CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-543

CHEMISTRY REVIEW(S)

NDA 21-543

Striant
(testosterone buccal system) mucoadhesive

Columbia Laboratories, Inc.

Rajiv Agarwal, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-543

2. REVIEW #: 1

3. REVIEW DATE: 18-JUN-2003

4. REVIEWER: Rajiv Agarwal

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL	13-AUG-2002
AMENDMENT	10-OCT-2002
AMENDMENT	18-MAR-2003
AMENDMENT	31-MAR-2003
AMENDMENT	03-APR-2003
AMENDMENT	11-APR-2003
AMENDMENT	14-APR-2003
AMENDMENT	22-APR-2003
AMENDMENT	01-MAY-2003
AMENDMENT	28-MAY-2003
AMENDMENT	04-JUN-2003
AMENDMENT	16-JUN-2003
AMENDMENT	17-JUN-2003
AMENDMENT	18-JUN-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Columbia Laboratories, Inc.

Chemistry Review Data Sheet

354 Eisenhower Parkway
Address: Plaza 1, Second Floor
Livingston, NJ 07039

Representative: Ms. Susan Witham

Telephone: 973-994-3999 Ext. 7907

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Striant
b) Non-Proprietary Name (USAN): Testosterone
c) Code Name/# (ONDC only): COL-1621
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY:

Testosterone replacement therapy in men for condition associated with a deficiency or absence of endogenous testosterone

11. DOSAGE FORM: Buccal System

12. STRENGTH/POTENCY: 30 mg

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

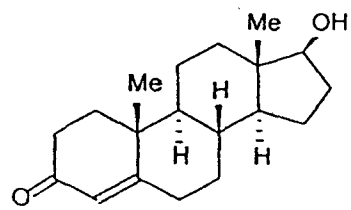
_____SPOTS product – Form Completed

___x___Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Testosterone
Chemical Structure:



Molecular weight: 288.42
Molecular formula: $C_{19}H_{28}O_2$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Testosterone drug substance	3	Adequate	15-OCT-2002	Reviewed for NDA 21-463 by Dr. Donna Christner
	III			3	Adequate	15-OCT-2001	DMF strike force review by Dr. Robert Seevers
	III			3	Adequate	29-OCT-1997	Reviewed for NDA 20-817 by Dr. Sung K. Kim. No further updates on this product.

Chemistry Review Data Sheet

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharm	Adequate	18-JUN-2003	Dr. Venkateswa R Jarugula
LNC	Adequate	23-MAY-2003	See page 55 of this review
Methods Validation	The method validation package will be sent to and validated by FDA laboratories		See page 52 of this review
DMETS	Adequate	19-FEB-2003	Ms. Alina Mahmud
EA	Adequate	01-MAY-2003	See page 56 of this review
Microbiology	Adequate	6-MAR-2003	Dr. Bryan Reiley

Executive Summary Section

The Chemistry Review for NDA 21-543

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Control and Manufacturing standpoint, this NDA may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There is no Phase 4 commitment.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product "Striant" is a sustained/controlled release mucoadhesive buccal system with a tablet-like appearance and contains 30 mg of testosterone (each system contains 30 mg of testosterone) and is indicated for *Testosterone replacement therapy in men for condition associated with a deficiency or absence of endogenous testosterone.*

Polycarbophil and Carbomer 934P, compendial excipients, are responsible for the mucoadhesive property of the system. Other compendial excipients are magnesium stearate, colloidal , talc, hypromellose (formerly known as hydroxypropyl methylcellulose), lactose (monohydrate and anhydrous) and starch. The manufacturing process of the mucoadhesive buccal system involves all the steps, which are typical to a tablet.

The buccal system is moistened by saliva and undergoes a process of progressive hydration resulting in the release of testosterone at a slow and controlled rate. It is by this process that controlled and sustained release is achieved. Only the part of the testosterone which is present in the hydrated (aqueous) fraction of the system is available for absorption (in vitro release rate at 12 hr. is 36%). The hydrated system forms a gelatinous mass, but is not designed to disintegrate or erode so it can be removed from its position on the gingiva (gum) after specific period (12 hours).

The acceptance criterion for in vitro adhesion test is in place and the values are within the limits.

In vivo study (treatment compliance and extent of exposure-study # COL-1621-05-US) using one of the — batch indicated that the incidence of adhesion problems associated with the buccal system was found to be low (4%), according to the results from patients self-reports of events (swallowed, dislodged/non-adhering, missed and replaced tablets). Additionally, the number of buccal system replacement events also indicates that the replacement had decreased over time as the patients gained more experience. First two weeks showed an increase in the system replacement.

