

**Food & Drug Administration  
Division of Urologic and  
Reproductive Drug Products**

# Fax

To: Sue Witham From: Mark Hirsch  
Fax: 973-994-3001 Pages: 6 (including cover)  
Phone: 973-222-3928 Date: 6-5-03  
Re: PPI CC:

- Urgent     For Review     Please Comment     Please Reply     Please Recycle

• Comments:

5 Draft Labeling Page(s) Withheld



# Facsimile Cover Sheet

To:	Eufrecina Deguia/ Dr. Hirsch
Company:	FOA
Phone:	301-827-4252
Fax:	301-827-4267
From:	Sue Witham
Company:	Columbia Laboratories, Inc.
Phone:	973-994-3999, ext. 7907
Fax:	973-994-3001
Date:	5/29/03
Pages including this cover page:	17 pages
Comments:	Revised Striant labeling (NOA No 21-543)

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354 Eisenhower Parkway, Livingston, New Jersey 07039 (973) 994-3999 Fax: (973) 994-3001

16 Draft Labeling Page(s) Withheld

**Deguaia, Eufrecina P**

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**From:** switham@columbialabs.com  
**Content:** Thursday, May 29, 2003 4:33 PM  
**To:** deguiaie@cder.fda.gov  
**Cc:** hirschm@cder.fda.gov  
**Subject:** Striant-Revised Package Insert

**Importance:** High



Study03,referePI-FDA revision  
ncedpages.pdf #1.doc

Hello Eufrecina and Dr. Hirsch,

Based upon our discussion yesterday, attached is a revised document incorporating a majority of the Division's comments on the proposed Striant package insert. I have also sent it by fax. The only outstanding issue that needs to be clarified is whether steady state is reached within 24-hours of initial dosing or by the second day. I am attaching the pages from the study report for Study No. COL 1621-03 that are referenced in the attached document. I did add a note explaining how we reach steady state within 24-hours of initial dosing. I do agree that the study report when reading it was not as clear as it could have been and could have easily cause confusion.

Thank you again for the time and consideration that the Division has spent on the labeling and our NDA application.

Could you please acknowledge back that you have received this email.

Best regards,  
Sue Witham  
Cell Telephone #973-222-3928 or Columbia 973-994-3999, extension 7907

(See attached file: Study03,referencedpages.pdf) (See attached file: PI-FDA revision #1.doc)

**BEST POSSIBLE COPY**

**Deguaia, Eufrecina P**

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**From:** switham@columbialabs.com  
**Sent:** Tuesday, May 27, 2003 6:06 PM  
**To:** deguiaie@CDER.FDA.gov  
**Subject:** Revised Striant Patient Leaflet

**Importance:** High

  
testPatientLeaflet  
revised2.doc..

Hi Eufrecina,

Per our discussion today, based upon the Division's comments to us regarding how important it is to ensure that the patient properly administers this product by rotating to alternate sides of the mouth with each application and that they should use the product properly, subsequently we had tested the proposed instructions that are currently in our NDA. The results of the testing helped us see where some of the current text was not so clear to the patient and would be confusing. Thus, attached is a revised patient leaflet highlighting in "red" the new proposed text and the original text is "strikethrough."

As we also discussed, we would appreciate if the Division could review the proposed text during your upcoming internal meeting for the Striant patient leaflet and send us back the Division's proposed language that you would like for us to incorporate. Based upon the Division's recommendations, I will then amend the file appropriately with revised labeling.

Thank you very much for your assistance and help. Please let me know if there are any problems with opening the attached file or if there are any problems with the 2 pictures that are attached to the file.

Best regards,  
Sue  
(See attached file: testPatientLeafletrevised2.doc)

**BEST POSSIBLE COPY**

27 Draft Labeling Page(s) Withheld



NDA 21-543

## DISCIPLINE REVIEW LETTER

Columbia Laboratories  
Attention: Susan Witham  
Vice President, Regulatory Affairs  
354 Eisenhower Parkway  
Plaza 1, Second Floor  
Livingston, NJ 07039

Dear Ms. Witham:

Please refer to your August 7, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Striant (testosterone buccal bioadhesive).

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. Please tighten the acceptance criteria of:
  - \_\_\_\_\_ to max.
  - shelf life for individual related substances and for total related substances to \_\_\_\_\_ and \_\_\_\_\_ respectively.
2. The \_\_\_\_\_ should be included in the \_\_\_\_\_
3. Please provide the name and addresses of the sources of the container closure system for the drug product in master and executed batch record.
4. The tabular list of samples for the method validation should also be provided.
5. The stability commitment should be revised with the following inclusions:
  - The \_\_\_\_\_ commercial batches with Columbia logo will be placed on long term (25°C/60% RH and tested at release, \_\_\_\_\_ and \_\_\_\_\_ thereafter) stability covering the proposed shelf life and on accelerated (40°C/75% RH) studies for \_\_\_\_\_
  - Withdraw from the market any batches found to fall outside the approved acceptance criteria for the drug product. The change or deterioration in the distributed drug product must be reported under 21CFR314.81 (b)(1).

6. Please revise the blister foil and carton labels as follows:

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~

7. The established name for the dosage form is under discussion and will be conveyed to you at a later time. Once it is finalized, please revise the blister and carton labels accordingly.
8. Please revise the storage conditions in both physician and patient insert to "Store at 20-25°C — - 77°F) [see USP Controlled Room Temperature]".
- 9. Please request categorical exclusion of the environmental assessment, if justified.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.  
Chemistry Team Leader, for the  
Division of Reproductive and Urologic Drug  
Products, HFD-580  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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

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Moo-Jhong Rhee  
4/17/03 11:51:42 AM



- ORIGINAL

April 3, 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

RECEIVED

APR 04 2003

FDR/CDER

NDA No. 21-543  
**Striant™ (testosterone) Buccal Bioadhesive**

N 2000 BM  
ORIG AMENDMENT

**General Correspondence: Response to FDA's Clinical Questions**

Dear Dr. Shames:

On March 24, 2003, Dr. Hirsch (Supervisory Medical Officer) and Ms. Eufrecina DeGuia (Regulatory Project Manager) telephoned Columbia Laboratories, Inc. (Columbia) to discuss the issues and questions that were raised by the Dermatologic and Dental Drug Division during their consult review of the Striant (testosterone) Buccal Bioadhesive, NDA No. 21-543.

The enclosed document addresses the following issues/questions raised by the Division during the teleconference:

- Were the gum checks performed adequately?
- The role of testosterone in gingivitis/Lack of a placebo-controlled group
- Incidence of gingivitis
- Potential for oral tumors/cancer
- What is Columbia's plan to communicate that the product should be rotated from one side of the mouth to the other side each time the product is applied?

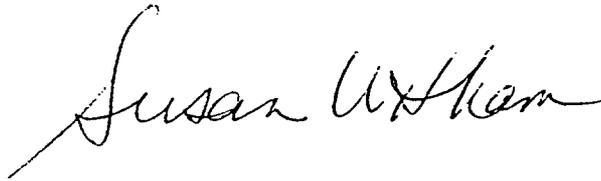
Columbia performed an extensive literature search related to the incidence of gingivitis and its potential for oral tumors/cancer. Please see Attachment B within the enclosed document for the overall summary of the literature findings and references.

Eisenhower Pky.  
za 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.

