CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-543

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

PATENT INFORMATION

Columbia Laboratories, Inc. hereby certifies that we own the following U.S. patents:

U.S. Patent Number 4,615,697 – "Bioadhesive Compositions and Methods of Treatment Therewith." This patent was invented by J.R. Robinson and filed December 20, 1984. The patent was issued October 7, 1996 and is set to expire on October 7, 2003.

U.S. Patent Number 6,248,358 – "Bioadhesive Progressive Hydration Tablets and Methods of Making and Using the Same." This patent was co-invented by W.J. Bologna, H.L. Levine, P. Cartier, and D. deZiegler and filed on August 23, 1999. The patent was issued on June 19, 2001 and is set to expire on August 23, 2019.

The following pending patents are also owned by Columbia Laboratories, Inc.:

U.S. Patent Application Serial Number 09/596,073 – "Bioadhesive Progressive Hydration Tablets." This patent was co-invented by W.J. Bologna, H.L. Levine and D. deZiegler. The patent was filed on June 16, 2000.

U.S. Patent Application Serial Number 09/877,218 – "Bioadhesive Progressive Hydration Tablets." This patent was co-invented by W.J. Bologna, H.L. Levine and D. deZiegler. The patent was filed on June 16, 2000.

All four patents are Composition and Method of Use patents.

Howard Levine, Pharm.D.
Vice President
Columbia Laboratories, Inc.

MAY 13, 2002
Date

ITEMS 13 & 14

Patent Information
Pursuant to 21 C.F.R. 314.53
for
NDA Number 21-543

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Tradename (testosterone) Buccal Bioadhesive
- Active Ingredient(s): testosterone
- Strength(s): 30 mg
- Dosage Form: buccal bioadhesive
- Approval Date: _____

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: 4,615,697

Expiration Date: October 7, 2003

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) ___Y _X_N
2. Drug Product(Composition/Formulation) _X_Y ___N
3. Method of Use _X_Y ___N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Method of providing controlled release of a treating agent using a controlled release composition.

Name of Patent Owner: Columbia Laboratories, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Not Applicable

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U.S. Patent Number: 6,248,358

Expiration Date: August 23, 2019

Type of Patent--Indicate all that apply:

4. Drug Substance(Active Ingredient) ___Y _X__N
5. Drug Product(Composition/Formulation) __X_Y ___N
6. Method of Use _X__Y ___N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Method of delivering an active ingredient using a progressive hydration bioadhesive.

Name of Patent Owner: Columbia Laboratories, Inc.

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Not Applicable

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B. The following declaration statement is required by 21CFR 314.53. If any of the submitted patents have Composition/Formulation or Method of Use claims, it should be submitted for each patent that contains composition/formulation or method of use claims.

The undersigned declares that the above stated United States Patent Number 4,615,697 and United States Patent Number 6,248,358 cover the composition, formulation and/or method of use of Tradename (testosterone) Buccal Bioadhesive. This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

OR

- _X__the subject of this application for which approval is being sought.

Signed: Susan A. Witham
Name: Susan A. Witham
Date:
Title: Vice President, Regulatory Affairs
Telephone Number: 973-994-3999, ext. 7907

The above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

EXCLUSIVITY SUMMARY for NDA # 21-543

Tradename Striant™ (testosterone buccal system) mucoadhesive

Applicant Name Columbia Laboratories HFD-580

Approval Date June 19, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_x__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_x__/

   If yes, what type(SE1, SE2, etc.)? N/A

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /_x__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_x_ _/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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 # 21-015 AndroGel NDA 20-791 Testoderm-AT

NDA # 21-454 Testim NDA 19-762 Testoderm

NDA # 20-489 Androderm

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.)

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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 9:**

(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 /_x__/ NO /___/

(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 /_x__/

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 # COL 1621-05

Investigation #2, Study # COL 1621-07

Investigation #3, Study # COL 1621-010

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 #__, Study # COL 1621-05

Investigation #__, Study # COL 1621-07

Investigation #__, Study # COL 1621-010

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 # 60,906 YES /_x__/ NO /___/ Explain:

Investigation #2 and #3

IND # 60,906 YES /_x__/ 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? **N/A**

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 /_x__/

If yes, explain: _____

_____

_____

Eufrecina DeGuia June 17, 2003

Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
6/19/03 04:14:37 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-543 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: August 19, 2002 Action Date: June 19, 2003

HFD 580 Trade and generic names/dosage form: Striant™ (testosterone buccal system) mucoadhesive

Applicant: Columbia Laboratories Therapeutic Class: 3S

Indication(s) previously approved: testosterone replacement in hypogonadal men

Number of indications for this application(s): 1

Indication #1: testosterone replacement in hypogonadal men

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

■ No: Please check all that apply: ___Partial Waiver ✓ Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ■ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): TBD (Development plan and study protocol will be submitted to FDA by December 2003.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eufrecina deGuia
6/19/03 02:57:37 PM

DEBARMENT STATEMENT

Columbia Laboratories, Inc. 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.

Howard Levine, Pharm.D.
Vice President
Columbia Laboratories, Inc.

MAY 13, 2002
Date

NDA 21-543

Medical Team Leader's Memorandum: NDA

Date submitted: August 7, 2002
Date received: August 8, 2002
Memo completed: June 11, 2003

Sponsor: Columbia Research Laboratories, Livingston, N.J.
Drug product: Striant (testosterone buccal system) mucoadhesive
Dose and frequency: 30 mg twice daily
Route: buccal
Indication:
Related INDs: #60,906

1. Executive summary:
The purpose of this memo is to convey my recommendation to the Division Director regarding regulatory action on this application. I recommend that this application should be **approved**, pending one outstanding matter: final recommendation from the Offices of Compliance and New Drug Chemistry for the Striant manufacturing site in Milan, Italy. The Office of Compliance is expected to convey its recommendation via EES on Thursday, June 19, 2003. Our chemists will provide their final recommendation to the Division Director on June 19th, subsequent to receiving the EES notice.

From all other review perspectives, the sponsor has provided substantial evidence that the product, Striant (testosterone buccal system), is safe and effective for the indication proposed. The product repletes serum testosterone levels to the normal range in the majority of hypogonadal men who were tested. The NDA revealed no unexpected or serious adverse events.

The only regulatory issue of note concerns a Phase 4 commitment. The sponsor has agreed to continue their currently ongoing long-term European and U.S. safety studies (COL-1621-08 and 09) for one additional year, so as to collect an additional year of safety experience in at least 50 patients. These 50 patients would thus have a total of approximately 3 years of exposure. The Division requested this commitment so that oral safety of the product could be further assessed after a longer period of exposure than that submitted in this NDA. This group of 50 patients serves as a "lead" or "signal" group to observe for potential oral safety problems at exposure durations greater than those submitted in the original NDA.

2. Scientific background:
Male hypogonadism is defined as an absence or deficiency of endogenous testosterone associated with symptoms that might reflect this deficiency. "Hypogonadal" male patients include those with primary (testicular) or secondary (pituitary/hypothalamic) causes. Currently, normative data for serum total testosterone is available only for young, healthy, eugondal men. While the specific limits of normal vary by laboratory, the Division has traditionally used 300 ng/dL to 1050 ng/dL to define "normal limits". It has been assumed that serum testosterone in the normal range is intrinsically associated with clinical benefits, principally the maintenance of adult male secondary sex characteristics, body composition and sexual function. These areas include such clinical parameters as: libido, erectile function, mood, energy level, lean body mass, muscular strength, and bone. For purposes of this brief memo, it is important to understand that the

association between biochemical hypogonadism and symptoms, and the replacement of testosterone and relief of symptoms is not so straightforward. Specifically, not all men with biochemical hypogonadism will describe "hypogonadal" symptoms and not all patients who receive testosterone will have relief from those symptoms. Research in this area continues.

In defining efficacy for testosterone drug products, the standard that has been used is replacement of serum testosterone to the within the normal range. Therefore, "the normal range" serum total testosterone concentrations serve in a sense as a "historical control" in quantifying the efficacy of new testosterone replacement products. The metrics we use to compare the historical control to the study population are pharmacokinetic parameters, e.g. maximum, minimum, and average total T concentrations. We also assess drug effect on serum estradiol (E_2) and dihydrotestosterone (DHT). Finally, it is common for the investigations to include some clinical measures of hyponadism and these have included: libido and mood questionnaires, erectile function assessments, measurements of body composition, muscle strength and bone density.

3. Regulatory history

On April 4, 2000, a Pre-IND meeting was held to discuss the development of this testosterone buccal "tablet" (COL-1621). At that meeting, the key discussion points included:

1. the Division's acceptance of a single, open-label Phase 3 study to support an NDA,
2. the need for regular assessments of buccal/gingival irritation in Phase 3
3. the use of total testosterone Cmin and Cavg as primary endpoints for determining efficacy of this product,
4. the use of Cmax as an important factor in evaluating safety, and
5. consideration of additional dosage strengths other than 30mg and smaller dose-ranging trials

On August 30, 2000, the original IND was submitted. The original IND contained the protocol for a 100-patient, 3-month, open-label, "pivotal" Phase 3 trial entitled COL-1621-05. The study was considered safe to proceed.

