be confirmed in a few additional well-designed studies.

Exhibit 2 at p. 190; emphasis added. The Clissold Review article also notes another serious design problem in the studies by Price *et al.* -- in parallel groups of subjects “the

different groups were not shown to be comparable at baseline.” *Id.* at p. 200. As a result of the researchers’ failure to ensure that the three comparison groups were comparable at baseline, differences between the groups cannot be shown to be related to differences in medication.

3. Impact of the ALZA Studies on Novartis’ Superiority Claims

The ALZA studies provide no support for Novartis’ claim that Transderm Scōp is clinically proven to be more effective than Dramamine. As noted in the Clissold review article, the available studies simply do not show a statistically significant difference between Transderm Scōp and dimenhydrinate. The statement in the Transderm Scōp package insert section on *Clinical Results* that “Transderm Scop provided significantly greater protection than that obtained with oral dimenhydrinate” is contradicted by the studies themselves. The clinical studies submitted to FDA and to which the package insert refers failed to show a significant difference in efficacy for the Transderm product when compared with oral dimenhydrinate.

Finally, as noted in the Clissold review article (Exhibit 2), the number of subjects used in the ALZA studies was small and the different groups in parallel exposures were not shown to be the same at baseline. Even if the results had been statistically significant, they involved too few subjects and lacked sufficient controls to support a generally applicable conclusion regarding the relative efficacy of the two drugs.

“[I]t is a fundamental principle of clinical testing that one cannot infer efficacy comparisons between two products . . . when those products have not been tested

against one another in a well-controlled head-to-head clinical study.” *Zeneca v. Eli Lilly & Co.*, No. 99-Civ. 1452 (JGK), 1999 U.S. Dist. LEXIS 10825, *99 (S.D.N.Y. 1999).

Moreover, each such “study or survey must be statistically significant and support the claim for which it stands.” *SmithKline Beecham Consumer Healthcare, L.P. v. Johnson & Johnson-Merck Consumer Pharm. Co.*, 95 Civ. 7011 (HB), 95 Civ. 7688 (HB), 1996 U.S. Dist. LEXIS 7257, * 32 (S.D.N.Y. 1996).⁷

Because the only head-to-head comparison studies of clinical efficacy between Transderm Scōp and dimenhydrinate did not show any statistically significant difference, Novartis’ physician package insert asserting that Transderm Scōp provided significantly greater protection than that provided by oral dimenhydrinate is literally false. Novartis’ promotional claim of clinically proven superior efficacy is therefore also false.

B. The inclusion of the Clissold review article in the package insert renders the insert internally inconsistent and confusing.

The *Clinical Results* section of the package insert specifically references the Clissold review article. This section of the package insert must be read in conjunction with the Clissold article itself.

When the package insert is read together with the Clissold review article, the reader is left with inconsistent messages. The Clissold article expressly contradicts

⁷ See also 21 C.F.R. § 202.1(e)(6), which states that advertisements that contain drug comparisons that represent or suggest that a drug is more effective than another,

the comparative sentence in the *Clinical Results* section. Doctors who obtain a copy of the Clissold article will know that the superiority assertion of the physician package insert is inaccurate. But those who do not obtain the article will have no way of knowing that the physician package insert statement is unsupported and false. Moreover, consumers who obtain a copy of the physician package insert are unlikely to obtain the reference article and therefore will commonly assume that the package insert claim is accurate.

Moreover, as noted above, Novartis bases its national direct-to-consumer advertising campaign on this single package insert sentence. Consequently, consumers throughout the country are being misled as a result of Novartis' false package insert statement claiming superior performance in clinical studies.

C. Novartis may not rely on a fundamentally flawed post-hoc meta-analysis to support its superior efficacy claims.

In 1979 ALZA defended its package insert statement by submitting to FDA a purportedly "confidential" statistical analysis pooling the data from the three clinical studies discussed above to yield a purportedly significant difference between Transderm Scōp and Dramamine. This reanalysis was submitted to FDA after FDA's Medical Officer initially recommended that ALZA delete the proposed superiority statement from its physician's package insert because it was "primarily promotional."

(...continued)

when it has not been so demonstrated by substantial evidence or substantial clinical experience, violate Section 502 of the Food, Drug and Cosmetic Act.

Novartis has refused to permit Pharmacia to review its data pooling, asserting that its data reanalysis is proprietary and confidential (*see* Exhibit 4 at p.5).⁸ However, based on Novartis' descriptions of the reanalysis, it is clear that ALZA's data pooling was scientifically inappropriate and failed to satisfy even the most rudimentary statistical principles. The re-analysis cannot meet scientific standards set by FDA or the scientific community in general for combining data from small clinical studies.

