CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-983/S-012

ADMINISTRATIVE DOCUMENTS

DEC 23 1998

Division of Over-the-Counter Drug Products
Labeling Review

NDA #: 19-983/SE-012
SUBMISSION DATE: September 23, 1998
SPONSOR: Elan Pharmaceutical Research Corp.
DRUG PRODUCT: Nicotine Transdermal System
INDICATIONS: Stop Smoking Aid
ACTIVE INGREDIENT: Nicotine
REVIEWER: Mary S. Robinson, M. S.
REVIEW DATE: December 11, 1998
PM: Sakineh Walther

We have reviewed the attached draft labeling submitted by Élan Pharmaceutical Research Corporation for Nicotine Transdermal System, 11 mg/day and 22 mg/day. The Prostep nicotine transdermal system has been available since 1992 for prescription use in two dosage strengths: 22 mg/day patch containing 30 mg of nicotine and 11 mg/day patch containing 15 mg nicotine. This supplement (19983/SE6-012) is a re-submission of the OTC switch application substituting an alternate matrix adhesive transdermal system previously approved by the Office of Generic Drugs as part of the Sano Corporation (now Elan Transdermal Technologies) applications ANDA #'s 74-612 (21 mg/day), 74-611 (11 mg/day) and 74-645 (7 mg/day). This is the alternate formulation, referenced in the CMC section of (S-011), which is proposed for use in the OTC environment. The sponsor states that the labeling has been revised to reflect the current proposed OTC guidelines as well as the accepted text from review of other commercially available OTC nicotine replacement products. This review is based on full color mock-ups of the draft labeling of the Outer Cartons for the 22 mg, Step 1 Starter Kit and Step 1 Refill Kit, the 11 mg, Step 2 Starter Kit and Step 2 Refill Kit, information leaflet, inner carton, disposal unit, user's action guide, and audio tape. See appendix (AP) 1-47). Unless otherwise noted, the reviewer's comments and recommendations refer to the labeling of both the 11 mg and the 22 mg drug products.

Reviewer's Comments and Recommendations on the Proposed Revised NicoPatch™ Labeling

Redacted 8

pages of trade secret and/or confidential commercial information

/S/

Mary S. Robinson, M. S.
Regulatory Review Chemist, HFD-560

/S/

Helen Cothran, B.S.
Team Leader, HFD-560

Ling Chin, M. D., M.P.H.
Medical Officer, HFD-560

/S/ 12/23/98

for Linda M. Katz, M. D., M.P.H.
Deputy Director, HFD-560

Because of the unique marketing aspects of OTC nicotine replacement drug products, we recommend that any nomenclature changes be submitted in pre-approval supplemental applications.

12/22/98

Chemistry Review 1	1. Division HFD-170	2. NDA Number 19-983
3. Name and Address of Applicant Elan Pharmaceutical Research Corporation 1300 Gould Drive Gainsville, Georgia 30504		4. Supplement Number Date SE6-012 Sept. 23,1998
5. Name of Drug Nicotine Transdermal System	6. Nonproprietary Name Nicotine	
7. Supplement Provides for: the clinical, pharmacokinetic, and labeling changes which supports the claims of supplement S-011 which provides for an alternate formulation of ProStep intended for use in the OTC market place		8. Amendment(s)
9. Pharmacological Category smoking cessation	10. How Dispensed OTC	11. Related Documents
12. Dosage Form transdermal	13. Potency(ies) 11 mg/day and 22 mg/day	
14. Chemical Name and Structure see USAN		

15. Comments

A. The applicant has submitted what appears to be final printed labeling for the following :

- Nicotine transdermal backing
- Nicotine Pouch labels(front and back)
- Inner Carton labels
- Outer Carton labels
- Patient Package Inserts
- Disposal Units

B. COMMENTS:

1. The applicant has shown us the front of the inner carton (pages 00058-00059) But what information will be printed on the back?

2 The inactive ingredients should be listed on the back or side of the inner cartons

3. The applicant has not indicated on any of the labels the manufacture's name and address

4. Each kit should contain disposal units equal to the number of patches, because it appears that once a patch is disposed of, the unit cannot be reused.