> **Reviewer's comment**: Despite Division's input regarding conducting additional dose-ranging "Phase 2-type studies", the sponsor submitted their pivotal Phase 3 U.S. study protocol (using 30 mg twice daily) in the initial IND. Also, there was no End-of-Phase 2 meeting held despite Division's recommendation to have one.

On October 3, 2000, a teleconference was held with sponsor to convey comments from the Division of Dermatological and Dental Drug Products (DDDP). The dental consultant agreed with the general design and procedures of the Phase 3 study, cautioning only the following:

1. additional gum checks should be conducted on Days 3 and 7 (but these could be done [*and were done*] in a smaller, 7-day, pK study [Study –03]),
2. the system placement should be frequently alternated between mouth sides, and
3. patients should examine their own gum application sites frequently and should contact the investigator for pain, local symptoms or signs.

On May 14, 2001, (in Serial 004 to the IND) the sponsor submitted the protocol for the U.S. long-term, open-label extension study (Study –09) to the single, pivotal Phase 3 clinical trial.

On December 5, 2001, a Pre-NDA meeting was held with sponsor. The major issues included:

1. the requirement for at least 50 patients to be exposed for at least 1 year – this experience could be submitted with the 4-month safety update,

2. Caverage could serve as the primary efficacy endpoint, although Cmin and Cmax would still be carefully evaluated,
3. there probably is little safety risk associated with swallowing Striant, since it is a non-methylated testosterone,
4. the sponsor should submit information regarding quality of mucoadhesion,
5. information about DHT should be submitted.

On August 7, 2002, the original NDA (21-543) was submitted.

4. Contents of the NDA (clinical)

From a clinical and clinical pharmacology perspective, this NDA is supported by a single Phase 3 "pivotal" trial, two Phase 2 comparative studies (one versus Androderm and one versus Androgel), two Phase 1 pK studies (one single-dose and one 7-day multiple dose study) and three long-term safety extension studies.

Reviewer's comment: The quality and number of trials is considered adequate in support of an NDA for testosterone replacement therapy.

These trials are summarized as follows:

1. COL-1621-05:
   This was the "pivotal" Phase 3 clinical study. The study was conducted in 98 hypogonadal male at nine U.S. centers. It was open-label in design and relied on serum levels of serum T as the primary endpoint. The treatment duration was 3 months. There was a single dose studied (30 mg twice daily).

2. COL-1621-07:
   This was a randomized, open-label, active-controlled, crossover study comparing Striant 30mg BID to *Androderm* 5mg daily. A total of 58 hypogonadal men were randomized and received 7 days of each treatment. Again, serum T served as the primary efficacy endpoint.

3. COL-1621-010:
   This was a randomized, open-label, active-controlled, parallel-arm design study comparing Striant 30mg BID to *Androgel* 5gm daily. A total of 28 hypogonadal men were evenly randomized (1:1) and received 14 days of one of the two treatments. Again, serum T served as the primary efficacy endpoint.

4. COL-1621-02 and -03:
   These were Phase 1 pharmacokinetic and preliminary efficacy studies.

   Study -02, was a randomized, double-blind, placebo-controlled, single-dose (30mg) pharmacokinetic study in 12 hypogonadal men.

   Study -03 was an open-label study in 12 hypogonadal males. Treatment consisted of 7 days of twice daily Striant 30mg.

5. COL-1621-04, -08 and -09
   These were open-label safety extensions to Studies -02, -03, -05 and -07.

Study –04 was the extension study to the Phase 1 single-dose and 7-day multiple-dose pK studies, (Studies -02 and –03, respectively). Study –04 was 12 weeks in duration and included 12 patients. A single dose was studied (30 mg twice daily).

Study –08 is the ongoing safety extension to Studies –04 and –07. It is being conducted outside the U.S. and is still ongoing. The study duration is one year. Twenty-nine patients are enrolled. At the time of the 4-month safety update, 20 patients had exceeded 6 months of exposure and 13 had exceeded 1 year. The dose is 30mg twice daily.

Study –09 is the ongoing safety extension to pivotal Study –05. It is being conducted entirely in the U.S. and is still ongoing. The study duration is one year. At the time of the 4-month safety update, one hundred sixty-three (163) patients were enrolled; 97 patients had at least 6 months of exposure and 38 had at least 1 year of exposure.

5. Clinical results

5.1. Efficacy results

Reviewer's comment: The results from the 5 relevant clinical studies are consistent. In summary, the results reveal that Striant at a dose of 30mg twice daily is effective in replacing testosterone to within the normal range in hypogonadal men. Herein, the results are reviewed in brief. For additional detail, please see Dr. Handelsman's primary clinical review and Dr. Jarugula's primary clinical pharmacology reviews.

5.1.1. Pivotal Study -05

Study –05 was an open-label study in 98 hypogonadal men (T <275 ng/dL) conducted at nine U.S. centers. This was the largest of the submitted clinical investigations. Results from the other trials were consistent with those from this pivotal. All patients received the same dose (30mg twice daily). The treatment duration was twelve weeks. Twenty-four hour pharmacokinetic (pK) assessments for serum testosterone were obtained after twelve weeks of therapy. The primary endpoint was:

> The percentage of treatment responders, defined as those patients having time-averaged steady-state total T concentrations ($C_{avg[0-12]}$ and $C_{avg[12-24]}$) within the normal physiological limits (300 to 1050 ng/dL) and the average of the total serum T concentrations *at the end of* each of the last two consecutive dosing intervals at Week 12 of at least 300 ng/dL or greater (the "trough level").

The sponsor requested to conduct (and Division agreed to review) an additional analysis, referred to in the NDA as the "supplemental primary efficacy endpoint", wherein the primary endpoint was defined as:

> The percentage of treatment responders, defined as those patients having time-averaged steady-state total serum T concentration over the last 2 consecutive 12-hour dosing intervals ($C_{avg[0-24]}$) within the physiologic range (300 to 1050 ng/dL)

Secondary endpoints and analyses included measures of free testosterone, dihydrotestosterone (DHT) and various other pK analyses of the total T data including Cmax, Cmin and AUC.

Overall, 98 patients were enrolled. Of these, 84 completed the entire study. Ten patients withdrew voluntarily ("patient desire to withdraw"). One patient missed several appointments and was withdrawn. One died as a result of a motor vehicle accident. Two additional patients were excluded from the efficacy analysis because of significant protocol violations at the time of the Week 12 serum sampling schedules.

Reviewer's comment: The number of withdrawals and reasons for withdrawals are acceptable in this study.

The mean age was 53.6 years (range = 20 to 75). Overall, 68 patients were Caucasian, 9 (9.2%) were black, 15 (15.3%) were Hispanic, 4 (4.1%) were Asian, and 2 were of "other" ethnic origin. The mean age was 92.2 kg (range: 50 to 128 kg). Forty-one (42%) patients drank alcohol. Ten patients (10.2%) reported current use of tobacco and 40 (41%) reported previous use. The mean baseline total serum T concentration (based upon a single AM draw) in the per-protocol population (n=80) was 149 ng/dL with a standard deviation of 88 ng/dL.

Reviewer's comment: The study demographics are appropriate for this indication

The results of efficacy testing are described in tabular format in Tables 1 and 2 and in Figure 1 below.

Table 1. Percentage of treatment responders at Week 12 in the per-protocol population (n=82)

Endpoint	**%(N)**	**95% CI**
Percentage of treatment responders (as per the primary endpoint)	72.0% (59)	60.9% - 81.3%
$C_{avg(0-12)}$ within physiologic range	84.1% (69)	
$C_{avg(12-24)}$ within physiologic range	80.5% (66)	
$C_{12/24(avg)}$ within physiologic range (trough)	90.2% (74)	
Percentage of treatment responders (using the "supplemental" primary endpoint)	*86.6%* (71)	*77.3% - 93.1%*

Reviewer's comment: The success rates reported in this trial are comparable to the currently approved testosterone drug products.

Table 2. Selected pharmacokinetic parameters for serum total testosterone at Week 12 in the per-protocol population (n=82)

Parameter	**Mean (±SD)**
$C_{avg(0-24)}$	520 ng/dL (±205)
$C_{max(0-24)}$	969 ng/dL(±442)
$C_{min(0-24)}$	291 ng/dL (±130)

Reviewer's comment: These mean values and standard deviations reflect replacement of T to within the normal range. The outliers are relatively few. Even in these few outliers, the deviation from normal limits is generally not excessive and dos not last very long (see additional details below).

Graphically, the mean serum total T concentration-time curve for the Week 12 twenty-four hour assessment (in the per-protocol population) is depicted in Figure 1.