1. Scientific Standards for Meta-Analysis.

One process of combining data from small studies to produce results large enough to be significant is known as "meta-analysis." Meta-analysis is a technique that searches for statistical trends by combining or integrating the results of several independent clinical trials considered by the analyst to be "combinable." Its application has been controversial because it is often used to find statistical significance where there is none present in the underlying studies, and thus poses the danger of combining biases inherent in the underlying studies.⁹ While meta-analysis can be a useful technique for elucidating trends in clinical data, it is generally not an appropriate tool for establishing an overall estimate of efficacy, except in "exceptional circumstances" where it is part of a

⁸ Novartis' assertion that its data "pooling" is proprietary is unreasonable. The studies that are pooled are all studies that have been submitted to FDA in support of product approval and specifically in support of comparative efficacy claims, and that have subsequently been published. There can be nothing proprietary in the data pooling methodology under these circumstances.

⁹ J. Lau, Summing Up Evidence: One Answer is Not Always Enough (Meta-analysis Duet), *The Lancet* 351: 123-128 (1998) (Exhibit 16).

prospectively designed series of clinical studies.¹⁰ This is in part because, as FDA's Dr. Robert Temple explained, "[u]nplanned meta-analyses, post hoc assemblages of randomized trials, pose greater problems of biased selection."¹¹

Indeed, in commenting on FDA's decision to reject the use of meta-analytic techniques as a comparator for one arm of active-control trials for a new drug, Dr. Thomas Fleming, a biostatistics consultant for the FDA Cardiovascular and Renal Drugs Advisory Committee, stated, "[i]t bothers me greatly when we have all the studies in hand and plan a meta-analysis – we [already] know what the results are."¹² A member of the same committee observed that "there is no way to do a meta-analysis of trials that are already completed without already knowing what the results are." *Id.*

In a recent article in *JAMA*, the authors discussed their concerns with reliance on meta-analysis in the drug approval process as follows:

The idea of using only a meta-analysis in the drug approval process may cause some discomfort. It seems prudent to require that at least one adequately powered, well-designed study be performed in support of efficacy.¹³

¹⁰ See International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials; Availability; Food and Drug Administration, 63 Fed. Reg. 49583, 49597 (1998) (Exhibit 17).

¹¹ R. Temple, Meta-analysis and Epidemiologic Studies in Drug Development and Postmarketing Surveillance, *JAMA* 281, at 842 (1999) (Exhibit 18).

¹² The Pink Sheet, FDC Reports, vol. 61, Issue 43 (10/25/99) (Exhibit 19).

¹³ J.A. Berlin, *et al.*, The Role of Meta-analysis in the Regulatory Process for Foods, Drugs, and Devices, *JAMA* 281:830-839 (1999) (Exhibit 20).

More succinctly, another commentator noted, “[i]f a medical treatment has an effect so recondite and obscure as to require meta-analysis to establish it, I would not be happy to have it used on me.”¹⁴

2. The studies cannot be combined to demonstrate superiority.

The meta-analysis conducted by ALZA apparently exemplifies these concerns. ALZA’s retrospective use of meta-analysis to combine the results of the three small-scale clinical trials – trials that had already failed to produce statistically significant results – was seriously flawed and improper for the following reasons:

- Current FDA standards require head-to-head clinical testing to demonstrate clinical equivalence or superiority. Retrospective meta-analysis of this nature is not appropriate to demonstrate the clinical superiority of one drug against another when the actual studies failed to demonstrate superiority.
- Even if meta analysis were appropriate here, the cardinal rule of meta-analysis is that the studies must be “combinable,” that is they must have highly similar study methods and endpoints. The three studies relied on by ALZA varied significantly in dosing regimen, in motion stimulus, in study population, in endpoint, and in control design.

¹⁴ H.J. Eysneck, Meta-analysis and Its Problems, *British Medical Journal*, 309:789-794

The lack of a significant difference in efficacy for the two drugs as measured in the Trobough study and the Price study is conceded in the published article by Dr. Price. *See Price, et al., supra* at p. 417 (Exhibit 8). Similarly, the lack of a significant difference between the two drugs as measured in the Jones/McCauley study is conceded in the published article by Dr. McCauley. *See McCauley, et al.* at p. 1110 (Exhibit 9).

None of the three studies can be properly combined, as they measure drug efficacy under three different motion sickness stimuli – calm seas, rough seas, and a linear oscillometer. It is an elementary principle of meta analysis that studies cannot be combined if they measure different effects. While the differences between the stimuli in the two studies that were conducted at sea might be considered sufficiently inconsequential to permit ALZA to combine those data, the use of a linear oscillometer is a completely different stimulus, and the resulting data cannot possibly be combined with data generated at sea. McCauley himself noted that desensitization is the probable effect of habituation to the motion itself in a repeated-motion design. Desensitization would affect the incidence of sickness. *See McCauley, et al., Exhibit 9*, at p. 1110. In addition, the McCauley study cannot be combined with the Price and Trobough studies because its design was fundamentally different from the latter studies. It used a cross-over design,

(...continued)
(1991) (Exhibit 21).

while the Price and Trobough studies used a parallel double-blind, placebo-controlled design.