5. The storage statement should be revised to read as follows:

16. Conclusions and Recommendations

At the time of the final printing,

- list the inactive ingredients on the side or back of the inner cartons
- include the name and address of the manufacturer
- revise the storage statement to read

- include disposal units equal to the number of patches in each carton.

Supplement can be approved

17. Name Juanita Ross	**Signature** /S/	**Date** 12/10/98
Team Leader **Albinus D Sa, Ph.D.**	/S/	12/10/98

cc:

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

To: Cynthia G. McCormick, M.D., Director, HFD-170
From: Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products /S/
Date: 5/4/98
Re: NDA 19-983/S010
Elan Pharmaceutical Research Group
ProStep (Nicotine Transdermal System) 11mg/day and 22 mg/day
Rx-to-OTC Switch Supplement
Submitted 11/10/97

This memo will convey my agreement with the review team regarding the non-approvability of this application to switch ProStep (Nicotine Transdermal System) from prescription to over-the-counter marketing. The administrative history of this product has been complex. I will attempt in this memo to provide a coherent, but not exhaustive, summary of that history, and to provide an overview of the issues raised during the review of the present supplement.

Administrative History

The IND application for Elan Pharmaceuticals' transdermal nicotine replacement product for smoking cessation was submitted in 2/88. The NDA was submitted in 6/89, but review revealed that the studies did not provide evidence of efficacy for the product. At the agency's request, to avoid the issuance of a non-approval action, Elan withdrew the application in 3/91. Additional efficacy studies were conducted, the NDA was re-submitted, and the product was approved in 1/92 for prescription use as "an aid to smoking cessation for the relief of nicotine withdrawal symptoms."

Shortly after ProStep was approved for Rx marketing, a study was published by F. Harchelroad and colleagues (Harchelroad, F. et al, (1992) "Oral Absorption of Nicotine from Transdermal Therapeutic Systems," Veterinary and Human Toxicology 34: 332) which reported that a 36 year-old male subject collapsed after oral exposure to ProStep. This subject, as well as four others, had successfully completed arms of the study which required holding Nicoderm and Habitrol patches against the buccal mucosa for 60 seconds. No other subjects were exposed to ProStep and the study was terminated. The agency was concerned about the results of this study and asked Elan to conduct a preclinical study involving dogs to explore the risks of buccal exposure to ProStep. It

was assumed that the unique response to ProStep was attributable to the design of the patch, which, unlike Nicoderm, Habitrol, and Nicotrol, lacks any mechanism for controlling the rate of release of nicotine from the patch.

In 1994, HFD-007 developed guidelines for switching nicotine replacement products to OTC. Elan undertook a development plan to support an efficacy supplement for Rx-to-OTC switch for ProStep. The division indicated that the results of the dog study would be required for filing, because the risk of accidental oral exposure to ProStep (particularly in children and pets) would be increased if the product were made more widely available.

The efficacy supplement for Rx-to-OTC switch was submitted in 4/96. It was withdrawn by the sponsor in 2/97 after safety concerns were identified by agency review (see below). The sponsor intended to improve the design of the patch to address these concerns, and submitted on 11/10/97.

Overview of Issues Raised in Review

The original OTC switch supplement. contained several efficacy studies intended to simulate OTC conditions, label comprehension studies, and the preclinical study investigating the effects of buccal exposure to ProStep in anesthetized dogs. The efficacy studies were reviewed by Dr. E. Douglas Kramer, Medical Officer, who concluded that the efficacy of ProStep in the low intervention studies appeared to be low, but it did appear to offer a consistent advantage over placebo. A more detailed summary of Dr. Kramer's efficacy review is provided below, in the discussion of Dr. Kramer also undertook a review of poison control center data, MedWatch reports, and the sponsor's summary of post-marketing safety data, and comparative safety review of all of the available nicotine transdermal systems. This review identified a number of safety concerns that were unique to ProStep.