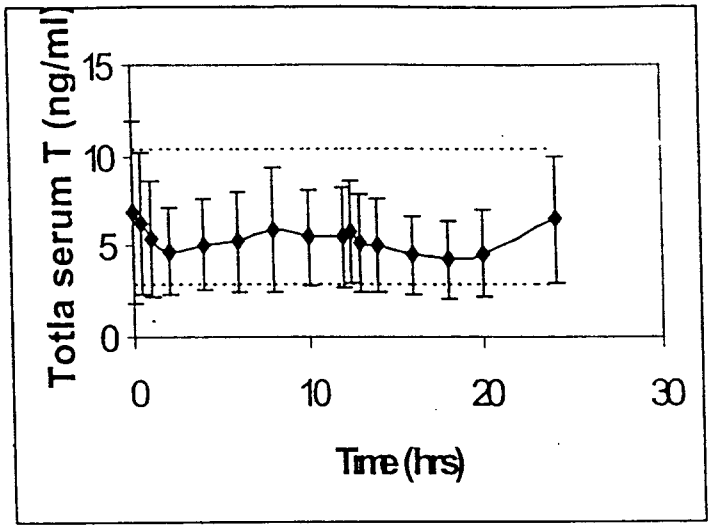

Figure 1. Mean (±SD) serum total T concentration-time curve for the Week 12 twenty-four hour assessment (in the per-protocol population)

Of note, the mean total T concentrations based upon a *single blood draw* in the 82 per-protocol patients at Baseline, at Week 4 and at Week 8 (4 to 8 hours after dosing) were: 149 ng/dL ± 88 ng/dL, 586 ± 340 ng/dL and 539 ± 328 ng/dL, respectively, reflecting adequate replacement of T in hypogonadal men.

At Week 12, in the per-protocol population, *the mean percentage of time* over the 24-hour sampling period in which serum T levels were within the normal range was approximately 75%. In the 71 responders (for the supplemental primary endpoint), this percentage was 84%.

> Reviewer's comment: These efficacy results in the per-protocol population support the efficacy of the product in replacing testosterone in testosterone deficient males.

In the 11 non-responders (for the supplemental primary endpoint), the principal reason for their non-response was Caverage below the limit of normal (n=9). Two patients failed as a result of $Caverage_{(0\text{-}24)}$ above the normal limit.

In the 23 non-responders (for the more rigorous "per-protocol" primary endpoint), the principal reason for their non-response was Caverage below the limit of normal (n=19). Four (4) failed as a result of $Caverage_{(0\text{-}24)}$ above the normal limit.

> Reviewer's comment: In my opinion, the extent of non-response as a result of inadequate serum concentrations is acceptable for a product of this type. The majority of patients are repleted to within the normal range.

In terms of excessive concentrations of serum total T (which we have traditionally approached as a potential safety issue but also has implications for efficacy), the sponsor and the Division analyzed the data for each individual patient with a Cmaximum (Cmax) above the upper limit of normal. A total of twenty (20) patients had a Cmax above the upper limit of normal. The clinical

and clinical pharmacology review teams concluded that a serum total T above 1500 ng/dL might be clinically relevant. Eleven patients (11) had such a value. Of these eleven, five (5) patients had a Cmax above 2000 ng/dL. The eleven patients with a Cmax of at least 1500 ng/dL are depicted in Table 3 below. In the table, Cmax is underlined for each patient. Times for application are approximately 8 a.m. and 8 p.m.

Table 3. Eleven patients with Cmax above 1500 ng/dL on Week 12. All serum total T concentrations listed. Dosing at 8 a.m. and 8 p.m. Maximum concentration underlined.

	#1005	#1009	#7003	#8002	#9002	#2018	#8020	#8017	#8005	#5032	#1007
7:45 a											
8:15 a											
8:45 a											
9:45 a											
11:45 a											
1:45 p											
3:45 p											
5:45 p											
7:45 p											
8:15 p											
8:45 p											
9:45 p											
11:45 p											
1:45 a											
3:45 a											
7:45 a											

Reviewer's comments:

1. In 6 of eleven patients, the maximum concentration is attained at 7:45 a.m., prior to the next dose. In a seventh patient, the maximum concentration is attained at 8:15 but that value is very close to the 7:45 a.m. concentration. In an eighth patient, the A.M. concentration was not maximum but it was consistent with the maximum. Thus, if a single blood drawn for serum total T was conducted on all these patients just prior to A.M. dosing, the maximum concentration (or essentially the maximum) would have been seen in 8 of 11 patients. I am comfortable in recommending such a draw in labeling as a reasonable and practical method to help avoid excessive serum T exposures.
2. In the patients that would not have been detected this way, the pK profile is not clinically worrisome since that the maximum concentration is short-lived and out of context for the remainder of the values.

5.2. Safety results

Reviewer's comment: In summary, the safety assessments in the Striant trials revealed the product to be well-tolerated. There were no unexpected serious adverse events. The majority of the commonly reported AEs were related to the mouth and gum. Others adverse events consistent with an androgenic pharmacological effect were reported. For additional details, the reader is referred to Dr. Handelsman's primary review.

Safety information was collected in each Striant trial but this section will focus on the data from the pivotal Phase 3 trial (Study 05) and the safety extensions (Studies 08 and 09). Herein these results are presented in brief:

In pivotal Study 05, 98 patients were enrolled and 84 patients had twelve weeks of exposure. These were hypogonadal men with a mean age of 53.6 years. Dosing was 30 mg twice per day (a.m. and p.m.). The study was open-label and there was no comparator group. Safety was assessed through the collection of clinical adverse events, monthly oral exam, measurement of vital signs and routine clinical laboratories.

There was one patient death (a motor vehicle accident). There were 2 other serious AEs (in one case, pneumonia and in the other, hyperkalemia due to acute renal failure). None of the 3 SAEs was attributable to Striant. There were 4 AES leading to subject discontinuation (4.1%). Two were gum irritation, one due to mouth irritation and one due to bad taste in mouth. All these events resolved within 8 days of subject discontinuation.

The most commonly reported clinical adverse events with at least a possible relationship to study drug are depicted in Table 4 below:

Table 4. Incidences of the most commonly report clinical adverse events judged by investigator to be at least possibly related to Striant; Study-05 (n=98).

Adverse event	**Striant™ (n=98)**
Gum or Mouth Irritation	9.2%
Taste Bitter	4.1%
Gum Pain	3.1%
Gum Tenderness	3.1%
Headache	3.1%
Gum Edema	2.0%
Taste Perversion	2.0%

In terms of the gum-related adverse events themselves, a total of 16 patients reported 19 gum-related adverse events. Of these, ten patients (10.2%) reported 12 events of mild intensity, four patients (4.1%) reported 5 events of moderate intensity, and two patients (2.0%) reported 2 events of severe intensity. Most of these events were judged probably or definitely related to treatment with Striant™. The majority of gum-related adverse events were transient. Gum irritation generally resolved in 1 to 8 days. Gum tenderness resolved in 1 to 14 days.

Other clinical adverse events reported in one patient each and at least possibly related to Striant included: abdominal cramp, acne, anxiety, asthma (acute), breast enlargement, breast pain, buccal mucosal roughening, difficulty in micturition, fatigue, gingivitis, gum blister, gustatory sense diminished, hematocrit increased, lipids serum increased, liver function tests abnormal, nose edema, stinging of lips, and toothache.

In the case of "hematocrit increased", Patient #2013 had a rise in the hemoglobin and hematocrit to a maximum of 18.6 g/dL and 60%, respectively, at Week 12. These were not associated with elevated serum total T, although the investigator still considered the event as definitely related to drug. One additional patient had a henatocrit of 55% at Week 12, but this was not reported as a clinical AE.

In the case of "lipids serum increased", Patient #8005 had hypertriglyceridemia at Week 12 (triglyceride level = 413 mg/dL) which was associated with a slightly excessive serum total T Cmax on that same week ( ). However, in this patient, serum total T level had been excessive at an earlier timepoint in this trial (at Week 8 the single-draw, pre-dose serum total T was . One other patient had increased triglycerides reported as a "non-related" clinical AE. In this patient (#4004), there was no evidence of excessive serum T.

Reviewer's comment: It is plausible that excessive serum T can lead to changes in the serum lipid profile.

In the case of "liver function tests abnormal", Patient #4009, had an increase in the serum ALT to 2.5X ULN at Week 12, not associated with excessive serum T. There were 5 other patients with shifts from normal to high ALT, but these were all approximately 2X ULN or less.

Reviewer's comment: There was no signal of hepatic toxicity in this trial.

Other routine labs, EKGs and vital signs were without clinically significant changes.

Finally, gum examinations were performed at baseline and monthly thereafter and these actually showed a diminution in the incidence of gingivitis over time (at Baseline [32.6%], at Week 4 [10.2%], at Week 8 [10.2%] and at Week 12 [11.2%]). No new oral lesions of any sort were noted.

The sponsor submitted an interim analysis of safety from the ongoing, long-term, safety extension Studies –08 and-09 (U.K. and U.S., respectively). In Study 08, 29 patients are enrolled; 20 have at least 6 months exposure and 13 at least one year. In Study 09, 163 patients are currently enrolled; 97 have at least 6 months exposure and 38 have at least one year.

In Study-08, there were no deaths, 1 SAE and 4 discontinuations due to AEs. The SAE was chest pain and this was considered unrelated to drug. The discontinuations were due to: gingival recession, anxiety aggravated, abdominal pain, and rash/medication error. Of twenty patients with 6 months exposure, eight reported an AE. Of thirteen patients with 12 months exposure, 5 reported an AE. Most of these were unrelated to drug. Those that were related to drug included gum and mouth irritation and these were mild to moderate in intensity.