Sincerely,

A handwritten signature in cursive script that reads "Susan Witham". The signature is written in black ink and is positioned above the typed name and title.

Susan Witham  
Vice President  
Regulatory Affairs

Submitted in duplicate

cc: Desk copies were sent to Ms. DeGuia and Dr. Hirsch

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: March 31, 2003  
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER  
21-543

APPLICANT INFORMATION

NAME OF APPLICANT Columbia Laboratories, Inc.	DATE OF SUBMISSION 4/3/03
TELEPHONE NO. (Include Area Code) (973) 994-3999	FACSIMILE (FAX) Number (Include Area Code) (973) 994-3001
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 354 Eisenhower Parkway Plaza 1, Second Floor Livingston, New Jersey 07039	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Not Applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Testosterone	PROPRIETARY NAME (trade name) IF ANY Striant™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Buccal bioadhesive	STRENGTHS: 30 mg	ROUTE OF ADMINISTRATION: Buccal

(PROPOSED) INDICATION(S) FOR USE:  
Testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

PRODUCT DESCRIPTION

APPLICATION TYPE (check one)  NEW DRUG APPLICATION (21 CFR 314.50)  ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)  BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE  505 (b)(1)  505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION  
Name of Drug \_\_\_\_\_ Holder of Approved Application \_\_\_\_\_

TYPE OF SUBMISSION (check one)  ORIGINAL APPLICATION  AMENDMENT TO PENDING APPLICATION  RESUBMISSION  PRESUBMISSION  ANNUAL REPORT  ESTABLISHMENT DESCRIPTION SUPPLEMENT  EFFICACY SUPPLEMENT  LABELING SUPPLEMENT  CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT  OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: Not Applicable

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY  CBE  CBE-30  Prior Approval (PA)

REASON FOR SUBMISSION  
General Correspondence: Response to FDA's Clinical Questions

PROPOSED MARKETING STATUS (check one)  PRESCRIPTION PRODUCT (Rx)  OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DMF # _____	DMF # _____
DMF # _____	DMF # _____
DMF # _____	

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

- 1. Index
- 2. Labeling (check one)       Draft Labeling       Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
  - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request).
  - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

**CERTIFICATION**

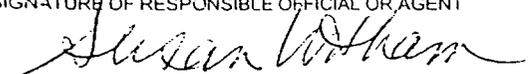
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Susan Witham, Vice President, Regulatory Affairs Columbia Laboratories, Inc.	DATE: 4/3/03
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ADDRESS (Street, City, State, and ZIP Code) 354 Eisenhower Parkway, Plaza 1, Second Floor, Livingston, NJ 07039	Telephone Number ( 973 ) 994-3999, extension 7907
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Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1443	Food and Drug Administration CBER, HFM-94 12420 Parklawn Dr., Room 3046 Rockville, MD 20852
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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.

Continuation Sheet to Form FDA 356h

ESTABLISHMENT INFORMATION:

Drug Substance is manufactured and tested at:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Contact:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
  
\_\_\_\_\_  
\_\_\_\_\_

Establishment number: CFN \_\_\_\_\_  
DMF Number - \_\_\_\_\_

The site will be ready for inspection any time.

Final dosage form is manufactured, tested, released and packaged at:

MiPharm S.p.A.  
Via Bernardo Quaranta Bernardo, 12  
11-20141 Milano  
Italy

Contact:  
\_\_\_\_\_

Regulatory Affairs

Telephone: \_\_\_\_\_  
Facsimile: \_\_\_\_\_

Establishment number: \_\_\_\_\_  
DMF Number - Not Applicable

The site will be ready for inspection on April 1, 2003.

The stability testing is also performed at the MiPharm location listed above.

## RESPONSES TO FDA QUESTIONS/COMMENTS

### **I. Were the gum checks performed adequately?**

All oral assessments were performed by the study investigators. The same investigators at each study site evaluated the patients. Each study site was provided with documentation of the oral findings (i.e., gingivitis, edema, ulceration, lesions, leukoplakia, and comments related oral problems) for which they were required to look for. This document included descriptions and pictures of normal gingiva, as well as descriptions and pictures of the clinical findings of various types and severities of gum abnormalities. The investigators were to evaluate both sides of the mouth. Please see Attachment A.

The results of the assessments were recorded on the patient's case report form. This form recorded the presence of any abnormality, and if present, its severity. Instructions on the completion of the case report form were reviewed with the investigators at each site prior to the commencement of the study as well as training on the site to each investigator regarding how to perform the gum checks. Special attention was paid to the sites of study drug application, the upper gum under the nose. No special tools were employed in the evaluation. Study investigators were instructed to stop the study drug and discontinue subjects from the study if significant oral irritation associated with administration of the study drug was seen.

At the baseline visit of each study, prior to receiving the first dose of Striant™, all subjects in the Striant studies were evaluated for gum abnormalities. All subjects were specifically queried with regard to any oral symptoms they may be experiencing. As stated above, each subject's gums were assessed for the presence or absence of gingivitis, edema, oral lesions and ulceration, and leukoplakia. Also at the baseline visit, all subjects were instructed to examine the application sites of the study drug daily, and to contact the investigator if any pain, ulceration or any other significant local symptoms were noted.

At each study visit (monthly for three months, then 2-4 weeks after discontinuation of study drug), subjects were again queried with regard to oral symptoms they had experienced since the last study visit. The subjects again had an assessment of their gums. At the interim visits, in addition to examining the application site where the tablet was applied, an examination was also performed on the side of the gums opposite to where the current tablet was applied. This was done to eliminate the potential of the study drug to hinder the evaluation. Investigators were also able to refer the subjects to a dentist for evaluation if warranted. This was never deemed necessary. The patients were instructed to rotate each application from one side of the gum to the other, using only the upper gum.

The incidence of gingivitis in the general population at any point in time is approximately 20-25%. In Study COL1621-07, the incidence of gum abnormalities at baseline was 9.1% (3 patients). There were only 33 patients randomized to the Striant group for 1-week. Based upon the incidence of the general population, theoretically 6 patients should have had a gum abnormality at baseline (3 patients short). The slightly lower incidence of gum abnormalities noted at baseline is probably related to the small number of patients randomized into the study.

In the pivotal trial, COL1621-05US, the incidence of gingivitis at baseline was 32.6%. There were 98 patients randomized in this study. The investigators found an incidence of gingivitis slightly greater at baseline than expected in the general population. Columbia believes that these results demonstrate that they took a conservative approach when examining and assessing gum diseases throughout the study. The same could be said about the incidence of edema, which was approximately 20% at baseline.

A review of the gum examination results from Study COL1621-05 revealed the following: Thirty-two (32.6%) had abnormal gum assessment at baseline visit. One subject did not have an abnormality at baseline; however, had mild edema noted only at the 1-month and 2-month visits and by the 3-month visit, the abnormality had resolved itself. The patients who had entered and continued in the study who had a gum abnormality noted at baseline, their condition did not get worse and in most cases the condition improved.

The incidences of gum abnormalities, specifically gingivitis and edema, were highest at baseline in Study COL 1621-05. At the follow-up study visits, the incidence of these findings decreased between 20-31% at the study visits at months 1, 2 and 3 as compared with the baseline incidences.