Major issues identified during the review of included:

- ProStep consists of a circular adhesive pad with a round foil well in the center. This well contains a with nicotine. ProStep's design, unlike the other patches, lacks a mechanism to control the rate of nicotine release from the patch. Review of the pre-clinical study revealed that application of ProStep to the buccal mucosa of anesthetized dogs resulted in more dramatic cardiovascular responses than application of other patches, likely because of this unique design. The study itself was flawed, in that measurement of cardiovascular parameters did not begin immediately after patch application, and, more significantly, because the measuring devices did not record blood pressures which fell above a pre-specified upper limit. Nevertheless, it was apparent on close inspection of the data that the study provided evidence that oral exposure to ProStep could produce significant cardiovascular effects.

- ProStep lacks secure attachment between the nicotine gel and the patch backing, allowing the nicotine gel to come loose during application, use, and removal. MedWatch reports included descriptions of children exposed to the detached gel. It was felt that the design of the patch increased likelihood of accidental pediatric exposure, particularly oral exposure, compared to a patch which remained intact and in the control of the user. This was confirmed by review of Poison Control Center data, which revealed that ProStep was involved in a disproportionate number of accidental exposures given its small market share.
- It was learned that Elan had done preliminary work on design improvements that might reduce these risks.

Thus, in light of the fact that the sponsor had available methods to reduce the risk, the agency felt switching the existing formulation to OTC was inappropriate, and Elan withdrew the supplement to complete the necessary design changes. The agency agreed that, should the re-designed patch be bioequivalent to the patches used in the efficacy studies, that no new efficacy trials would be needed and the original trials could be resubmitted.

Summary of Issues Raised in Review of the Present Supplement

Elan chose to produce a modified patch consisting of the original adhesive backing and nicotine gel disc, but covering the entire surface with a thin paper overliner. The present supplement, contains the clinical trials conducted to establish safety and efficacy in the OTC setting and label comprehension studies (using a label quite dissimilar to the labeling now proposed, which resembles the labeling of approved NRT products) which were previously submitted to and a single bioequivalence study on the new formulation.

Issues to be addressed in the review of were the following:

1. Did the clinical trials on the original patch establish efficacy in the OTC environment?
2. Were any issues of special concern raised by the adverse events recorded during the clinical trials?
3. Is the proposed to-be-marketed formulation bioequivalent to the formulation used in the studies, so that the clinical trials can be regarded as substantial evidence in support of this supplemental application?
4. Is the re-designed patch an improvement over the original patch, as evidenced by a lower likelihood of gel detachment?
5. Is the re-designed patch appropriate for use in the OTC environment, given its efficacy, adverse event profile (safety for the user), and the data on the risks of pediatric poisoning (both likelihood, as evidenced by Poison Control Center data, and potential outcome, as extrapolated from pre-clinical data), and has the re-design reduced the likelihood of such poisoning?

The review of this application, as is the policy for applications for Rx-to-OTC switch was conducted jointly by DACCADP, DODP, and DDMAC. DACCADP's reviews addressed the first four questions listed and provided input into the fifth question. The conclusions are summarized below.

1. **Did the clinical trials on the original patch establish efficacy of ProStep when used under OTC conditions?**

The supplement contains a total of 6 low-intervention studies of various types ("real world" Rx usage, OTC usage, placebo-controlled) which were reviewed by Dr. Kramer, and Dr. Thomas Permutt, Mathematical Statistician. The study reports submitted to were identical to those submitted to , therefore, the reviews prepared by Drs. Kramer and Permutt for the previous supplement have been filed to this supplement as well. There was no further review of this material undertaken.

The supplement contains a total of 6 low-intervention studies of various types. Key aspects of these studies are described in the table below.

