d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-612, 20-066 → (Nicorette Gum 2 mg + 4 mg)

NDA # 20-536 - Nicotrol Patch 20-385 - Nicotrol Nasal Spray

NDA # 20-165 - NicoDERM 20-714 - Nicotrol Inhaler
20-076 - Habitrol 19-983 - ProStep

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY

TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

APPEARS THIS WAY
ON ORIGINAL

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 0893-002

Investigation #2, Study # 0694-003

Investigation #3, Study # 0694-001

#4 0993-001

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 0893 -002

Investigation #2, Study # 0694 -003

Investigation #3, Study # 0694 - 001

Investigation #4, Study # 0993 - 001

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /✓/ Explain _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓___/

If yes, explain: _____

_____

_____

_____

/S/

Signature

Title: _____

1/26/99

Date

/S/

Signature of Division Director

1/26/99

Date

cc: Original NDA 19-983 Division File HFD-85 Mary Ann Holovac

élan

DEBARMENT CERTIFICATION
(NDA 19-983, S011 and S012, Prostep® (Nicotine Transdermal System)

Elan Pharmaceutical Research Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Sharon Hamm, Pharm. D., R.Ph.
Senior Vice President
R&D Technical Operations

DEC 18 1998

DOCUMENTATION OF TELECONFERENCE

Date: December 18th, 1998 3:00pm

Between: FDA (HFD-170, Division of Anesthetics, Critical Care, and Addiction Drug Products).
Division Director: Cynthia G. McCormick, M.D.
Clinical: Celia Winchell, M.D./Team Leader
Chemistry: Albinus D'Sa, Ph.D./Team Leader
Biopharm: Ramana Uppoor, Ph.D./Team Leader 12/22/98
Suresh Doddapaneni, Ph.D./Reviewer 12/22/98
CSO: Indira Kumar
And
Company Name: Elan Pharmaceutical Research Corporation
Contact: Diane Servillo/Sano, (954) 430-3340 ext. 298
Sharon Hamm/Elan, (770) 534-8239
Robert Simons, Director of Analytical Research and Development
Michael Schroder, Vice President of Regulatory Affairs
Brian Morgan, Manufacturing
Nancy Buc, Legal Consultant to Elan/Sano
Ms. Beardsley, Legal Consultant to Elan/Sano

Topic: NDA 19-983 ProStep (nicotine transdermal system) Supplement 011 – Phase IV Commitment.
NDA 19-983 ProStep (nicotine transdermal system) Supplement 012 – Biopharm Data and the ProStep name.

Discussion: The FDA initiated the telecon to discuss the following issue on Biopharm Dissolution Specifications:

The Division would like the sponsor to agree to the following phase IV Commitment before a regulatory action is taken on the CMC supplement S-011 and Over-the-Counter (OTC) switch supplement S-012:

Using your proposed dissolution method, it is recommended that the following dissolution specifications be used on an interim basis:

Also, the Agency expects you to provide the dissolution test data on the following lots to enable the finalization of these specifications within 1 year of the approval date:

The sponsor agreed to the above as a phase IV commitment to the NDA 19-983 within the 1 year schedule.

The sponsor initiated a discussion on the use of the name "nicotine transdermal system" instead of the trade name ProStep. Nancy Buc noted that Elan plans to manufacture the patches and a different company will be distributing the patches to many retailers. Many of the patches will be marketed in the "private label" market. The sponsor would like to use the established name for their product, allowing the retailers to sell the patch under their store name, such as, "Store Proprietary name nicotine transdermal system". If Elan places a proprietary name on the patches, then the retailers will be forced to use a proprietary name even if they do not want to. Elan would have to create many different labels for the many different retailers.

She also noted that upon her research of the Federal Regulations, that FDA regulations require the use of an established name in prescription drug labeling and the labeling of Over-the-Counter (OTC) drugs must include an established name. However, there is no requirement in FDA's regulations that a drug even have a proprietary name (trade name).

Dr. McCormick asked Nancy Buc to present the company position on the product's name in a letter and send it to the Division as soon as possible and the matter will be discussed further by the Over-the-Counter Division, FDA's nomenclature staff and the Legal staff.

The sponsor agreed to do so.