The reason for this decrease is not known, but can be postulated. One theory is that such effects could be related to the study hormone's effect on local inflammatory mechanisms and tissue repair; another is that increased attention to oral hygiene during the study may have improved oral conditions. In either case or a combination of both theories, the decreased incidence in oral abnormalities noted in Study COL1621-05 could not associate the study drug as a causative or contributing factor to developing or accelerating oral disease.

## **II. The role of testosterone in gingivitis/Lack of placebo control group**

### **The role of testosterone in gingivitis:**

As increases in gingivitis have been noted during puberty, sex hormones were thought to play a role in its development. Closer examinations of this report shows, in fact, the female sex hormones, especially progesterone and to a lesser extent estrogen, appear to be related to the development of gingivitis. Children followed prospectively through puberty were found to have an increase in the gingival index if they were female or if

they had gingivitis present prior to puberty (Nakagawa et al, 1994). Gingivitis-free boys showed no significant increase in any clinical parameters. A more recent study concluded that testosterone had no effect on gingival inflammation during puberty (Morishiti et al, 1998). Studies indicate that testosterone may be anti-inflammatory and anabolic in its activities interacting with oral tissues. A thorough assessment of the literature search on the effect of testosterone on oral tissues accompanies this submission. Please see Attachment B.

There is also extensive information available on the polymers (Polycarbophil and Carbomer) contained in the Striant™ formulation. These polymers are used in the formulations of other approved products such as Crinone® (progesterone gel) and Replens® Vaginal Gel and are safe when applied to other mucosal surfaces of the body (i.e., vaginal mucosa).

#### **Lack of placebo control group:**

Had there been a significant problem noted in the pivotal trials for Striant™ regarding gum abnormalities that were not mild and transient in nature, a placebo control group may have been informative. However, based upon the following reasons, a placebo control group is not necessary:

- All of the treatment-emergent gum abnormalities observed during the pivotal trials were mild or moderate in intensity, short duration, and transient.
- Patients who dropped out due to irritation, the adverse events were mild to moderate intensity, transient and reversible.
- The patients who continued from the two pivotal trials (Study Nos. COL1621-05 and COL1621-07) into the extension studies, there were no signs of cumulative irritation or worsening over time. The gum abnormalities improved or disappeared over time.
- The patients were instructed to rotate the application site; thus, there was a 12-hour drug free period each day.
- In Study COL1621-07, Andropatch® was the active control group in this study. The active control group served as a surrogate placebo control group because a comparison can be made between the two groups.

### **III. Incidence of gingivitis**

The incidence of gingivitis seen at the baseline evaluation of studies of COL-1621 is very similar or slightly higher than that seen in the general population (20-25%). This correlation of the incidence at the study baseline and that seen in the general population provides assurance that the examinations and assessments were satisfactory in looking for gum diseases throughout the study as highlighted in Point I above.

The Dermatologic and Dental Division had noted that the low incidence of gingivitis recorded at the baseline of studies COL1621-08EU and COL1621-09US were low at 0%

and 10%, respectively. Therefore, questioning that this decreased incidence was unexpected and unexplained.

The reduced incidences noted in these two studies can be easily explained. Study Nos. COL 1621-08 and COL1621-09 are extension studies of COL 1621-07 and COL 1621-05, respectively. The extension studies evaluated the long-term safety and efficacy of Striant™. Patients from Studies COL 1621-02, COL 1621-03 and COL 1621-04 were also eligible for enrollment into Study No. COL 1621-08. Patients that were already being treated with Striant™ and had completed the study were offered to continue receiving treatment for one year or longer in the extension studies.

In study COL 1621-09, approximately 60 subjects were enrolled in the study directly upon completion of, and from, study COL 1621-05. This represents approximately 40% of the total population of subjects enrolled in the study. An additional 85 “new” subjects were enrolled. Almost all subjects who continued from COL 1621-05 into the long-term study did not have gingivitis. Therefore, the incidence of gingivitis at baseline in study COL 1621-09 is lower due to the fact that about 40% of the subjects had the benefit of the treatment (improved oral hygiene) from the 3-month study. It is expected that the incidence of gingivitis in the 85 “new” subjects is 20% or 17 subjects. If the number of subjects with gingivitis is 17 out of a total of 145 subjects, the expected incidence at baseline of study COL 1621-09 is approximately 11.7%, very similar to what was seen in the study (10%). We are using expected numbers since the actual numbers are not yet identified since the study is on-going and a study report has not been generated. Also, the patients from Study COL 1621-05 were randomized into Study COL 1621-09 using a new patient identifier.

In COL 1621-07, only two patients in the Striant™ group (6.1%) developed gum abnormalities from baseline to follow-up. One patient had gum irritation at the site of tablet application from Day 4 to Day 7 of treatment that resolved while the patient was still taking the product, and one patient had blistering of the gum at follow-up. This patient had discontinued from the study because of this event.

In Study COL 1621-05, more gum abnormalities were seen at baseline and follow-up than during treatment. The most common gum abnormality during treatment was mild or moderate gingivitis. No severe abnormalities were reported. The following is a table highlighting the number of patients with gum abnormalities at baseline, during treatment, and at follow-up for Studies COL 1621-05.

**Patients with gum abnormalities at baseline, during treatment,  
and at follow-up for Studies COL 1621-05\***

**Patients with gum abnormalities at baseline, during treatment,  
and at follow-up for Studies COL 1621-05\***

	Gingivitis		Edema		Lesions
	Mild	Moderate	Mild	Moderate	Mild
Baseline	26 (26.5%)	6 (6.1%)	18 (18.4%)	2 (2.0%)	3 (3.1%)
Week 4	9 (9.2%)	1 (1.0%)	7 (7.1%)	0	2 (2.0%)
Week 8	9 (9.2%)	1 (1.0%)	6 (6.1%)	0	1 (1.0%)
Week 12 AM	9 (9.2%)	2 (2.0%)	4 (4.1%)	0	1 (1.0%)
Week 12 PM	9 (9.2%)	2 (2.0%)	4 (4.1%)	0	1 (1.0%)
Follow-up	15 (15.3%)	4 (4.1%)	8 (8.2%)	1 (1.0%)	5 (5.1%)

\*No ulcerations, leukoplakia or moderate lesions were reported at the gum examination over the duration of the study. This table can be located in the NDA Module 2.7.4, Section 2.7.4.4.2.2, Table 32, page 68.

The incidence of gingivitis seen in the results of the gum examinations at baseline correlates to what is expected in the general population. This again demonstrates that the investigators were properly trained in evaluating gum diseases and that a conservative evaluation was conducted by the investigators.

#### IV. Potential for Oral Tumors/Cancer

The incidence of oral cancers in males in the US is approximately 11 per 100,000 person years. The risk factors for oral cancers include tobacco, alcohol (including mouthwash), diet and nutrition, dentition, and possibly viruses (human papillomavirus and Epstein-Barr).

An extensive review of the literature did not find an association of testosterone with oral neoplasia. In the oral cavity, testosterone does not undergo metabolic transformation to reactive intermediates that have been associated with the potential to induce neoplastic changes. Animal studies have shown that direct injection of testosterone into the submandibular glands of mice will increase the production of epithelial growth factor, but does not promote the development of submandibular gland carcinoma.

The findings of the oral examinations performed on subjects who have used COL 1621 for over one year have not shown any findings nor signals that suggest the potential for neoplastic changes in the oral cavity.