Study	Rx	Eligible Smokers
893 004 1134 Sites N = 9271	22 mg	Rx usage; age>=18 appropriate to 22mg patch. Exclusions per Rx labeling (e.g. uncontrolled or accelerated hypertension, recent MI); Rx recommended 4 to 8 weeks. Telephone f/u at 1 week, visit at 1 month.
893 003 Sites=5 N = 802	22 mg vs placebo	>=20 cig/day; >=5/10 motivation score;
694 003 Sites=5 N = 643	22 mg vs placebo	>15 cig/day; >=7/10 motivation score;
694 001 Sites=5 N = 632	11 mg vs placebo	<15 cig/day; >=7/10 motivation score;
993 001 Sites=1 N = 108	11 mg vs placebo	<20 cig/day; >=5/10 motivation score;
694 002 Sites=5 N = 315	22 mg	"OTC" usage; >15 cig/day; >=7/10 motivation score; Patches cost $21/box of 7.

Most of these studies were similar to one another. Physician contact was not allowed, medical exclusion was for recent MI, subjects were age 18 or over, patches were provided free of charge, and treatment lasted 6 weeks with weekly visits. They were conducted at the same sites by 1 to 3 investigators. The study called an "OTC" usage trial appears to

have been called such because it was the only study in which subjects were asked to pay for the patches; otherwise it is similar in design to the low-intervention placebo controlled trials. Dr. Kramer reviewed Study 893-003 in detail and the other efficacy studies in a briefer overview. The Rx usage study (893 004) was intended to estimate the incidence of adverse events in prescription use. A total of 1134 physicians were sent 1 month supplies of ProStep to dispense to their patients. Exclusions were based on the Rx labeling. Treatment was recommended for 4 to 8 weeks, but up to 12 weeks was allowed. There was telephone follow-up by the study center at 1 week, 2 months and 6 months and an office visit at one month. Unscheduled office visits were also allowed. Dr. Kramer reviewed this study only for safety.

The largest of the trials, Study 893 003, differs from the other low-intervention placebo controlled studies and the "OTC" study primarily by the screening method used. Study 893 003 included a label comprehension phase to screening. In the other studies here, initial screening was done by phone.

Study 893-003, was a two investigator, five site, double-blind, placebo-controlled study of ProStep (22mg/24 hours) use in a simulated OTC environment. Eligible smokers were at least 18 years of age who smoked at least 20 cigarettes per day and had smoked for at least one year. Potential subjects were screened by reading a mock up label that listed medical conditions for which they should see their doctor, but all smokers who met the basic criteria were allowed to participate so long as they had not had an MI in the last month and were not pregnant or nursing a baby. Eligible participants had to score at least 5 on a 10 point scale rating their motivation to quit. The protocol excluded those who had used tobacco products other than cigarettes or other forms of nicotine in the last 30 days and allowed only one person per household to enter.

Consumers who met the screening criteria were given a self-help book and were asked to schedule a quit date within 7 days. On their quit date they returned to the study site, gave study consent, provided a baseline breath CO, gave a medical and smoking history, were randomized to either active or placebo treatment and applied the first patch at the study site. They were given diary cards and 14 patches (2 boxes). Participants returned to the clinic weekly for the next 6 weeks for evaluations (including smoking status, CO, adverse events) and drug dispensing. Participants were called by the study sites before each appointment and were not required to return to the study site for a visit if they were smoking. Persons who were smoking at 6 weeks ended the study at that time. Persons who were abstinent at 6 weeks were followed at 16 and 24 weeks. ProStep was not supplied after 6 weeks. No study physician contact was allowed during the study.

Of 1844 potential candidates screened for this trial, 802 were randomized (401 to ProStep, 401 to placebo patch). 157 subjects who received ProStep and 104 who received placebo completed the study through 6 weeks.

The protocol specified success as total abstinence from smoking from weeks 3 to 6 with CO verification. Dr. Kramer's analysis revealed that 12% of smokers on active drug reported quitting for four weeks compared to 5% on placebo, as shown in the table below.

	ProStep™ 22mg N=401	Placebo N=401
Success	**47(12%)**	**21(5%)**
Failure	**354(88%)**	**380(95%)**
P-value	**<0.002**	

Table made by Dr. Kramer from the sponsor's electronic data. Quit rates for each of the 4 sites varied from 7 to 14% for active drug, and 4 to 7% for placebo, with the active quit rate being at least 3% greater than the placebo quit rate at each site.