In Study –09, there were no deaths, 7 SAEs, and 11 discontinuations due to AEs. None of the SAEs were considered even possibly related to drug except one: one patient reported a diagnosis

of prostate cancer thought possibly related to "unmasking" of latent prostate cancer by drug. The discontinuations were due to: gingivitis (3 patients), nervousness and fatigue aggravated, serum PSA increased, polycythemia (2 patients), headache, taste perversion, pruritis, and eye infection.

Of the 97 patients with 6 months exposure, 35 reported an AE. Of the 38 patients with one year of exposure, 10 reported an AE. In the 6 months group, about half of the AEs were considered at least possibly related to drug and these included: polycythemia (in two patients), depression, hypertension, pruritis, buccal inflammation, elevated PSA (in two patients), anxiety, stomatitis, bitter taste, gingivitis (in two patients), nausea, toothache, renal function abnormality and URI. In the 12 months group, about 40% of the reported AEs were considered at least possible related to study drug and these included: depression, hypertension, renal function abnormality, nausea and URI. The intensity of most of these events was mild to moderate. The only severe adverse events were: abdominal pain, elevated serum PSA, unstable angina, and paralysis/dizziness (in one patient and not related to drug).

Reviewer's comments:

1. There is no evidence that the incidence or severity of adverse events increases with increasing Striant exposure.
2. The gum-related adverse events with Striant appear to be mild to moderate in intensity, are easy to diagnose, and resolve with stoppage of drug.
3. Events potentially related to androgen therapy were seen in the Striant safety database and these included: increased serum PSA, prostate cancer (in one case), emotional changes (e.g. anxiety), hypertension, and headache. It is not possible to quantify the exact role of the androgen in these events due to the inherent background incidence and the lack of a placebo control
4. Polycythemia was noted in several patients, the maximum hemoglobin noted was 18.6 gm/dL (maximum hematocrit =60%). Testosterone does increase erythropoiesis. This risk is stated in the package insert and the label instructs prescribers to regularly measure the effect of Striant on hemoglobin/hematocrit. The actual incidence of polycythemia is infrequent. It does not appear that erythropoiesis is directly related to excessive serum T levels, but the actual pathophysiology remains unclear.

6. Clinical and regulatory issues from the other review team disciplines

6.1 Office of Drug Safety: Division of Surveillance, Research, and Communication Support (ODS/DSRCS)

Ms. Best and Ms. Piazza-Hepp provided an extensive review of the Patient Package Insert (PPI). Their review comments focused on the fact that testosterone is a controlled substance and must be handled by patients accordingly. They also revised the format of the PPI to meet the new FDA criteria. Finally, they inquired as to whether kissing might lead to exposure of partners to testosterone.

The proposed PPI revisions were incorporated into the Division's version of the PPI. Sponsor agreed with the revisions, including specific information about controlled substance care and potential drug risks. The clinical review team and clinical pharmacology team indicated that swallowing drug testosterone was not expected to have a clinical effect and in addition, the

amount of testosterone in the saliva at any given time was very, very little. Therefore there would be no precaution added about kissing.

6.2 Office of Drug Safety: Division of Medication Errors and Technical Support (ODS/DMETS)

Ms. Mahmoud and Ms. Holguist conveyed the DMETS opinion regarding the tradename and the container/carton labeling. DMETS had "no objection" to the proposed tradename, Striant. DMETS did comment that the established name would require consultation from Dan Boring, Chair of the Labeling and Nomenclature Committee. This issue was resolved during a meeting of Office of New Drug Chemistry representatives and Dan Boring. The established name was set as (testosterone buccal system) mucoadhesive. Sponsor concurred.

All container/carton and blister card comments were noted by the chemistry reviewer and successfully applied through cooperative negotiations with sponsor. Package insert labeling comments were also noted. In response to the DMETS suggestion to add pictorials to the PI, clear pictorials were added to the PPI (which is physically attached to the PI). Further, the instructions to patients regarding system fall-off were revised for clarity, as recommended.

6.3 Division of Drug Marketing, Advertising and Communications (DDMAC)

Ms. Benedetto and Ms. Masucci provided comments about the package insert and patient package insert from the perspective of DDMAC. All these comments were noted and were incorporated into the Division's revision of the PI. These were successfully negotiated with the sponsor

6.4 Office of Biometrics

Dr. Welch provided a brief memo to the action package. He described the results as "descriptive" in terms of statistical analyses. He found there to be no reason to doubt the sponsor's actual reporting of these results. Therefore, for the testosterone replacement therapy indication, the reporting and analyses of the efficacy results were acceptable to Biometrics and the analysis itself was deferred to Clinical and Clinical Pharmacology disciplines.

6.5 Pharmacology/Toxicology

Drs. Thornton and Jordan provided a brief memo to the action package. The NDA was considered "approvable".

Dr. Thornton notes that there are no safety concerns for testosterone due to extensive clinical experience. For Striant specifically, there appeared to be only two potential safety issues: local toxicity and toxicity of the excipients. According to Dr. Thornton (and confirmed by the clinical

review), local adverse events were reported at a low rate of incidence, providing no evidence of significant local toxicity. The components of the system, including colloidal silicon dioxide, ——, polycarbophil, hydroxypropylmethylcellulose, and —starch are used in other products that are administered buccally as well as via other routes. From a literature review of these components, there was no evidence of a safety concern. Thus, she concluded that there were no relevant non-clinical safety issues for the proposed human use of Striant.

6.6 Microbiology

Drs. Riley and Cooney found the NDA to be "acceptable" on the basis of product quality microbiology. In summary, they commented that stability testing during the development has demonstrated that the drug product is of appropriate microbial quality and is likely to remain so over time. Therefore, they conclude that Striant presents "very little risk" from the standpoint of product quality microbiology.

6.7 Financial Disclosure

Dr. Handelsman reviewed the financial disclosure materials submitted by the sponsor. He concluded (and I agree) that adequate documentation was submitted to comply with 21 CFR 54. Further, there was no disclosure of financial interests that could bias the outcomes of the Striant trials.

6.8 Division of Dermatological and Dental Products (DDDP, HFD-540)

Since Striant is to be applied to the buccal mucosa, DDDP was consulted during the IND development phase and at the time of the NDA. As noted above, protocol review comments from DDDP were conveyed to sponsor for the pivotal trial (COL-1621-05) via project manager teleconference. Drs. Hyman and Kelsey also provided formal consult to DRUDP at the time of the NDA.

DDDP's NDA consult focused on several areas of concern:

1. Is testosterone itself a factor in the development of gingivitis?
2. Were "gum checks" performed adequately in Phase 3?
3. Would a placebo control in the pivotal Phase 3 trial have allowed for more useful safety results regarding gingivitis?
4. How does one explain the reduction (not increase) in incidence of gingivitis over time in the pivotal Phase 3 trial?
5. How does one explain the low incidences of gingivitis at baseline in the safety extension studies?
6. Is there evidence in the literature that testosterone itself is a factor in causing oral tumors?
7. Would a longer-term Phase 4 study in "well-monitored" patients provide better answers to these safety questions than the studies conducted in support of this NDA?

Dr. Handelsman and I reviewed the Dental consult in great detail. We also discussed each point with sponsor and received sponsor's written responses to each issue. Finally, we discussed the potential oral safety issues with an expert in otolaryngology. After careful consideration, I hold that none of the comments in the Dental consult should preclude approval of Striant.

In terms of the individual issues, the following comments address some of the dental issues:

1. Testosterone itself does not appear to cause gingivitis. Some authors have noted an increase in gingivitis during puberty, but this appears to be related to progesterone and perhaps estrogen, but not testosterone. In fact, some studies show that testosterone may actually act as an anti-inflammatory agent.
2. Evidence exists that the gum checks in Phase 3 were adequate. The study investigators were not dentists, per se, but the sponsor provided extensive investigator education including photo-documentation and other materials. The investigators were all qualified endocrinologists and internists generally located at prestigious university institutions. They all had experience in conducting clinical trials. They were asked to comment on gingivitis, edema, ulceration, plaques and leukoplakia, including severity. Dental consultation was available as necessary. Separate CRFs for oral health were maintained at baseline and at each monthly visit. Both sides of the mouth were checked at each visit (without product in place). I am comfortable that these checks were adequate.
3. A placebo group may have helped clarify the independent effect of testosterone, but the lack of one does not preclude the overall safety conclusion: Striant was only mildly irritating in the clinical trials.
4. The baseline incidence of gingivitis in the U.S. pivotal study, COL-1621-05, was as expected in the general population. We agree that there was a reduction in incidence of gingivitis over time in this study. This may have been due to improved patient oral health compliance or perhaps due to withdrawal of subjects with gingival irritation. Nonetheless, in my opinion, the results of the study are believable, accurate and not worrisome.
5. The baseline gingivitis rates in the extension studies were low. This again was to be expected as "veteran" patients from previous studies had fairly low incidence rates at the final visit of their previous study. There were some "new" patients in the U.S. extension study, COL-1621-09, and thus, the baseline gingivitis rate is slightly higher in U.S. Study -09 compared to the European extension study, -08.
6. The literature does not support an association between testosterone and oral cancer in either humans or animals. The major excipients in Striant are carbomer and polycarbophil. These polymers are used chronically and widely in the approved drugs Crinone and Replens. There has been no evidence that these excipients cause cancer.
7. Despite the overall oral safety of the product as seen in the NDA, the sponsor is willing to continue a long-term extension study for an additional year in order to collect approximately 3 years of safety information on approximately 50 well-monitored patients. Finally, the sponsor is also willing to acknowledge in the label that there is a current lack of safety data greater than 1 year in duration.