As mentioned above, alcohol and tobacco have been associated with oral cancers secondary to their irritant effect on the oral mucosa. There is no reason to believe that COL 1621 would produce similar effects or add to the irritation from these agents. In contrast, testosterone and its metabolite (DHT) increase the repair potential and suppress

the inflammatory response in the peri-dental tissues. Please see Attachment B for the assessment that was performed on the literature search.

It is important to note the mechanism of delivery of testosterone from the Striant™ Buccal Bioadhesive product. Although testosterone is present in the product, it is not all available at any point while applied to the oral mucosa. The hormone is very slowly released as the tablet slowly hydrates. The hydration allows for very small quantities of testosterone to become soluble and available for absorption through the buccal mucosa. As the tiny quantities of testosterone solubilize, it is rapidly absorbed into the circulation. Thus, the amount of testosterone free in the oral cavity at any time is extremely small, small enough to have little, if any local effect.

The gum abnormalities reported during the Striant studies at baseline that had either disappeared or improved during treatment, it could be concluded that if there was a serious problem at baseline, you would expect the problem to worsen while on Striant treatment. This was not the case.

The literature review accompanying this submission reviews the issues surrounding testosterone and neoplasia.

As previously mentioned, there is extensive information available on the polymers (Polycarbophil and Carbomer) contained in the Striant™ formulation. These polymers are used in the formulations of other approved products such as Crinone® (progesterone gel) and Replens® Vaginal Gel and are safe when applied to other mucosal surfaces of the body (i.e., vaginal mucosa). These two polymers are not known to cause cancer.

Based upon the low incidences of gum abnormalities reported during the long-term studies and the low incidence of gum abnormalities while on Striant noted during all of the clinical studies, the results of the literature search, and that the gum abnormalities were mild to moderate intensity and transient, Columbia Laboratories, Inc. believes that there is not an issue of the Striant Buccal Bioadhesive product causing cancer or tumors while on chronic therapy. The company; however, would like to offer the following Phase 4 commitment in order to further evaluate the long-term safety of the product and additional statement to the proposed draft labeling. (Revised draft labeling will be submitted once discussions with the Agency are initiated.)

Phase 4 Commitment:

\_\_\_\_\_

\_\_\_\_\_

Proposed draft labeling text: Under Carcinogenesis, mutagenesis, impairment of fertility subsection of the PRECAUTIONS section of the package insert, under Human data, add the following statement, "Striant \_\_\_\_\_ has been evaluated in patients for 1-year without reports of cancer related to the product. However, safety in patients beyond 1-year has not been established."

V. What is Columbia's plan to communicate that the product should be rotated from one side of the mouth to the other side each time the product is applied?

[Redacted content]

APPEARS THIS WAY  
ON ORIGINAL

17 Page(s) Withheld

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## MEMORANDUM OF TELECON

DATE: March 24, 2003

APPLICATION NUMBER: NDA 21-543, Striant (testosterone buccal system) mucoadhesive

**BETWEEN:**

Name: Susan Witham, Vice President, Regulatory Affairs  
Phone: (973) 994-3999  
Representing: Columbia Laboratories, Inc.

**AND**

Name: Eufrecina DeGuia, Regulatory Health Project Manager  
Mark Hirsch, M.D., Medical Team Leader  
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Information Request by FDA during the NDA review

**Background:**

Consultation report from Division of Dermatologic & Dental Drug Products has been received by HFD-580 in regard to NDA 21-543; DRUDP would like to share some of the dental consult's concerns with sponsor; DRUDP seeks additional information in regard to some of these concerns

- Issues include:
  - Were the gum checks done adequately?; Please submit additional info to support these as adequate.
  - Is there are role for testosterone in gingivitis? Was a placebo group necessary? Please submit additional info/literature in regard to the role of T in gingivitis.
  - Why was the incidence of gingivitis so low at baseline in the long-term extension studies? Why did the incidence of gingivitis decrease over time in Study 05? Please submit additional info to explain these incidences.
  - Is there a potential for either testosterone or the other excipients to induce oral lesions/tumors? Is a longer-term study necessary? Please provide information relevant potential oral tumorigenicity of Striant.
  - Alternating sides of the mouth was recommended in Phase 3 and may reduce irritation. Is this noted prominently in the label? Please submit a revised PPI with clear instructions to patients about rotating sites.

- Columbia agreed to provide the requested information via NDA amendment as soon as possible. Columbia stated that they believed that these issues could be resolved.

*(See appended electronic signature page)*

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Mark Hirsch, M.D.  
Medical Team Leader

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/s/

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Mark S. Hirsch  
6/17/03 12:40:45 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): Office of Division of Surveillance, Research and Communication Support (DSRCS) Attention: Leslie Stephens Office of Drug Safety			FROM: Freshnie DeGuia, Regulatory Health Project Manager Division of Reproductive and Urologic Drug Products HFD-580; (301) 827-4252		
DATE December 6, 2002	IND NO.	NDA NO. 21-543	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT August 7, 2002	
NAME OF DRUG Striant (testosterone buccal bioadhesive)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG androgen	DESIRED COMPLETION February 6, 2003	
NAME OF FIRM: Columbia Laboratories					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL		<input type="checkbox"/> PRE-NDA MEETING		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER	
<input type="checkbox"/> PROGRESS REPORT		<input type="checkbox"/> END OF PHASE II MEETING		<input type="checkbox"/> FINAL PRINTED LABELING	
<input type="checkbox"/> NEW CORRESPONDENCE		<input type="checkbox"/> RESUBMISSION		<input type="checkbox"/> LABELING REVISION	
<input type="checkbox"/> DRUG ADVERTISING		<input type="checkbox"/> SAFETY/EFFICACY		<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE	
<input type="checkbox"/> ADVERSE REACTION REPORT		<input type="checkbox"/> PAPER NDA		<input type="checkbox"/> FORMULATIVE REVIEW	
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION		<input type="checkbox"/> CONTROL SUPPLEMENT		<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Safety Review	
<input type="checkbox"/> MEETING PLANNED BY					
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW			<input type="checkbox"/> CHEMISTRY REVIEW		
<input type="checkbox"/> END OF PHASE II MEETING			<input type="checkbox"/> PHARMACOLOGY		
<input type="checkbox"/> CONTROLLED STUDIES			<input type="checkbox"/> BIOPHARMACEUTICS		
<input type="checkbox"/> PROTOCOL REVIEW			<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> OTHER (SPECIFY BELOW):					
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE			
<input type="checkbox"/> BIOAVAILABILITY STUDIES		<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS			
<input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> IN-VIVO WAIVER REQUEST			
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY		
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES			<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE		
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)			<input type="checkbox"/> POISON RISK ANALYSIS		
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP					
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review attached Labeling and Patient Information. This NDA is the first buccal bioadhesive (dosage form) to be reviewed in the Division. Please let me know if you need additional materials for your review. Thanks. PDUFA DATE: June 19, 2003					

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/s/

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Eufrecina deGuia  
12/6/02 11:42:13 AM

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

**REQUEST FOR CONSULTATION**

TO (Division/Office): Jerry Phillips, R.Ph.  
Attention: Sammie Beam  
Associate Director, Medication Error Prevention  
Division of Medication Error and Technical Support, HFD-400  
(Rm. 15B-03, PKLN Bldg.)