The results remain statistically significant (34/401 active vs. 18/401 placebo, p≅0.03) if a stricter definition of abstinence (no missed visits) is applied.

A summary of the efficacy outcomes of the other trials is presented in the table below.

Study	ProStep Quitters	Placebo Quitters	P-value
893 004 22mg Rx	1011/9271(11%)		n/a
893 003 22mg	34/401(8%)	18/401(4%)	.03
694 003 22mg	28/321(9%)	17/322(5%)	.12
694 001 11mg	35/315(11%)	16/317(5%)	.008
993 001 11mg	6/53(11%)	1/55(2%)	n/a
694 002 22mg "OTC"	33/315(10%)		n/a

Data taken by reviewer from the sponsor's study reports or the review of study 893003. Values are number (%) of enrolled subjects. CO-confirmed abstinence (weeks 3 to 6) was used in all studies except the Rx use study (where CO was not obtained). Values for the Rx use study are based on 4 weeks continuous self reported abstinence during the 6 month study. P-values are calculated Dr. Kramer (Chi square with continuity correction) except for study 993 001 where the number of abstinent subjects was too small. Abstinence figures for studies 893 003 and 694 003 were validated by Dr. Kramer using the sponsor's CANDA submission.

Dr. Kramer concludes that the efficacy of ProStep in the low intervention studies appears to be low, but it does appear to offer a consistent advantage over placebo. The 22 mg strength appears to be effective in persons smoking 15 or more cigarettes per day (studies 893 003 and 694 003) while the 11mg is likely to be effective in persons smoking less.

Because labeling for the other nicotine replacement products switched from Rx to OTC has, in some cases, relied on evidence taken from both the OTC switch program and the original prescription trials and Rx labeling, it is important to note that Dr. Kramer's recommendations, based on the OTC development program, differ from the regimens described in the approved prescription labeling for ProStep. ProStep's prescription labeling recommends use of the 22 mg/day patch for all patients except those weighing less than 100 pounds, for whom the 11 mg/day dose is recommended. An "optional weaning dose" (11 mg/day for 2-4 weeks) is included in the labeling for those who begin on 22 mg/day, but the clinical trials described in the label include two trials which used 22 mg/day without weaning and two which used weaning. (The trials differed somewhat in others aspects as well). *Only the fixed dose, "no weaning," Rx trials demonstrated*

superiority to placebo. Therefore, neither the OTC program nor the existing prescription labeling seems to offer substantial evidence for using ProStep in a "step-down" fashion.

2. **Were any issues of special concern raised by the adverse events recorded during the clinical trials?**

Adverse events were assessed at weekly visits. No serious adverse effects attributable to ProStep were reported. A high rate of skin reactions is mentioned in the prescription labeling, and might have been predicted in the OTC trials. The rate of adverse skin reaction in the OTC trials was 47% for ProStep quitters, 36% for ProStep failures and 19% for placebo failures and 17% for placebo quitters. Labeling contained strongly worded language about skin reactions and none of the enrolled subjects reported a baseline problem with skin disease. Dr. Kramer's previous review of post-marketing safety suggested that ProStep stood out among the drugs in this category as most likely to induce dermatologic adverse events. The high rate of skin reactions in the trials, even with labeling which tended to screen out individuals with predisposition to skin problems, is consistent with this impression. This suggests that, rather than adopting the language used on labeling for the other two OTC patches, the OTC labeling for ProStep should be specific to this product so that it can convey the appropriate information about the risk of skin reactions.