The final dental comment is that alteration of application site between left and right mouth sides was done in Phase 3 and this may limit adverse events. Therefore, the labeling (especially the PPI) instructs patients to use both sides of the mouth and to alternate sides.

6.9 Division of Scientific Investigations (DSI)

Clinical site inspections were not conducted for this NDA. On December 3, 2002, the Division requested site inspections. On January 3, 2003, Mr. Blay stated that inspections may not be warranted for this NDA unless the medical officer had "particular concerns". Since there were no particular concerns noted in the application, DSI opted to not conduct clinical site inspections. The clinical review team agreed with this decision.

6.10 Office of New Drug Chemistry (ONDC)

Drs. Agarwal and Rhee found the application to be "approvable" from a chemistry, manufacturing and controls perspective. At this time, the final recommendation cannot be "approve" until Compliance conducts the Milan maufacturing site inspection and conveys an "acceptable" recommendation.

The major issue was the dosage form name. Ultimately, through ONDC consensus, it was agreed that the established name would be: (testosterone buccal system) mucoadhesive. While the product may appear "tablet-like" and may be produced like a tablet, it was believed that the word "tablet" might imply a product that is swallowed or allowed to disintegrate under the tongue. In this case, the product is intended not to disintegrate but to slowly hydrate and thus release drug substance into the saliva. Therefore, the word "system" appeared more appropriate to describe the product.

Another issue is that of adhesion. Dr. Agarwal writes that adhesion quality will be maintained through an in-vitro adhesion test and acceptance criteria for this test are in place and obtained values were within normal limits.

The final issue of note was that of stability with and without
Comparative stability, dissolution and adhesion data between
systems were available and did not demonstrate any significant differences. Therefore, a
for marketing was found acceptable.

6.11 Pediatric Information

Therefore, I believe that a deferral of pediatric studies is appropriate at this time, especially considering the sponsor's expressed commitment to pursue this matter in the near future.

6.12 Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

Drs. Jarugula and Parekh worked closely with the clinical review team on this application, as is generally the case with testosterone drug products. OCPB found the application to be "acceptable". The following are relevant comments from the review:

1. Dr. Jarugula agreed with the clinical team that Striant was shown to replete testosterone to normal limits in the majority of hypogonadal men studied. He did acknowledge that a small percentage of patients "failed to respond" as a result of inadequate Caverage levels and an even smaller percentage failed as result of excessive Caverage levels.

   Reviewer comment: For the supplemental primary endpoint, approximately 10% of patients failed as a result of low Caverage and approximately 2.5% failed as a result of high Caverage. In my opinion, this is clinically acceptable for a product of this type.

2. Twenty men (20) had Cmax above normal range. Nine had potentially clinically relevant Cmax of 1500 ng/dL or greater and 5 of these had a Cmax of 2000 ng/dL or greater. Dr. Jarugula did acknowledge that in these patients, the excessive Cmax levels were transient.

   Reviewer's comments:
   1. I am under the impression that there are 11 men with Cmax > 1500 ng/dL while Dr. Jarugula believes that there are nine. This makes little clinical difference.
   2. In these patients, the elevated Cmax was transient, lasting no more than 4 hours of the day, while most other values obtained during the day were within normal limits. The majority of the elevations occurred just prior to A.M. dosing. Therefore, as a means of managing this issue, it was decided that the labeling should advise physicians to check their patients' serum total T concentrations at Week 4 or later, just prior to A.M. dosing in order to check for excessive serum T levels. If such a result was noted, Striant should be discontinued. Sponsor agreed with this approach. I find this approach clinically acceptable.

3. Neither eating nor drinking appeared to affect Striant efficacy in the Phase 3 pivotal trial.

4. Mean serum DHT was in the normal range. Ratios of serum T to DHT ranged from 9-12 and were generally within normal range. Some individuals did have serum DHT concentrations above the upper limit of normal.

   Reviewer's comment: It is my understanding the 5-alpha-reductase is not found in the buccal mucosa. This is proven by the normal range of serum T/DHT concentrations seen in the pivotal trial

5. The percentage of swallowed buccal systems was low. In the Phase 3 trial, twenty-one (21) patients reported swallowing a total of 78 systems resulting in an incidence of swallowed systems of 78/15,890 (or 0.49%).

   Reviewer's comment: Swallowed systems should be rapidly metabolized and should have no pharmacological androgenic effect. Since the product is not methylated and since there was no evidence of hepatic toxicity in any Striant trial, it is considered unlikely that swallowed Striant will injure the liver. In my opinion, the percentage of swallowed systems and the lack of demonstrable clinical toxicity associated with swallowing the system (in the clinical trials) is clinically acceptable.

7. Forty-nine patients reported 362 events of "dislodged" or "non-adherent" system. The overall incidence for lack of adhesion of system (by patient) was 2.3%. System adhesion appeared to improve with continued patient use. In Study –05, at study start, the total number of systems requiring replacement was approximately 160 and in the last week of the study the number requiring replacement was 33.

   Reviewer's comment: The incidence of detachment appears to improve with use. Sponsor argues that this is a matter of patient education and experience with using the product. In addition, sponsor argues that the product should still be considered as "adhered" and is effective even if it is stuck to the lip or check and not the actual gum.

8. Striant provided consistent mean serum T levels across at least 3 different trials.

9. Assessment of interaction with drugs known to cause dry mouth was limited in scope and should be seen as exploratory.

   Reviewer's comment: Since the product works by hydration, then at worst, dry mouth would probably lead to lack of efficacy not toxicity. Currently, we do not have sufficient information to provide clinical guidance in the label on this issue.

10. There appeared to be no difference in serum T levels between those with gum abnormalities and without gum abnormalities.

    Reviewer's comment: There were no exclusions for gum abnormalities in the Phase 3 pivotal trial. There is no current restriction in the label regarding gum abnormalities.

11. The performance of Striant was found to be comparable to Androgel 5mg daily (a low non-titrated dose) in a single, small and exploratory comparator trial.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark S. Hirsch
6/12/03 12:18:04 PM
MEDICAL OFFICER

Daniel A. Shames
6/12/03 07:00:36 PM
MEDICAL OFFICER

MEMORANDUM

Date: June 6, 2003

From: Harry Handelsman, D.O.
Medical Officer
DRUDP (HFD-580)

Re: Review of financial disclosure documents

To: NDA 21,543

I have reviewed the financial disclosure information dated May 29, 2002 and submitted August 8, 2002. by Columbia Laboratories, Inc.in support of their NDA 21,543.for Striant® (testosterone) buccal bioadhesive.

Five pharmacokinetic studies involving 64 subjects, and 7 clinical studies involving 323 subjects, were conducted by a total of 78 principal and subinvestigators at 24 clinical sites.

Documents Reviewed:

Financial certification information submitted August 8, 2002 by the sponsor, certified that no financial arrangements were made with any listed clinical investigator as defined in 21 CFR 54.2(a). The sponsor further certified that no listed clinical investigator had a proprietary interest in this product or significant equity in the sponsor as defined in 21 CFR 54.2 (b), or was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of these trials.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Harry Handelsman
6/9/03 11:11:05 AM
MEDICAL OFFICER

Mark S. Hirsch
6/12/03 12:15:00 PM
MEDICAL OFFICER
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: September 30, 2002
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSER
Columbia Laboratories, Inc.

2. DATE OF SUBMISSION
5/28/03

3. ADDRESS *(Number, Street, City, State and Zip Code)*
354 Eisenhower Parkway
Plaza 1, Second Floor
Livingston, New Jersey 07039

4. TELEPHONE NUMBER *(Include Area Code)*
(973) 994-3999

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
COL- 1621 (testosterone buccal system) mucoadhesive

6. IND NUMBER *(If previously assigned)*
60, 906

7. INDICATION(S) *(Covered by this submission)*
Testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.
Pending NDA No. 21-543
DMF
DMF DMF
DMF DMF

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 2 2

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☒ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☒ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- ☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☒ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

[redacted], consultant for Columbia Laboratories, Inc.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

[redacted], consultant for Columbia Laboratories, Inc.