FROM: Freshnie DeGuia, Regulatory Project Manager  
Division of Reproductive and Urologic Drug Products  
HFD-580; (301) 827-4252

DATE December 3, 2002	IND NO.	NDA NO. 21-543	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT August 7, 2003
NAME OF DRUG Striant (testosterone buccal bioadhesive)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG androgen	DESIRED COMPLETION DATE March 19, 2003	

NAME OF FIRM: Columbia Laboratories

**REASON FOR REQUEST**

**I. GENERAL**

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| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER           |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                  |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION                       |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE             |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW                      |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

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| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

**IV. DRUG EXPERIENCE**

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

**V. SCIENTIFIC INVESTIGATIONS**

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|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review the information provided in support of the proposed Striant™(testosterone ) buccal bioadhesive . Labeling and Patient Information attached.

PDUFA DATE: June 19, 2003

ATTACHMENTS: labeling

CC:

Archival NDA 21-463

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Eufrecina deGuia  
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NDA 21-543  
 Striant (testosterone) buccal bioadhesive  
 Columbia Laboratories

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): Division of Drug Marketing, Advertising and Communications; Attention: Andrew Haffer and Barbara Chong			FROM: Freshnie DeGuia, Regulatory Project Manager Division of Reproductive and Urologic Drug Products HFD-580; (301) 827-4252	
DATE December 9, 2002	IND NO.	NDA NO. 21-543	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT August 7, 2002
NAME OF DRUG Striant (testosterone) buccal bioadhesive	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG androgen	DESIRED COMPLETION DATE February 9, 2003	
NAME OF FIRM: Columbia Laboratories				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Please review the labeling provided. PDUFA DATE: June 19, 2003 ATTACHMENTS: labeling CC: Archival NDA 21-543 HFD-580 Division File; HFD-580-DeGuia/Kober				

NDA 21-543  
Striant (testosterone) buccal bioadhesive  
Columbia Laboratories

HFD-Handelsman,Hirsch,Agarwal,Rhee	
SIGNATURE OF REQUESTER Eufrecina DeGua	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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12/9/02 08:43:29 AM

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

## REQUEST FOR CONSULTATION

To (Division/Office): Office of New Drug Chemistry;  
Attn: Peter Cooney, Ph.D., Microbiology Team Leader  
HFD-805

FROM: HFD-580 (Division of Reproductive and Urologic Drug  
Products) Freshnie DeGuia, Regulatory Project Manager

DATE: December 3, 2002	IND NO.:	NDA NO.: 21-543	TYPE OF DOCUMENT : New NDA	DATE OF DOCUMENT: August 7, 2002
NAME OF DRUG: Striant (testosterone buccal bioadhesive)	PRIORITY CONSIDERATION: Standard Review	CLASSIFICATION OF DRUG: androgen	DESIRED COMPLETION DATE: March 3, 2003	

NAME OF FIRM: Columbia Laboratories

### REASON FOR REQUEST

#### I. GENERAL

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| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | OTHER (SPECIFY BELOW):                                 |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

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| STATISTICAL EVALUATION BRANCH                    | STATISTICAL APPLICATION BRANCH            |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY     |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER:           |
| <input type="checkbox"/> OTHER:                  |   |

#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

#### IV. DRUG EXPERIENCE

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|---|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE,<br>ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)            | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP          |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Dr. Cooney: This is a consult request from Dr. Rajiv Agarwal, Chemistry Reviewer, HFD-580. Review package will be hand-delivered to the Office of Microbiology.

HFD-580/Div. Files  
HFD-580/EDeGuia/MRhec/RAgarwal  
HFD-805/PCooney/ PTuegel

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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Eufrecina deGuia  
12/3/02 03:35:12 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0338 Expiration Date: March 31, 2003 See OMB Statement on page 2.	
<b>APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE</b> (Title 21, Code of Federal Regulations, Parts 314 & 601)		FOR FDA USE ONLY	
		APPLICATION NUMBER 21-543	
<b>APPLICANT INFORMATION</b>			
NAME OF APPLICANT Columbia Laboratories, Inc.		DATE OF SUBMISSION 8/15/02	
TELEPHONE NO. (Include Area Code) (973) 994-3999		FACSIMILE (FAX) Number (Include Area Code) (973) 994-3001	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 100 North Village Avenue, Suite 32 Rockville Centre, NY 11570		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	
<b>PRODUCT DESCRIPTION</b>			
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)			
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Testosterone		PROPRIETARY NAME (trade name) IF ANY Tradename (testosterone) Buccal Bioadhesive	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)		CODE NAME (if any) COL-1621	
DOSAGE FORM: Buccal bioadhesive	STRENGTHS: 30mg	ROUTE OF ADMINISTRATION: Buccal	
PROPOSED INDICATION(S) FOR USE: Testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.			
<b>PRODUCT DESCRIPTION</b>			
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.84) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)			
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)			
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug _____		Holder of Approved Application _____	
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER			
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____			
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)			
REASON FOR SUBMISSION FDA Request for Information			
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)			
NUMBER OF VOLUMES SUBMITTED    1    THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC			
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.			
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)			
DMF # _____			
DMF # _____			
DMF # _____			

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

- 1. Index
- 2. Labeling (check one)       Draft Labeling       Final Printed Labeling
- 3. Summary (21 CFR 314.50 (c))
- 4. Chemistry section
  - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (f)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306 (k)(1))
- 17. Field copy certification (21 CFR 314.50 (l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE

DATE:

*Susan Witham*

Susan Witham, Vice President Regulatory Affairs

8/15/02

ADDRESS (Street, City, State, and ZIP Code)

Telephone Number

220 South Orange Avenue, Second Floor, Livingston, NJ 07039

( 973 ) 994-3999, ext. 7907

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information, and comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
CDER, HFD-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFM-94  
12420 Parklawn Dr., Room 3046  
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.

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

Form Approved: OMB No. 0910-0297  
Expiration Date: February 29, 2004.

## USER FEE COVER SHEET

### See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pduta/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Columbia Laboratories, Inc. North Village Avenue, Suite 32 Rockville Centre, NY 11570</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</p> <p>NDA No. 21-543</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>( 973 ) 994-3999</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p> <p>_____</p> <p>(APPLICATION NO. CONTAINING THE DATA).</p>
<p>3. PRODUCT NAME</p> <p>Tradename (testosterone) buccal bioadhesive</p>	<p>6. USER FEE I.D. NUMBER</p> <p>ID No. 4409</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
- A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
- THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
- THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
- THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

Department of Health and Human Services  
Food and Drug Administration  
CDER, HFM-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

and Food and Drug Administration  
CDER, HFD-94  
12420 Parklawn Drive, Room 3046  
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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

*Susan Workman*

TITLE

Vice President, Regulatory Affairs

DATE

August 14, 2002

## CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Howard Levine, Pharm.D.	Vice President
FIRM/ORGANIZATION	
Columbia Research Laboratories	
SIGNATURE	DATE
	MAY 29, 2002

### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 1-4C-03  
Rockville, MD 20857

Columbia Research Laboratories: COL-1621  
List of Investigators, Sub-Investigators and Study Coordinators

<u>Study No.</u>	<u>Investigator</u>
1621-01	Dr. N. Watson, Inveresk Clinical Research
COL-1621 IS 01	Irving Spitz, M.D.
1621-02	Dr. Derek R. Cullen
1621-03	Dr. Derek R. Cullen
1621-04	Dr. Derek R. Cullen until September 30, 2001 Pr. Richard Ross from October 1, 2001
1621-05	Glenn Cunningham, M.D.  _____  _____  Adrian-Sandra Dobs, M.D.  _____  _____  Theodore Friedman, M.D.  _____  Laurence Katznelson, M.D.  _____  _____  Mark Kipnes, M.D.  _____  _____  _____  _____  _____

Columbia Research Laboratories: COL-1621

List of Investigators, Sub-Investigators and Study Coordinators

<u>Study No.</u>	<u>Investigator</u>
	Peter Snyder, M.D. _____ _____ _____
	Christina Wang, M.D. _____ _____ _____ _____
	Thomas Weber, M.D.
	Alvin Matsumoto, M.D. _____ _____ _____
1621-06	Pr. Christoph Beglinger
1621-07	Pr. Ashley B. Grossman  /
1621-08	Pr. Ashley B. Grossman  /
1621-09	Theodore Friedman M.D., Ph.D. _____

Columbia Research Laboratories: COL-1621  
List of Investigators, Sub-Investigators and Study Coordinators

Study No.      Investigator  
1621-09      Laurence Katznelson, M.D.