DEC 9 1998

DOCUMENTATION OF TELECONFERENCE

Date: December 9th, 1998 5:00pm

Between: FDA (HFD-170, Division of Anesthetics, Critical Care, and Addiction Drug Products).
Division Director: Cynthia G. McCormick Cynthia McCormick 12/10/98
Chemistry: Albinus D'Sa, Ph.D./Team Leader 12/9/98
Juanita Ross, ~~Ph.D.~~/Reviewer JR 12/10/98
CSO: Indira Kumar 12/9/98

And

Company Name: Elan Pharmaceutical Research Corporation
Contact: Diane Servillo/Sano, (954) 430-3340 ext. 298
Sharon Hamm/Elan, (770) 534-8239
Robert Simons, Director of Analytical Research and Development
Debra Ramos, Manager of Quality Assurance
Jesus Mirana, Vice President of Research and Development
Michael Schroder, Vice President of Regulatory Affairs
Brian Morgan, Manufacturing

Topic: NDA 19-983 ProStep (nicotine transdermal system) Supplement 011 – Phase IV Chemistry and Manufacturing (CMC) Commitment.
NDA 19-983 ProStep (nicotine transdermal system) Supplement 012 – Biopharm Data and Transitioning Production and Marketing of the currently prescription ProStep patch.

Discussion: The FDA initiated the telecon to discuss the following issues:

The Division would like the sponsor to agree to the following phase IV CMC Commitment before a regulatory is taken on the CMC supplement S-011:

The sponsor agreed to the above as a phase IV CMC commitment to the NDA 19-983 within the 6 month timeframe.

The Division also informed the sponsor that the review process is continuing on the Supplement 012 – the OTC Switch Supplement. The Biopharmacology review is almost complete and that the sponsor may be contacted on dissolution specifications.

The Division also asked the sponsor to send a letter of reference of the biopharmacology data submitted to Supplement 012 to Supplement 011, in order to link all data of the 2 pending supplements.

The sponsor agreed to do so.

The Division requested a letter from the sponsor that would document the transition from the currently approved ProStep patch to the new patch that is the subject of the pending manufacturing supplement 011. The process described by the Sponsor during the telecon was the discontinuation of production and manufacturing of the existing patch (date of cessation will be provided for the FDA records by the Sponsor) as the Sponsor awaits actions of supplements 011 and 012.

The sponsor informed the Division that they are not actively producing any more lots of the prescription ProStep patch in the US and that they will send in a letter stating this to the FDA.

DEC 8 1998

DOCUMENTATION OF TELECONFERENCE

Date: December 8th, 1998 2:45pm

Between: FDA (HFD-170, Division of Anesthetics, Critical Care, and Addiction Drug Products).
Chemistry: Albinus D'Sa/ Team Leader 12/8/98
Juanita Ross/ Chemistry Reviewer
CSO: Indira Kumar 12/8/98

And

Company Name: Office of Generic Drugs (OGD), HFD-650
Contact: Ubrani Venkataram, Ph.D./ OGD Chemistry Reviewer
Phone: (301) 827-5849

Topic: NDA 19-983/S-011 – CMC Supplement for the OTC Switch of ProStep (S-012) – Elan/Sano Patch (generic Habitrol patch).

Discussion: FDA initiated the telecon to discuss the following issues.

HFD-170 informed Dr. Venkataram that Elan Pharmaceutical Research Corporation has bought Sano Corporation. In the process, Elan acquired the Sano generic equivalent patch to Habitrol (ANDAs 74-611, 74-612, 74-645 for strengths of 22 mg/day, 14 mg/day and 7 mg/day - approved November 1997 by OGD). Elan/Sano submitted a supplement S-012 on September 23rd, 1998 for the over-the-counter (OTC) switch of the Sano generic Habitrol patch. Elan is substituting their ProStep (nicotine transdermal system) 11mg/day and 22mg/day patches (NDA 19-983) with the Sano generic patches (21 mg/day and 14 mg/day). The company submitted bioequivalent studies under S-012 for the 21/22mg and 11/14mg patches.

The reviewing chemists of Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170 wanted to inform the reviewing chemist of Office of Generic Drugs, HFD-650 of this application (NDA 19-983/S-011) and to get feedback on the review of the generic applications.