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Susan Witham Vice President, Regulatory Affairs Columbia Laboratories, Inc.	Susan Witham	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
354 Eisenhower Parkway Plaza 1, Second Floor Livingston, NJ 07039	(973) 994-3999, ext. 7907	5/28/03

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
01 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

16 Page(s) Withheld

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: December 3, 2003	DUE DATE: February 7, 2003	ODS CONSULT #: 02-0219

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Freshnie DeGuia
Project Manager
HFD-580

PRODUCT NAME:	NDA SPONSOR: Columbia Laboratories.
Striant (Testosterone) Buccal Bioadhesive 30 mg NDA#: 21-543	

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Striant" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS: DMETS has no objections to the use of the proposed proprietary name Striant. DDMAC finds the name acceptable from a promotional perspective. DMETS recommends implementation of the labeling revision outlined in section III of this review to minimize potential errors with the use of this product. Additionally, please consult Dan Boring, Chair of CDER's Labeling and Nomenclature Committee for guidance on the proper designation of the established name.

DMETS decision is considered tentative. This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

/S/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 23, 2003

NDA# 21-543

NAME OF DRUG: **Striant**
(Testosterone) Buccal Bioadhesive
30 mg

NDA HOLDER: Columbia Laboratories

I. INTRODUCTION:

This consult is written in response to a request from the Division of Reproductive and Urologic Drug Products, for an assessment of the proposed proprietary name, Striant. Blister labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Striant contains the active ingredient testosterone, and is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The recommended dosing schedule for Striant Buccal Bioadhesive therapy is the application of one buccal bioadhesive (30 mg) to the gum region twice daily; morning and evening. The Striant Buccal Bioadhesive product should be placed in a comfortable position just above the incisor tooth (on either side of the mouth). Upon opening the packet, the rounded side surface of the product should be placed against the gum and held firmly in place with a finger over the lip and against the product for 30 seconds to ensure adhesion. The buccal bioadhesive is designed to stay in position until removed. If the product fails to properly adhere to the gum or should fall off during the 12 hour dosing interval, the old product should be removed and a new one applied. If the product falls out of position 4 or less hours prior to the next dose, replace the product with a new one. The new product can remain in place without replacement and be the second dose within a 24 hour period. During the dosing period extra caution should be taken to avoid dislodging the product. Striant Buccal Bioadhesive product should not be chewed or swallowed. The remove the Striant Buccal Bioadhesive product, gently slide the product downwards from the gum towards the tooth to avoid scratching the gum.

Striant Buccal Bioadhesive is a Schedule III controlled substance and will be supplied in transparent blister packs containing 10 doses.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Striant to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Striant. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified the proprietary name, Atrovent, as having the potential for confusion with Striant. One additional product name, Estring, was found after an independent review. These products are listed in table 1 (see page 4), along with the usual dosage and available dosage forms.

2. DDMAC did not have concerns about the name Striant with regard to promotional claims.

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[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within Chemknowledge, Drugsknowledge and Regsknowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Striant	Testosterone Buccal Bioadhesive 30 mg	**One buccal bioadhesive applied to the gum region twice daily; morning and evening.**	
Atrovent	Ipratropium Bromide Inhaler **Aerosol:** Each actuation delivers 18 mcg In 14 g metered dose inhaler w/mouthpiece (200 inhalations). **Solution for Inhalation:** 0.02% (500 mcg per vial) Preservative free. In 25 unit dose vials per foil pouch. **Nasal spray:** 0.03%. Each spray delivers 21 mcg In 30 ml bottles with spray pump (345 sprays). 0.06%. Each spray delivers 42 mcg	Aerosol: The usual dose is 2 inhalations (36 mcg) 4 times a day. Patients may take additional inhalations as required; however, do not exceed 12 inhalations in 24 hours. Solution: The usual dose is 500 mcg (1 unit dose vial) administered 3 to 4 times a day by oral nebulization, with doses 6 to 8 hours apart. The solution can be mixed in the nebulizer with albuterol if used within 1 hour. Nasal spray: 0.03%: The usual dose is 2 sprays (42 mcg) per nostril 2 or 3 times daily (total dose, 168 to 252 mcg/day). 0.06%: The recommended dose is 2 sprays (84 mcg) per nostril 3 or 4 times daily(total dose, 504 to 672 mcg/day).	**L/A
Estring	Estradiol Ring 2 mg	Insert as deeply as possible into the upper 1/3 of the vaginal vault. The ring is to remain in place continuously for 3 months, after which it should be removed and, if appropriate, replaced by a new ring. Assess the need to continue treatment at 3- or 6-month intervals.	**S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Striant with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Striant (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION

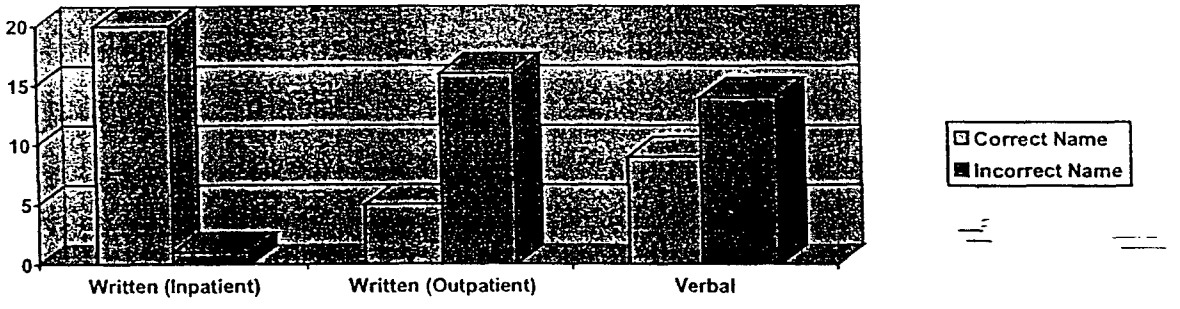
Outpatient RX:	Striant, use one twice daily. Dispense 30.
Striant 1 BID #30	
Inpatient RX:	
Striant 1 PO BID	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	32	21 (41%)	20 (95%)	1 (5%)
Written Outpatient	39	21 (37%)	5 (31%)	16 (69%)
Verbal	35	23 (63%)	9 (39%)	14 (61%)
Total	106	65 (46%)	34 (52%)	31 (48%)



Among the verbal prescription study participants for Striant, 14 of 23 (61%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Striant". The incorrect responses were *Trient, Striat (3), Strient (4), Stryant (2), Istrent, Strat, Strycinth,* and *Stryeth.*

Among the written prescription study participants for Striant, 17 of 42 (40%) of the participants interpreted the name incorrectly. The incorrect responses were *Stuant (3), Striart (5), and Stiant.* Additionally, eight (8) study participants interpreted the proposed name as *Stuart* which is utilized in the English language as a name of a person.

C. SAFETY EVALUATOR RISK ASSESSMENT:

1. Look-alike and sound-alike names

In reviewing the proposed proprietary name "Striant", the primary concerns raised were related to two look-alike and/or sound-alike names. The products considered to have potential for name confusion with Striant were Atrovent and Estring.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Striant and Atrovent or Estring. Eight study participants interpreted the proposed name as Stuart which the name of a person in the English Language. This interpretation should not pose as a safety problem with the proposed drug product since additional prescribing characteristics for the drug will be present to aid in clarifying any type of confusion that may arise. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Striant. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Atrovent has the potential to look like the proposed proprietary name, Striant. Atrovent contains the active ingredient ipratropium bromide which is an anticholingeric agent. Atrovent Inhalation Aerosol and Inhalation Solution are indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Atrovent Nasal Spray is indicated for the symptomatic relief of rhinorrhea associated with allergic and non-allergic perennial rhinitis in adults and children age 6 years and older. When scripted, Atrovent and Striant can look similar (see writing sample below); however, Atrovent is longer in length by one letter. The drug products differ in dosage form (aerosol, solution for inhalation, and nasal spray vs. buccal bioadhesive) and dosing regimen (inhaler: 2 inhalations 4 times daily, solution: one unit dose vial administered 3 to 4 times daily by oral nebulization or nasal spray: 2 sprays 2 to 3 times daily vs. one buccal bioadhesive applied to the gum region twice daily). Since several different dosage forms of Atrovent exist, Atrovent will most likely be ordered with a dosage form descriptor (inhaler, solution for inhalation, or nasal spray). Additionally, Atrovent and Striant will not be stored next to each other on pharmacy shelves. Although the names look similar, the differences between Striant and Atrovent should reduce the potential for confusion.

After an independent review, Estring was found to have sound-alike potential with the proposed name, Striant. Estring contains 2 mg of estradiol and is available as a vaginal ring. Estring is indicated for the treatment of urogenital symptoms associated with post-menopausal atrophy of the vagina (such as dryness, burning, pruritus and dyspareunia) and/or the lower urinary tract (urinary urgency and dysuria). One Estring is to be inserted as deeply as possible into the upper one-third of the vaginal vault. The ring is to remain in place continuously for three months, after which it is to be removed and, if appropriate, replaced by a new ring. The beginning of the name sounds similar ("Estr" vs. Str") as does the ending since they share the letter "n". However, the names are differentiated by the long "i" sound and strong "t" sound in Striant. The drug products differ in route of administration (buccal vs. intravaginal), dosage form (buccal bioadhesive vs.

vaginal ring), and dosing regimen (twice daily vs. once every 3 months). Striant and Estring will not be stored near each other on pharmacy shelves. Given the above mentioned differences and a lack of convincing sound-alike potential, the likelihood of confusion is minimal.