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Mark Kipnes, M.D.

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Christina Wang, M.D.

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Evangeline Gonzalez, M.D.

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Barry Horowitz, M.D., FACP

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Glenn Cunningham, M.D.

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Adrian-Sandra Dobs, M.D.

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Thomas Weber, M.D.

Matthew D. Beasey, M.D.

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\_\_\_\_\_  
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Columbia Research Laboratories: COL-1621  
List of Investigators, Sub-Investigators and Study Coordinators

Study No.

Investigator

Richard K. McDavid, M.D.

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Jorge A. Pino, M.D.

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Alvin Matsumoto, M.D.

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Frederick C. Robinson, M.D.

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COL-010

Adrian-Sandra Dobs, M.D.

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Mark Kipnes, M.D.

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Columbia Research Laboratories: COL-1621  
List of Investigators, Sub-Investigators and Study Coordinators

Study No.

Investigator

Alvin Matsumoto, M.D.

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Christina Wang, M.D.

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## Meeting Minutes

**Date:** December 5, 2001      **Time:** 11:00 AM – 12:15 PM      **Location:** Parklawn; Conf. Rm. "K"

**IND** 60-906      **Drug:** COL-1621      **Indication:** testosterone replacement

**Sponsor:** Columbia Research Laboratories

**Type of Meeting:** Pre-NDA

**Meeting Chair:** Mark Hirsch, M.D.

**External Lead:** Howard Levine, Pharm.D.

**Meeting Recorder:** Jeanine Best, M.S.N., R.N. (for Eufrecina DeGuia)

### FDA Attendees:

Dan Shames, Deputy Director, Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Mark Hirsch, M.D., Urology Team Leader, DRUDP (HFD-580)

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)

Venkat Jarugula, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Dhruba Chatterjee, Ph.D., Clinical Pharmacology Reviewer, OCPB @ DRUDP, (HFD-580)

Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Amit Mitra, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Mike Welch, Ph.D., Statistical Team Leader, Division Of Biometrics II (DBII) @ DMIRDP (HFD-160) and DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Senior Regulatory Associate, DRUDP (HFD-580)

### External Attendees:

Howard Levine, Pharm.D., Vice President Research & Development, CRL

Fred Wilkinson, President and CEO, CRL

**Meeting Objective:** To discuss the proposed NDA for COL-1621, testosterone bioadhesive buccal tablets, projected to be submitted 1<sup>st</sup> quarter 2002.

**Background:** COL-1621, testosterone bioadhesive buccal tablets have been developed in the U.S., and Europe for testosterone replacement in hypogonadal men. The delivery system consists of a bioadhesive buccal tablet (30 mg) that allows a controlled, sustained release of testosterone over 12 hours (BID administration). The buccal route of administration also circumvents first-pass hepatic metabolism.

**Discussion and Questions:  
Manufacturing and Control**

**1. MiPharm (Milan, Italy) manufactures the testosterone bioadhesive buccal tablet formulation. Confirm the acceptability of MiPharm's acceptance criteria for API and excipients.**

- the drug substance DMF should be adequate to support the NDA
- if the excipient used in the drug product is monographed in the USP, it should be tested according to the USP
- since Polycarbophil and \_\_\_\_\_ are used as bio-adhesives, USP acceptance criteria may not be enough to assure batch to batch adhesion consistency of the drug product; submit the CMC information of the two polymers such as batch composition, manufacturing process, and characterization of molecular weight distribution, average molecular weight, and degree of cross-linking (those properties are not tested by the USP methods); alternatively, DMF references for \_\_\_\_\_ and Polycarbophil may suffice, if the DMF holders do these testing

**2. Does the Division have comments on tests and specifications proposed for in-process controls, release or shelf-life testing?**

- provide information on the in-process testing of the \_\_\_\_\_ and report if the \_\_\_\_\_ during the manufacturing process has been established in \_\_\_\_\_ batches or proposed commercial scale batches
- provide information on the drug product specification; all acceptance criteria must be justified according to the ICH-Q6A.; the \_\_\_\_\_ acceptance criteria on expiry is too high; provide information on the effect of in-vivo adhesion at \_\_\_\_\_, if available
- the sponsor reported that they do not have a test that correlates the *in vitro* adhesion with the *in vivo* performance of the product, but they report that the *in vivo* performance data to date is very consistent
- since the product \_\_\_\_\_, herefore, an acceptance criterion for \_\_\_\_\_ should be established on stability
- provide individual dissolution and adhesion data for stability batches and clinical batches separately
- the tablet should be identified with an identifier mark (per CFR), and the identifier mark should be part of appearance specification; provide data assuring *in vitro* and *in vivo* adhesion remains the same for both sides of the tablet (marked and unmarked); it will be a review issue if a difference is apparent: the sponsor has stated that adhesion, with regard to either side of the tablet, and with regard to buccal surface, gum versus cheek, has wide inter-patient variability; therefore, the sponsor has not determined which side of the tablet will be marked

**3. Comment on proposed 2-year expiration based on the stability data available at time of the NDA submission and updates provided during the review process.**

- the batch size of the primary stability lots indicates that it is about \_\_\_\_\_ of the commercial lots; however, the manufacturing process and equipment were not adequately described to determine the relationship with the commercial scale; those items should be included in the NDA with a justification that the scale-up has no impact on the quality of the product; the shelf life will be given based on the real time data (since adhesion is a critical parameter for the drug product), unless justified; stability data for all test parameters will be analyzed for evaluation of proper shelf life; any

extrapolation of shelf life should be justified; the individual data point from the release rate studies, and adhesion measurements should be provided in the NDA

- the shelf-life will be determined after review of appropriate data submitted in the NDA
4. **Comment on the proposal for not including \_\_\_\_\_ as part of the shelf-life specification.**
- both \_\_\_\_\_ need to kept the specification; upon collection of more data, post- approval, the sponsor may ask for deletion of testing those attributes
  - a \_\_\_\_\_ specification for the drug product should be adopted since the drug product \_\_\_\_\_, and change the *in vivo* adhesion characteristics
5. **Confirm that testosterone bioadhesive buccal tablets will be exempt, under 21 CFR 25.24, from the requirement for an Environmental Impact Assessment.**
- calculate and submit for review in the NDA the "Expected Introduction Concentration from Use (EIC)" to make a claim for categorical exclusion from EA