3. Even if the Studies Could Be Combined, their Results Do Not Show a Statistically Significant Difference between Transderm Scōp and Dimenhydrinate.

Even if the three studies could be properly combined, despite their differences, the combined results do not produce statistically significant differences. When the results of the three studies are combined, the p-value of the combined differences is still greater than 0.05. Therefore, the differential results are not rendered significant by data pooling.

In the McCauley study, there were 32 patients per group as a crossover trial. Of the 32, 5 vomited on Transderm Scōp and 10 vomited on dimenhydrinate. In the Price studies, 4 of 26 patients on Transderm Scōp and 7 of 25 on dimenhydrinate vomited. Combining these numbers, 9 of 58 patients on Transderm Scōp vomited compared to 17 of 57 receiving dimenhydrinate. The p-value for this difference is 0.07 and thus not at or below the 0.05 level required by FDA for significance.

The only way that ALZA could have achieved a p-value below 0.05 is to have added the results of the two studies comparing Transderm Scōp with placebo (studies that did not involve administration of dimenhydrinate). This would add 53 patients to the population, of whom 5 vomited. The addition of these to the Transderm Scōp total makes the numbers for Transderm Scōp a total of 111, of whom 15 vomited. Comparing this to the number of dimenhydrinate subjects who vomited, as reported in the

three comparative studies, would produce a p-value of less than 0.01. However, this type of statistical manipulation is patently indefensible.

III. The Physician Package Insert Is Being Misused to Support Direct-to-Consumer Advertising.

FDA approved the physician package insert only after being told by ALZA that its concerns about the comparative language being “primarily promotional” were wrong because the statement was intended to provide doctors with clinical perspective. Over the past few years, however, Novartis has ignored that representation and has instead used the comparative physician package insert statement as support – indeed as the sole support – for its national comparative direct-to-consumer advertising campaign. Because of ALZA’s non-promotional justification given to FDA for the physician package insert language, Novartis’ use of the package insert to justify its direct-to-consumer advertising campaign is inappropriate.

Even if FDA agreed with ALZA that the “*Clinical Results*” information did provide physicians with a legitimate clinical perspective, despite its inaccurate representation of significantly superior performance for Transderm Scōp, it did not permit the same representations to be made in advertising directed to consumers. If Novartis is correct in asserting that FDA approved the language of ALZA’s “*Clinical Results*” insert in 1979, such approval for ALZA would not justify Novartis’ use of that physician-directed language to support national advertising directed to consumers. Indeed, at the time the package insert was approved, manufacturers of prescription medications were not allowed to advertise directly to consumers.

Moreover, it is important to note that at the same time as ALZA was obtaining FDA approval for its physician package insert, it also was obtaining FDA approval for a new patient package insert. But ALZA never requested, and FDA never approved, any comparable comparative efficacy statement in the patient package insert. The patient package insert, which was approved by FDA at the same time as it approved the physician package insert, contained no similar statement comparing Transderm Scōp with dimenhydrinate. A copy of the patient package insert is attached hereto as Exhibit 22. FDA's approval of the *Clinical Results* language in the physician package insert certainly cannot be interpreted as the agency's approval of Novartis' national direct-to-consumer advertising campaign making a "clinically proven" superiority claim for Transderm Scōp.

Conclusion

The *Clinical Results* section of the physician package insert for Transderm Scōp represents that Transderm Scōp provided significantly greater protection against motion-induced nausea and vomiting than did dimenhydrinate. Novartis uses FDA's approval of this statement as substantiation for an extensive direct-to-consumer advertising campaign which claims that Transderm Scōp has been clinically proven to be more effective than Dramamine. The Novartis advertising claim is false. There is not a single clinical study in which Transderm Scōp has been proven more effective than Dramamine. Nor can the existing studies be combined to show statistically significant superiority for Transderm Scōp.

FDA should review the physician package insert statement described herein and should direct that it be deleted for the following reasons:

1. The comparative statement is literally false.
2. There are no clinical studies that prove that Transderm Scōp is superior to Dramamine.
3. The ALZA data pooling submitted to FDA is flawed and does not prove that Transderm Scōp “provided significantly greater protection” than Dramamine.
4. The comparative statement is contradicted by the reference to the Clissold article, thereby rendering the *Clinical Results* section internally inconsistent and confusing.
5. The physician package insert is being used by Novartis for promotional purposes, despite ALZA’s assurance to FDA – in response to FDA’s concerns about the promotional nature of the statement – that the statement was intended to provide physicians with clinical perspective on the drug.

Environmental Impact

Petitioner claims a categorical exclusion from the preparation of an environmental assessment pursuant to 21 C.F.R. § 25.30(General) and 21 C.F.R. § 25.31 (Human drugs and biologics).

Economic Impact

Information regarding the economic impact will be submitted if requested by the Commissioner following review of the petition.

Certification

The undersigned certifies that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that they are aware of no data or information which is unfavorable to the petition.

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by:



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