2. Established Name

The term "buccal bioadhesive" is not an officially recognized dosage form. Please consult Dan Boring, Chair of CDER's Labeling and Nomenclature Committee for guidance on the established name.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the blister label, carton, and insert labeling of Striant, DMETS has focused on safety issues relating to possible medication errors. We have identified the following areas for possible improvement, which might minimize potential user error.

A. BLISTER CARD LABEL

B. CARTON LABELING

C. PACKAGE INSERT LABELING

DOSAGE AND ADMINISTRATION

1. See comment B5.

2. Please include pictorials with the instructions to assist individuals with each step. For example, the positioning of the tablet in the gum region may be difficult to identify by the lay public based the description provided (incisor tooth).

3. The statements "If the ——— fails to properly adhere to the gum or should fall off during the 12-hour dosing interval, the old product should be removed and a new one applied. If the product falls out of position 4 or less hours prior to the next dose. ——— ——— remain in place ——— 1" are confusing as it does not clearly provide guidance on the use of this product.

D. PATIENT INFORMATION MATERIALS

DMETS' comments on the patient information materials (patient package insert) will be forwarded in a joint review from the Division of Surveillance, Research, and Communication Support (DSCRS).

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary name Striant.

2. DMETS recommends implementation of the labeling revision outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the name acceptable from a promotional perspective.

4. Please consult Dan Boring, Chair of CDER's Labeling and Nomenclature Committee for guidance on the proper designation of the established name " Testosterone Buccal Bioadhesive".

DMETS decision is considered tentative. This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

S

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alina Mahmud
2/19/03 04:02:49 PM
PHARMACIST

Carol Holquist
2/19/03 04:15:53 PM
PHARMACIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

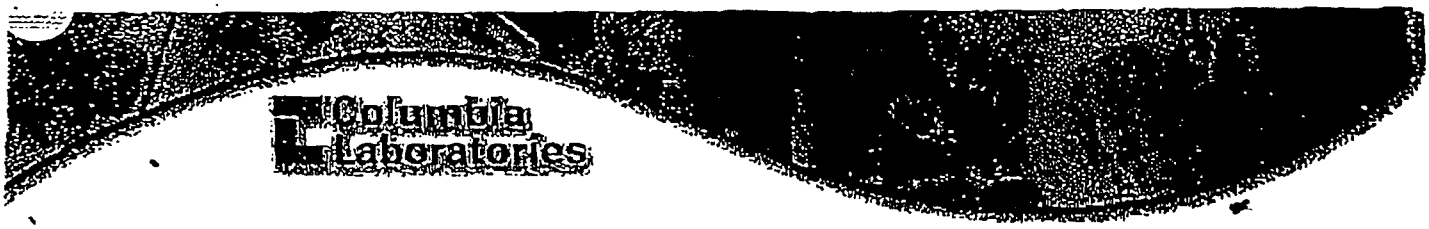
DATE: June 19, 2003

To: Susan Witham Vice President, Regulatory Affairs	**From:** Freshnie DeGuia Regulatory Health Project Manager
Company: Columbia Laboratories	Division of Reproductive and Urologic Drug Products (HFD-580)
Fax number: 973-994-3001	**Fax number:** (301) 827-4267
Phone number: 973-994-3999/7907	**Phone number:** (301) 827-4260

Subject: APPROVAL Letter for NDA 21-543 Striant (testosterone buccal system) mucoadhesive

Total no. of pages including cover: 24

Document to be mailed: (YES) NO



Facsimile Cover Sheet

To:	M. Kober, Dr. Hirsch, E. DeGuira
Company:	FDA
Phone:	301-827-4243
Fax:	301-827-4267
From:	Stu Michalsky
Company:	Columbia Laboratories, Inc.
Phone:	973-994-3999, ext. 7926
Fax:	973-994-3001
Date:	6/17/03
Pages including this cover page:	21
Comments:	As per email - PIE PPI

Stuart Michalsky
06/17/2003 07:03 AM

To: degulae@cder.fda.gov
cc: Dan Gipe/Clabsnj@Clabsnj, Fred Wilkinson/Clabsnj@Clabsnj, Meg Coogan/Clabsnj@Clabsnj, Pat Caputo/Clabsnj@Clabsnj, Robert Mills/Clabsnj@Clabsnj, Susan A Witham/Clabsnj@Clabsnj
Subject: Re: Striant PI and PPI FDA revision 061603

Dear Ms. Deguia:

Please find attached the final PI and PPI accepting all of FDA's changes verbatim. I will also be forwarding fax copies to you all.

Regards

Stu

---- Forwarded by Stuart Michalsky/Clabsnj on 06/17/2003 06:55 AM ----

Michael McGrane
06/16/2003 06:09 PM

To: Stuart Michalsky/Clabsnj@Clabsnj
cc: Dan Gipe/Clabsnj@Clabsnj, Fred Wilkinson/Clabsnj@Clabsnj, Meg Coogan/Clabsnj@Clabsnj, Pat Caputo/Clabsnj@Clabsnj, Robert Mills/Clabsnj@Clabsnj
Subject: Re: Striant PI and PPI FDA revision 061603

Stu,

Attached are the final PI and PPI accepting all of FDA's changes verbatim. Please return by email to Ms. Deguia, and fax copies to her and Dr. Hirsch.

Mike

Striant PI Col revision 061703.d Striant PPI Col revision 061703.c
Stuart Michalsky

Stuart Michalsky
06/16/2003 03:32 PM

To: Michael McGrane/Clabsnj@Clabsnj, Meg Coogan/Clabsnj@Clabsnj, Fred Wilkinson/Clabsnj@Clabsnj, Pat Caputo/Clabsnj@Clabsnj, Dan Gipe/Clabsnj@Clabsnj
cc: Robert Mills/Clabsnj@Clabsnj
Subject: Striant PI and PPI FDA revision 061603

---- Forwarded by Stuart Michalsky/Clabsnj on 06/16/2003 03:30 PM ----

"Deguia, Eufrecina P" <DEGUIAE@cder.fda.gov>
06/16/2003 03:25 PM

To: "'switham@columbialabs.com'" <switham@columbialabs.com>, "'smichalsky@columbialabs.com'" <smichalsky@columbialabs.com>
cc:
Subject: Striant PI and PPI FDA revision 061603

Hi Su,

Just got back into the swing of things again, esp. on the label. We had our meeting with our Director this afternoon to discuss the labeling changes/ revisions that came out of the Clin Pharm end-of-review briefing he

concurred. Please see the revisions/edits on pages 2,3, 12 of the PI and pages 2, 3 and 4 of the PPI.

I would appreciate it very much if you could respond by tomorrow.

Thanks.
Freshnie

Sufrecina DeGuia
Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Tel: (301) 827-4260
Fax: (301) 827-4267

<<Striant PI FDA revision 061603.doc>> <<Striant PPI FDA revision 061603.doc>>


Striant PI FDA revision 061603.d Striant PPI FDA revision 061603.c

COLUMBIA
ABORATORIES, INC.

June 16, 2003

Daniel Shames, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic
Drug Products-HFD-580
5600 Fishers Lane
Rockville, MD 20857-1706

NDA No. 21-543
Striant™ (testosterone buccal system) mucoadhesive
General Correspondence: Columbia's Agreement to a Phase 4 Commitment

Dear Dr. Shames:

Reference is made to NDA No. 21-543 for Striant™ (testosterone buccal system) mucoadhesive from Columbia Laboratories, Inc. (Columbia). This letter serves as our agreement to the following Phase 4 commitment for Striant™:

"To continue ongoing Study Nos. COL 1621-08 (Europe) and COL 1621-09 (US) in order to accumulate a total of 50 patients with at least 2-years of continuous treatment on Striant™. During the conduct of these two trials, Columbia agrees that if there is evidence of a gum lesion, the investigator will perform a biopsy or will refer the patient for biopsy. Columbia also agrees that the case report forms for this trial will include a special listing in regard to whether there was lack of adhesion of the buccal system."

Columbia also commits to the following timeframes:

Protocol amendment submission: Within 2 weeks of the date of the action letter.

Study start: Ongoing as of the date of the action letter.

Final report submission: Within fifteen to eighteen months of the date of the action letter.

If there are any questions or comments, please contact me at (973) 994-3999, extension 7907, or by cell phone at 973-222-3928.

Sincerely,

for Susan Witham

Susan Witham
Vice President
Regulatory Affairs

Submitted in duplicate

Attachments

cc: Desk copies to Ms. Eufrecina DeGuia and Ms. Margie Kober

Eisenhower
Kway
:or – Plaza I
NJ

(973) 994-3999
(973) 994-3001

Hirsch, Mark S

From: switham@columbialabs.com
Sent: Saturday, June 14, 2003 6:14 PM
To: Hirsch, Mark S
Cc: 'switham@columbialabs.com'; 'smichalsky@columbialabs.com'; Deguia, Eufrecina P; Kober, Margaret
Subject: Re: Regarding the Phase 4 commitment

Hi Dr. Hirsch,

Columbia agrees with the attached language for the Phase 4 commitment. Continuing Studies 08 and 09 an additional year after the PDUFA date, 50 patients will be exposed to drug for 2-years if not longer. We will submit a letter to the file and fax it to the Division by Monday.