3. **Is the proposed to-be-marketed formulation bioequivalent to the formulation used in the studies, so that the clinical trials can be regarded as substantial evidence in support of this supplemental application?**

The biopharmaceutics study (Study 0394009) was reviewed by Dr. Suresh Doddapaneni, who found that the study was **not acceptable** from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. Dr. Doddapaneni's review explains that the results of the bioequivalency study are invalid for two reasons. First, the study was not conducted on the to-be-marketed modified patch made by the final to-be-marketed manufacturing procedures (i.e., the overliner was not presealed around the gel matrix but was physically placed around the gel matrix just before the patch was applied at the application site). Second, the study was conducted in an unrandomized fashion (i.e., all subjects received the "reference" patch in period one followed by the "test" patch). As such, the results of this study cannot be used to assess if the to-be-marketed modified patch made by the final manufacturing procedures is bioequivalent to the original ProStep patch. Lastly, *in vitro* dissolution testing has not been conducted on the modified patch (i.e., testing has only been done on the patches without the overliner).

Elan has indicated in correspondence that it was their understanding that the division had agreed that this pilot biopharm study would suffice for approval and that additional

bioequivalence studies on the patches manufactured under the planned conditions would be conducted as a Phase IV commitment. It should be noted that the flaws in study design pointed out by Dr. Doddapaneni were not made plain at the time that the pilot study was discussed with the division. As always, agreements-in-principle regarding the adequacy of a study on the basis of a *description* are subject to modification upon review and identification of deficiencies of the study in question.

4. **Is the re-designed patch an improvement over the original patch, as evidenced by a lower likelihood of gel detachment?**

After being presented with the division's concerns about the poisoning risk related to the detachment of the nicotine gel , Elan met with the division in November, 1996 to discuss possible modifications. At that time, the overliner approach was described. The description indicated that the overliner resulted in "gel prevented from dislodging." (From slide presented by sponsor at meeting). These dislodgment were considered significant because MedWatch data showed that incidents had occurred in which small children were found chewing or sucking on the gel disc, which had "fallen out" of the patch during use. The agency felt that if the gel dislodges during use, no amount of child-safe packaging or disposal mechanisms can prevent exposure to the gel.

However, in the cover letter for the sponsor described the overliner's purpose as "to minimize visible accessibility of the nicotine and, in keeping with this purpose, provided no data on the effect of the overliner on keeping the gel in place. The chemistry review noted a need for information describing how often the overliner gel matrix dislodges from the backing foil when opened, test methods, and acceptance criteria used in setting specifications for the product. This information was intended to ensure that patches purchased by the consumer would be intact (i.e. gel in place, overliner membrane intact) upon opening. The non-overliner patch was prone to dislodgment of the gel upon opening, to the extent that the pouch included instructions on how to return the gel to the proper place on the patch before applying.

Information was also requested on the condition of the patch when subjected to stress conditions, such as bending, folding, and stretching. This information was intended to provide some assurance that the gel would not dislodge during use, as has been known to occur.

Elan was also asked to include other tests to ensure product integrity in the specifications for the product. These requests were conveyed to the sponsor shortly after filing of the supplement and a response was received in February. However, the review chemist, Juanita Ross, M.S., notes, "These responses could be categorized as a work in progress. However, no data has been submitted." Along with other deficiencies concerning stability, this lack of data led Ms. Ross to conclude that from the CMC standpoint, the application is **not acceptable**.

5. **Is the re-designed patch appropriate for use in the OTC environment, given its efficacy, adverse event profile (safety for the user), and the data on the risks of pediatric poisoning (both likelihood, as evidenced by Poison Control Center data, and potential outcome, as extrapolated from pre-clinical data), and has the re-design reduced the likelihood of such poisoning?**

The final question to be addressed is whether Elan should continue to pursue OTC switch of the modified ProStep patch, via repeating the bioequivalence study in the hope of meeting criteria and addressing the chemistry deficiencies. Dr. Ling Chin, Medical Officer in the Division of Over-the-Counter Drug Products, assessed the overall issue of appropriateness for the OTC market. Issues included both safety for the user, and safety for others who might not be the intended user (which can be considered in assessing the appropriateness of an OTC switch).

Safety for the user was assessed through postmarketing reports and clinical trials ADE experience. Dr. Chin concluded that, "There is no data to suggest that the rate of occurrence of serious events or deaths for ProStep is substantially different from that observed with any of the other three patches." However, Dr. Chin noted, as had Dr. Kramer, that ProStep accounted for a disproportionate share of ADE's related to the skin, considering its small market share.