HFD-170 will continue to inform HFD-650 of any CMC changes regarding these applications and asked HFD-650 to do the same. Dr. Venkataram agreed to do so.

HFD-170 also wanted to discuss CMC issues such as: Adhesion Test, Tact and Peel Tests, Shear Test, and Steel Test and stability data.

DEC 8 1998

Dr. Venkataram noted that for the finished product, at release the firm will test for appearance, ID, potency, impurities, CU, microbial, adhesion (on the final laminate), pouch integrity, shear (on the final laminate), tack and drug release. The adhesion and shear tests are done as in-process tests since these tests may be difficult (because of experimental design) to carry out on the cut pieces. The stability testing includes all the above except adhesion and shear, again for the same reason as above. He asked the Division to talk to Don Kline who is reviewing Buspirone TDS from Elan. He also forward a copy of the Non Approvable letter for the new supplements.

Dr. D'sa informed Dr. Venkataram that HFD-170 will be asking the sponsor to include adhesion and shear tests in the stability protocol.

HFD-170 will maintain a working relationship with HFD-650 regarding these applications.

DOCUMENTATION OF TELECONFERENCE

Date: September 10th, 1998 2:00pm

Between: FDA (HFD-170, Division of Anesthetics, Critical Care, and Addiction Drug Products).
Chemistry: Albinus D'Sa, Ph.D./Team Leader
Juanita Ross, Ph.D./Reviewer
CSO: Corinne P. Moody/Chief, Project Management Staff
Indira Kumar
And
Company Name: Elan Pharmaceutical Research Corporation
Contact: Diane Servillo/Sano, (954) 430-3340 ext. 298
Sharon Hamm/Elan, (770) 534-8239
Dennis Myers/Elan Regulatory - D.C.
Robert Simon, Director of Analytical Research and Development
Debra Ramos, Manager of Quality Assurance
Michael Schroder, Vice President of Regulatory Affairs
C. Betlach – Sano Research and Development
M. Gonzales – Quality and Assurance
J. Hodge – Quality Control, B. Morgan - Manufacturing

Topic: NDA 19-983 ProStep Supplement 011 – CMC Issues

Discussion: The FDA initiated the telecon to follow up on the following issues:

1. Proposed and executed batch records should be provided for the 11 mg strength patch.

   The sponsor agreed to provide this information to the FDA – (the executed batch record should be available in about 3 weeks).

2. Please submit all available stability data on all strengths.

   The sponsor will submit this data, including ANDA batches, commercial batches, accelerated /room temperatures.

3. Please include a regulatory specification sheet for all tests, such as Adhesion, Peel, Tack, and residual solvents.

   The sponsor will include all tests requested in a regulatory specification sheet via a commitment after enough data has been collected.

4. Please include a certificate of analysis for all lots of all strengths manufactured to date.

   The sponsor agreed to this.

5. Please include a validation report for the 22 mg and 7 mg patches.

The sponsor also agreed to submit data on the 11 mg strength when available.

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA # 19-983 Supplement # S-012 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF Trade and generic names/dosage form: Nicotine Transdermal System 22 mg/day & 11 mg/day
Action: AP AE NA

Applicant: Elan Pharmaceutical Research Corp. Therapeutic Class: 4 S

Indication(s) previously approved An Aid to stop smoking cigarettes.
Pediatric information in labeling of approved indication(s) is adequate inadequate

Indication in this application: The Over-the-Counter marketing of Nicotine Transdermal System as an aid to stop smoking cigarettes. (For supplements, answer the following questions in relation to the proposed indication.)

___1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

_X_3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

___a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___c. The applicant has committed to doing such studies as will be required.
(1) Studies are ongoing,
(2) Protocols were submitted and approved.
(3) Protocols were submitted and are under review.
(4) If no protocol has been submitted, attach memo describing status of discussions.

___d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.
See phase IV commitments in approval letter attached.

/S/ 12/23/98

Signature of Preparer and Title: Indira Kumar, CSO HFD-170 Date

cc: Orig NDA# 19-983
HF /Div File
NDA/PLA Action Package
HFD-006/K. Roberts (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)
(Rev. 12/22/98 IK/11:00am/ 12/23/98 2:05pm)