Best regards,

Sue

"Hirsch, Mark S" <HIRSCHM@cder.fda.gov>
06/14/2003 04:19 PM AST

To: "'switham@columbialabs.com'" <switham@columbialabs.com>, "'smichalsky@columbialabs.com'" <smichalsky@columbialabs.com>
cc: "Deguia, Eufrecina P" <DEGUIAE@cder.fda.gov>, "Kober, Margaret" <KoberM@cder.fda.gov>
bcc:
Subject: Regarding the Phase 4 commitment

Stu and Sue:

Attached herein is proposed specific language for the Phase 4 commitment.
This is a crucial part of the action. If you concur with language as is,
please return it to the Division in the form of a letter of commitment on
Monday via electronic attachment and fax. Please cc Margie and Freshnie.
Please note that the Director and Chief of the Project Management staff may
continue to "tweak" the commitment and will contact you for revisions.

If you do not agree with the specific language, please contact me on Monday.
I will be in a meeting from 11 a.m. to 1 p.m.

While your letter of June 9th was a good start, I think we need to be more
specific about the exact nature of the commitment. The object of the commitment (as I understand it) is to gain longer-term data (such as

two
years of exposure in 50 patients), not just more 1-year exposure data on a
greater number of people.

Mark Hirsch
<<striantPhase4commitment.doc>>

Proposed language for the action letter

We remind you of your postmarketing study commitment in your submission dated June 9, 2003. This commitment is listed below.

1. To continue ongoing Studies COL 1621-08 (Europe) and COL 1621-09 (U.S.) in order to accumulate a total of 50 patients with at least 2 years of continuous treatment on Striant™.

During the conduct of these two trials, you have agreed that if there is evidence of a gum lesion, the investigator will perform a biopsy or will refer the patient for biopsy. You have also agreed that the case report forms for this trial will include a special listing in regard to whether there was lack of adhesion of the buccal system.

Protocol amendment submissions:	Within two weeks of the date of this letter
Study start:	Ongoing as of the date of this letter
Final report submission:	Within fifteen to eighteen months of the date of this letter.

Hirsch, Mark S

From: switham@columbialabs.com
Sent: Thursday, June 12, 2003 3:43 PM
To: hirschm@cder.fda.gov; koberm@cder.fda.gov
Cc: deguiae@cder.fda.gov; smichalsky@columbialabs.com; agarwalr@cder.fda.gov
Subject: Revised Patient Leaflet-Striant

striantppjune1 1.doc

Hi Dr. Hirsch and Margie,

Attached is a revised patient leaflet for Striant. We have incorporated all your changes and have added new text based upon your recommendations.
We also included a recent change from Dr. Agarwal. We will also be faxing
a copy of this document to both of your attention.

As I had mentioned in the Phase 4 Commitment letter from Columbia, we will
be submitting the new amendment #3 for 08 by June 27th. I forgot to mention in that letter that I will also include a special listing in the CRF for whether there is lack of adhesion of the buccal system (this was based awhile ago on a comment you mentioned came from Dr. Agarwal). We will also amend study 09 to include this information and the additional information about the gum examines.

On a separate note, the inspection did start today at Mipharm and the inspector mentioned that if everything goes well he will end the inspection
on the morning of June 19 (Italy time). He will be contacting the Center
with the results of the inspection that day.

If you need any further assistance, please contact Stu Michalsky at (973)
994-3999, extension 7926 or myself at (973) 222-3928. I appologize that the my cell phone has not been working very well in Italy.

Best regards,
Sue

Hirsch, Mark S

From: switham@columbialabs.com
Sent: Monday, June 09, 2003 12:05 PM
To: koberm@cder.fda.gov; hirschm@cder.fda.gov
Cc: deguiaE@cder.fda.gov
Subject: Phase 4 Commitment Letter from Columbia for Striant

Importance: High

StriantPhase4letter.pdf

Hello Margie and Dr. Hirsch,

Attached is a letter from Columbia addressing the Phase 4 commitment for Striant. If there are any comments, please contact me at 973-222-3928.

This document was faxed as well as submitted to the NDA in duplicate.
Best regards,
Sue
(See attached file: StriantPhase4letter.pdf)

COLUMBIA
LABORATORIES, INC.

June 9, 2003

Daniel Shames, M.D., Director
Food & Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic
Drug Products, HFD-580
5600 Fishers lane
Rockville, MD 20857-1706

NDA No. 21-543
Striant™ (testosterone buccal system) mucoadhesive
General Correspondence: Phase 4 Commitment

Dear Dr. Shames:

Columbia Laboratories, Inc. (Columbia) commits to continue the ongoing studies for Striant™ (testosterone buccal system) mucoadhesive as a Phase 4 Commitment under NDA No. 21-543. The two studies that are currently ongoing are Study Nos. COL 1621-08 (Europe) and COL 1621-09 (US). The total number of patients that will be exposed to Striant™ for an additional year after the PDUFA date will be at least 50 patients. Thus, 50 patients will be exposed to the product for up to 3 years.

Columbia had amended IND No. 60, 906 (Serial No. 022) on May 28, 2003 with Protocol Amendment #3 that addressed the additional extension study for Study No. COL 1621-09 (US). Columbia will also amend the IND for Study COL 1621-08 (EU). We are currently notifying the investigators in Study COL 1621-08 (EU) regarding this amendment. Columbia will also amend both study protocols in order to include gum evaluations at each visit for the addition extension. We will also state in the protocols amendments that if there is any evidence of gum lesions, that the investigator must perform a biopsy [redacted]. The protocol amendments will all be filed to the IND by June 27, 2003.

The last patient to complete the additional extension study is in [redacted] Columbia commits to submit to the Agency a combined safety report for both studies within [redacted]

Columbia also commits to submit a letter to the Agency requesting a meeting to discuss a pediatric development program for Striant.

354 Eisenhower Pky.
Plaza 1 Second Floor
Livingston, NJ 07039

Tel: (973) 994-3999
Fax: (973) 994-3001

If there are any comments or questions, please contact me at (973) 994-3999, extension 7907 or cell number (973) 222-3928.

Sincerely,

Susan Witham

Susan Witham
Vice President
Regulatory Affairs

Submitted in duplicate
cc: Ms. Eufrecina DeGuia (Regulatory Project Manager) and Dr. Hirsch (Supervisory Medical Officer)

LUMBIA
ABORATORIES,INC.

May 28, 2003

Daniel Shames, M.D., Director
Food & Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic
Drug Products, HFD-580
5600 Fishers Lane
Rockville, MD 20857-1706

IND No. 60, 906
COL-1621 (testosterone buccal system) mucoadhesive
PROTOCOL AMENDMENT: CHANGE IN PROTOCOL/UPDATED FDA 1572 FORM

SERIAL NO. 022

Dear Dr. Shames:

Reference is made to the response that was submitted to the Agency on April 3, 2003 by Columbia Laboratories, Inc. (Columbia) addressing clinical questions that were raised during the review of the Striant™ (testosterone buccal system) mucoadhesive, NDA No. 21-543.

Columbia had offered to extend Study No. COL 1621-09 (US) [redacted] as a Phase 4 commitment.

In accordance with 21 CFR 312.30 (b), Columbia Laboratories, Inc. (Columbia) herewith submits Protocol Amendment #3 for Study No. COL 1621-09 (US). The attached Protocol Amendment #3 has been sent to five (5) of the investigator's who currently have patients still participating in the extension trial. There are approximately 42 patients who are willing to participate in Protocol Amendment #3.

PROTOCOL AMENDMENT: CHANGE IN PROTOCOL

Study No. COL 1621-09 (US) entitled, "An open label Phase III, multicenter study of COL 1621, a bioadhesive testosterone buccal tablet, for the long-term safety, tolerability and efficacy in testosterone deficient patients."

Originally Submitted on May 14, 2002, Serial No. 004

3[illegible] Eisenhower Pky.
1 Second Floor
..igston, NJ 07039

Tel: (973) 994-3999
Fax: (973) 994-3001

The following are the investigator's who will be continuing their participating in the attached Protocol Amendment #3:

[redacted]
Site #4
Site #6
Site #7
Site #8
Site 10

In accordance with 21 CFR 312.30(c), Columbia would also like to notify the Agency of the following changes that have been made to FDA 1572 form signed by [redacted] (Site #6):

- New research facilities that will also be conducting the clinical investigation for this study.
  - [redacted]
  - [redacted]
- Deletion of sub-investigator's
  - [redacted]
  - [redacted]

If there are any comments or questions, please contact me at (973) 994-3999, extension 7907.

Sincerely,

Susan Witham

Susan Witham
Vice President
Regulatory Affairs

Submitted in triplicate

Desk copies to Ms. DeGuia (Regulatory Project Manager) and Dr. Hirsch (Supervisory Medical Officer).