Safety for others in the OTC environment was considered, chiefly by examining Poison Control Center data which gives insight into the likelihood of pediatric poisoning, and by examining the results of preclinical studies in which various patches were applied buccally to anesthetized dogs. Poison Control Center data summarized by Dr. Kramer included information from 1992-1994, when all patches were available only by prescription; Dr. Chin reviewed an update which encompasses 1995-1996, therefore spanning a period during which two of the patches were switched from Rx to OTC and ProStep's market share had declined significantly. Dr. Kramer's analysis, and Dr. Chin's to a lesser degree, suggested that ProStep was involved in cases of exposure (particularly oral exposure) to young children at a rate disproportionate to its market share. Although the cases reported did not include any deaths, the potential for serious outcomes can be concluded from the results of preclinical studies.

Three preclinical studies also provided information about the safety of the product in the OTC setting by giving insight into the possible outcomes of accidental oral exposures. As discussed above, prior to submission of Elan conducted, at the request of the agency, a study comparing the cardiovascular effects of various patches under conditions

of buccal exposure in dogs. This study was submitted in and reviewed by the review pharmacologist, Dr. Harry Geyer. The design and data collection were flawed, but Dr. Geyer was able to determine on close inspection of the data that ProStep produced more dramatic cardiovascular responses than the other patches.

The sponsor having made a good faith effort to answer Dr. Geyer's questions, it was deemed inappropriate to request a second study of Elan. To examine the issue more closely, Drs. Geyer and Kramer worked with the FDA Office of Testing and Research (OTR) to design a dog study which met their precise specifications. Furthermore, Elan spontaneously undertook an additional dog study which examined the effects of used patches. Unfortunately, this study was designed and performed without FDA consultation. The results of these two additional dog studies were reviewed by Dr. Geyer.

Elan's study employed used patches which had been scored with a razor. This would be expected to disrupt the membrane-controlling features of Nicoderm, Nicotrol, or Habitrol, but would have little effect on the gel in ProStep. It was also noted by Dr. Geyer that the membranes on the patches cannot be punctured by chewing, but the gel could very well be disrupted by chewing. Therefore, he concludes that the results should be viewed as an indication of the maximum effect of the membrane-bound patches and a testing of the minimum effect of the gel product. This being said, while ProStep produced the highest nicotine blood levels of all patches tested, cardiovascular changes observed for all patches were relatively minor, providing some reassurance that the possible dangers of used patches is less than the dangers of the unused patches.

The OTR study addressed the effects of the unused ProStep patch (without overliner), the dislodged gel, two membrane-controlled patches, and, to place the risk of buccal exposure to nicotine transdermal systems in context, Skoal Bandit brand pouches of snuff. This study corrected the flaws of Elan's original study in that measurements began earlier and the measuring device did not censor values above a pre-specified cutoff (which had been the case in the original study).The study was carried out using ten adult, anesthetized, male beagle dogs instrumented to record blood pressure, heart rate, EKG and plasma nicotine levels. Each dog was buccally exposed for five minutes to each of 5 nicotine preparations, with recovery periods of 2 weeks between each test. Test materials consisted of intact ProStep, 22 mg, ProStep, 22 mg, as the dislodged hydrogel matrix, Habitrol, 21 mg, Nicoderm, 21 mg, and a Skoal Bandit tobacco plug, which served as a comparator. The dogs were monitored prior to and for 90 minutes following the administration of each of the test materials. ProStep, whether intact or dislodged from its backing, produced dramatic increases in both systolic and diastolic blood pressures within 2 minutes which were significantly greater than with any of the other nicotine products tested. The other products were not significantly different from each other. In the dogs given ProStep, mean systolic blood pressure increased approximately 145 mmHg to 290 mmHg, while diastolic pressure increased a mean of 92 mmHg to 168 mmHg. Mean heart rate with ProStep increased 139 beats per min to 218 at 90 seconds. Cardiac arrhythmias were observed in all of the 10 dogs, either with dislodged gel, intact