#### Preclinical

1. **The nonclinical section will be comprised of literature information. Does the Division concur with the search criteria? Should the NDA contain copies of all articles cited in the review, or will it be sufficient to have the articles available on request?**
- the nonclinical section of the NDA is acceptable; provide a list of publications with the NDA; publications will only be requested if are not available in the Agency library

#### Clinical Pharmacology Comments

- DHT levels were not presented in the Meeting Package; the sponsor reported that the ratio of DHT:T 10:1, remained consistent throughout treatment to ensure a physiological relationship
- provide data on the effect of mucoadhesion with use of concomitant medications that can cause a dry mouth (i.e., anticholinergics)
- provide data on the effect of food and beverage on adhesion and PK parameters
- provide absorption data on use in patients with co-existing periodontal disease; the sponsor responded that patients with periodontal disease were not excluded from the trials and neither were denture wearers; the sponsor can perform a comparison between users with and without periodontal disease; the Division will consult this data to the Dental Division for review
- provide data on *post vivo* use, specifically, the amount of testosterone remaining in the tablet; the sponsor responded that limited data is available for this parameter
- if formulation changes are anticipated from the clinical trial batches to the to-be-marketed formulation, then bioequivalence will need to be established; the sponsor reported that no formulation changes are anticipated
- the four-timepoint approach to dissolution testing is acceptable; provide information on the method development; the final specifications will be based on the review of the data submitted from the clinical batches and the final stability batches

**Clinical  
Efficacy**

**1. Comment on the proposed statistical analysis plan for efficacy measures.**

- proposal is acceptable; statistics are for descriptive purposes only; the submission should also present individual study analyses; the main review focus for efficacy will be on the US Study 05

**2. Comment on the proposal for presentation of information from Studies COL-1621-02 and COL-1621-05 in the NDA.**

- the sponsor clarified this purpose of this study for the Division; to determine acceptability and tolerability of the product after initial clinical study; a descriptive presentation (based on answer provided to a questionnaire) of patient acceptability and tolerability of the product will be provided in the NDA; the Division responded that this proposal is acceptable, but the study is exploratory only, and as a secondary endpoint, will not be presented in the labeling

**Clinical  
Safety**

**3. Comment on the proposal for integrating safety data for the clinical summaries.**

- the proposal is acceptable; the main safety concern is gum irritation and gum related adverse events may be of concern; unfortunately, it does not appear possible to duplicate gum irritation studies in animal models

**4. Confirm that 70 patient/six month safety data will be adequate for the initial NDA submission.**

- the initial NDA submission will require 70 patients exposed for six months
- the initial NDA submission should also contain 50 patients exposed continuously (interruption  $\leq 3$  days) for a year since this is a chronic use product; the Division will compromise and accept this data four months after the NDA submission (with the 4-Month Safety Update); if the data is not received within the four months after the NDA submission, the Division may defer review of the data until the next review cycle

**5. Comment on the proposal to include data for subjects with treatment gaps in the 70 patient/6 month safety database.**

- since this is a chronic use product with a chronic use irritation aspect, patients may not have a treatment interruption of greater than 3 days

**6. Comment on the proposal for presentation of the long-term safety data in the NDA submission.**

- proposal is acceptable but must receive the final study report at the 4-Month Safety Update submission

**Format of the Application**

1. **Comment on the acceptability to prepare the package insert according to the new format, as proposed in the December 21, 2000, Federal Register Notice.**
  - submit the package insert per current guidance; the new format is still under development and the guidance is not final and may change
2. **Is the Division prepared to accept and review a submission prepared according to the existing CTD guidances? Comment on the proposed Table of Content format proposed.**
  - an NDA submission in the CTD format is acceptable; the CTD Guidance should be followed for formatting of all sections, including the Table of Contents
  - provide patient data, clinical data, and PK summary data in electronic format; follow the Electronic Submission Guidance and submit the CDs to the Electronic Document Room
3. **The ISS and ISE will be incorporated in the CTD summaries and overview. Is this acceptable?**
  - acceptable if submitted per the CTD Guidance
4. **Raw data listing will be provided in each clinical study report. Will this suffice for the case report tabulations?**
  - acceptable
5. **Confirm that it will not be necessary to provide any case report forms with the application other than those of the few study subjects who experienced discontinuations due to adverse events or death.**
  - submit all Serious Adverse Event reports with regard to attribution to drug, as well as those for deaths or discontinuations

**Discussion on Sponsor Slides:**

- the sponsor presented slides on preliminary results on their pivotal Phase 3 protocol (US Study 05):
  - the data as presented, showed consistency between studies
  - the data as presented, showed minimal fluctuations in PK data
  - $C_{ave}$  will be the primary endpoint
  - individual  $C_{min}$  and  $C_{max}$  will be secondary endpoints
  - nonresponders comprise about 5% of the studied patients; no common patient characteristics identified at this time among the nonresponders, i.e.; increased body weight
  - an a priori responder rate was not established; however, a 70% response (point estimate) is indicated
  - not a safety concern if the tablet is swallowed; the testosterone is not methylated, therefore, there is little bioavailability through the GI tract

**Decisions made:**

- the sponsor will provide identifying mark — information on the tablet to the chemistry review team for further comment
- the initial NDA submission will require 70 patients exposed for six months

- the initial NDA submission should also contain 50 patients exposed continuously (interruption  $\leq$  3 days) for a year since this is a chronic use product; the Division will compromise and accept this data four months after the NDA submission (with the 4-Month Safety Update); if the data is not received within the four months after the NDA submission, the Division may defer review of the data until the next review cycle

**Action Items:**

- Meeting Minutes to the sponsor within 30 days

S

\_\_\_\_\_  
Minutes Preparer

S

\_\_\_\_\_  
Concurrence, Chair

**Note to Sponsor:** These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

IND 60,906  
Meeting Minutes  
Page 7

cc:  
Original IND 60,906  
HFD-580/DivFile  
• HFD-580/PM/DeGuia  
HFD-580/Shames/Hirsch/Batra/Jarugula/Chatterjee/Rhee/Mitra/Raheja/Welch

drafted: JAB/December 5, 2001  
concurrence: Chatterjee, 12.05.01/Welch, 12.05.01/Rhee/12.05.01/Mitra, 12.05.01/Jarugula, 12.10.01/  
Hirsch, 12.13.01/Shames, 12.14.01  
final: JAB/December 14, 2001  
MEETING MINUTES

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

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

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Mark S. Hirsch  
12/14/01 11:22:20 AM

## **Request for a Deferral of the Pediatric Study Requirement**

Tradename (testosterone) Buccal Bioadhesive proposed indication is for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The product will be indicated in adult males 18-years and older.

On May 24, 2002, Columbia Laboratories, Inc. (Columbia) had submitted a proposal to the Agency requesting a deferral of the pediatric study requirement until the adult indication is approved. Testosterone deficiency is observed in males above the age of 18-years old; however, it can also occur in adolescence boys, ages 12 to under 18. The rationale for requesting deferral of the pediatric study requirement is that the further development of this product is based upon achieving approval of the adult indication for testosterone replacement in hypogonadal men.

On June 4, 2002, the Agency contacted Columbia and stated that they accepted the rationale for deferring the pediatric study requirement until after approval of the adult indication.

Like with other testosterone products that are on the market, Columbia has included a statement in the draft package insert stating that, "Safety and effectiveness in pediatric male patients below the age of 18 have not yet been established."

**APPEARS THIS WAY  
ON ORIGINAL**

5 Page(s) Withheld

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**Division of Reproductive and Urologic Drug Products (HFD-580)**

**ADMINISTRATIVE REVIEW OF APPLICATION**

Application Number: NDA 21-543

Name of Drug: Testosterone Buccal Bioadhesive

Sponsor: Columbia Research Labs

Material Reviewed: Module 1

~~Submission Date: August 7, 2002~~

Receipt Date: August 19, 2002 (Receipt date of User Fee)

Filing Date: October 18, 2002

User-Fee Goal Date(s): June 19, 2003

Proposed Indication: testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone.

Other Background Information:

Regulatory Project Manager Review

**PART I: OVERALL FORMATTING<sup>a</sup> and REGULATORY REQUIREMENTS**

Y = Yes (Present), N = No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	x		
2. Form FDA 356h (original signature)	x		
a. Reference to DMF(s) & Other Applications			
3. Patent information & certification	x		
4. Debarment certification (note: must have a definitive statement)	x		
x			

6. Comprehensive Index	x		
7. Pagination	x		
8. Has the applicant submitted a complete Environmental Assessment, that addresses 21 CFR 25.31 or provided a request for categorical exclusion under 21 CFR 25.24?	x		
9. On its face, is the NDA legible?	x		
10. Has the sponsor submitted all special Studies/ data requested during Presubmission discussions?	x		
11. Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with Part 58 or a statement why it has not complied?	x		
12. If required, has the applicant submitted carcinogenicity studies?			No studies were conducted but literature article citations were requested.
13. On its face, does the application contain at least two adequate and well-controlled clinical trials?	x		
14. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	x		
15. Have all articles/ study reports been submitted either in English or translated into English?	x		
16. Summary Volume	x		
17. Review Volumes			
18. Labeling (PI, container, & carton labels)	x		
a. unannotated PI	x		
b. annotated PI			
c. immediate container	x		
d. carton	x		

e. foreign labeling (English translation)			N/A
19. Foreign Marketing History			N/A
20. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	x		Some were requested
21. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	x		Some were requested

Y = Yes (Present), N = No (Absent)

## PART II: SUMMARY<sup>b</sup>

Y = Yes (Present), N = No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	x		
2. Summary of Each Technical Section	x		
a. Chemistry, Manufacturing, & Controls (CMC)	x		
b. Nonclinical Pharmacology/Toxicology	x		
c. Human Pharmacokinetic & Bioavailability	x		
d. Microbiology	x		
e. Clinical Data & Results of Statistical Analysis	x		
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies			
Summary of Safety	x		

5. Summary of Efficacy	x	

Y = Yes (Present), N = No (Absent)

### PART III: CLINICAL/STATISTICAL SECTIONS<sup>c</sup>

Y = Yes (Present), N = No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	x		
2. Controlled Clinical Studies	x		
a. Table of all studies	x		
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	x		
c. Optional overall summary & evaluation of data from controlled clinical studies	x		
3. Integrated Summary of Efficacy (ISE)	x		
4. Integrated Summary of Safety (ISS)	x		
5. Drug Abuse & Overdosage Information	x		
6. Integrated Summary of Benefits & Risks of the Drug	x		
7. Gender/Race/Age Safety & Efficacy Analysis Studies	x		

Y = Yes (Present), N = No (Absent)

## PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population			Pediatric Studies deferred granted.
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 8.0	x		
b. Stability data in SAS data set format			N/A
c. Efficacy data in SAS data set format			N/A
d. Biopharmacological information & study summaries in MS WORD 8.0			N/A
e. Animal tumorigenicity study data in SAS data set format			N/A
3. User-fee payment receipt	x		User Fee # 4409

Y=Yes (Present), N=No (Absent)

<sup>a</sup>[GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS] (FEBRUARY 1987) and 21 CFR 314.100(d)

<sup>b</sup>[GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS] (FEBRUARY 1987).

<sup>c</sup>[GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS] (JULY 1988).

**Additional Comments:**

**Conclusions: This NDA is fileable.**

Eufrecina DeGuia  
Regulatory Health Project Manager

cc:

Original NDA  
HFD-580/Div. Files

**ADMINISTRATIVE REVIEW**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-543

Columbia Laboratories  
Attention: Susan Witham  
Vice President  
220 South Orange Avenue  
Second Floor  
Livingston, NJ 07039

Dear Ms. Witham:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Testosterone Buccal Bioadhesive
Review Priority Classification:	Standard (S)
Date of Application:	August 7, 2002
Receipt Date of User Fees:	August 19, 2002
Our Reference Number:	NDA 21-543

This application was originally considered incomplete because the required user fee was not paid. Subsequently, we received the fee on August 19, 2002. This date is now considered the new receipt date for this application.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 18, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 19, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

NDA 21-543  
Page 2

U.S. Postal Service/Courier/Overnight Mail:  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
Attention: Division Document Room, 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Margaret Kober, R.Ph.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

-----  
Margaret Kober  
8/20/02 03:40:18 PM  
Chief, Project Management Staff



August 14, 2002

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  
Tradename(testosterone) Buccal Bioadhesive

AMENDMENT TO A PENDING NEW DRUG APPLICATION:  
REVISED USER FEE SHEET AND FDA 356h FORM

Dear Dr. Shames:

On June 4, 2002, the Division of Reproductive and Urologic Drug Products had contacted Columbia Laboratories, Inc. (Columbia) responding to Columbia's letter dated May 24, 2002, regarding whether Tradename (testosterone) Buccal Bioadhesive NDA No. 20-543 met the 505(b)(1) or 505(b)(2) criteria. The Division responded that we did meet the 505(b)(2) criteria. On August 14, 2002, the Division had contacted Columbia Laboratories, Inc. (Columbia) stating that the NDA should have been filed as a 505(b)(1) application since there is clinical efficacy and safety data in the NDA which is the basis for approving the proposed indication and new delivery system.

Columbia has agreed to change the application status to a 505(b)(1).  
Enclosed are copies of the following revised documentation:

- Revised User Fee Sheet (User Fee ID No. 4409).
- Revised FDA 356h Form

A User Fee of \$313,320.00 was sent by FedEx to Mellon Client Service Center on August 14, 2002 for overnight delivery.

Since Columbia was originally informed by the Division that the NDA met the 505(b)(2) criteria and that was the reason for why a User Fee was not submitted with the application, we would hope that the Division would understand the situation that the Company is now placed under and would appreciate the Division's cooperation in not sending Columbia a non-

220 South Orange Avenue  
Second Floor  
Livingston, NJ 07039

TEL: (973) 994-3999  
FAX: (973) 994-3001

acceptance letter. To demonstrate our good faith and to confirm that a User Fee was sent to the Mellon Client Service Center today, a copy of the signed check, letter to the Mellon Client Service Center and the FedEx shipping statement are also enclosed. Again, we would appreciate that a non-acceptance letter does not get sent to us since we have quickly corrected the misunderstanding and provided the Agency with the required documents.

Sincerely,



Susan Witham  
Vice President,  
Regulatory Affairs

Submitted in duplicate

cc: Faxed a copy to Ms. Eufrecina Deguia, Regulatory Project Manager

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                     Draft Labeling Page(s) Withheld