The manufacturing process is well controlled with in-process acceptance criteria, and several critical attributes are tested during the manufacturing of the tablet. The — is controlled during — . Several in-process control parameters of tabletting addressed the various test (e.g. — to assure the reproducibility of the manufacturing process.

The quality of the buccal system is controlled by the tests (e.g. — that are unique to the tablet dosage form. Other tests include, —

A satisfactory real time data of 24-months and — on — batches and — validation batches, respectively, were provided. All these batches do not have — Since, applicant is planning to market the drug product with — comparative stability data on the batches with and without — were provided. Based on the comparative stability data including adhesion and in vitro release data between batches — , it is concluded that the — would not significantly affect the performance of the drug during the shelf life. Therefore, 24-month of the expiration date is granted.

The buccal system is packaged in a transparent — blister foil — , containing 10 systems per foil, to provide additional protection from the moisture ingress. Stability data on the drug product also support the usage of this container/closure system.

The drug substance is testosterone, USP, and is manufactured by — The Chemistry, Manufacturing and Control information of the drug substance is described in — DMF — and deemed adequate to support the NDA.

B. Description of How the Drug Product is Intended to be Used

The recommended dosing schedule for Striant therapy is the application of one buccal system (30mg) to the gum twice daily: Morning and evening. The system should be

placed just above the incisor tooth (on either side of the mouth). The rounded side of the system should be placed against the gum and held firmly in place with a finger over the lip and against the product for 30 seconds.

A 24-month of expiration date is granted as described above.

The storage condition for the drug product is "Store at 20-25^{0}C (68 – 77^{0}F) [see USP Controlled Room Temperature]. Protect from heat and moisture".

C. Basis for Approvability or Not-Approval Recommendation

- The chemistry deficiencies delineated in the 17-APR-2003 chemistry letter have been satisfactorily resolved through the amendments dated 01-MAY-2003, 28-MAY-2003, 04-JUN-2003, 16-JUN-2003, 17-JUN-2003 and 18-JUN-2003.
- Division of Medication Errors and Technical Support, Office of Drug Safety, found the proprietary name "Striant" acceptable on 19-FEB-2003.
- All the labeling (blister card, carton, and inserts) comments communicated to the applicant via telephone conferences on 27-MAY-2003 and 02-JUN-2003, were resolved satisfactorily. The revised blister and carton mock-ups and inserts are now also satisfactory.
- A new established name for this new dosage form was established on 23-MAY-2003 as testosterone buccal system.
- The acceptance criteria for in vitro-release were established to include an additional testing time point at [redacted] (acceptance criterion=NLT [redacted]
- The final recommendation from the Office of Compliance for the drug product-manufacturing site is **ACCEPTABLE (see Attachment–1)**.

III. Administrative

A. Reviewer's Signature: Electronically entered in the DFS

B. Endorsement Block:

ChemistName/Date:	Rajiv Agarwal, Ph.D/19-JUN-2003
ChemistryTeamLeader:	Moo-Jhong Rhee, Ph.D
ProjectManager:	Eufrecina De-Guia

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/s/

Rajiv Agarwal
6/19/03 03:11:03 PM
CHEMIST

Moo-Jhong Rhee
6/19/03 03:16:14 PM
CHEMIST
I concur

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21543/000
Stamp: 08-AUG-2002
Regulatory Due: 19-JUN-2003
Applicant: COLUMBIA LABORATORIES INC
100 NORTH VILLAGE AVE STE 32
ROCKVILLE CENTRE, NY 11570
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 21-APR-2003
Brand Name: TESTOSTERONE BUCCAL BIOADHESIVE
Estab. Name:
Generic Name: TESTOSTERONE BUCCAL BIOADHESIVE
Dosage Form: (CONTROLLED RELEASE TABLET)
Strength: 30 MG

Application Comment: DRUG PRODUCT LOOKS LIKE A TABLET BUT ACTS LIKE A PATCH AND DOSAGE FORM IS DESCRIBED AS 'BUCCAL BIOADHESIVE'.
FOR THE EES ENTRY, "CONTROLLED RELEASE TABLET" HAS BEEN CHOSEN TO INITIATE THE PROCESS. THIS REVIEWER IS INTERESTED IN PARTICIPATING IN THE INSPECTION OF DRUG PRODUCT MANUFACTURING SITE IN ITALY.
DIVISION IS RECOMMENDING THE DOSAGE FORM OF THE DRUG PRODUCT TO BE "BUCCAL SYSTEM" AND THE ESTABLISHED NAME SHOULD BE CHANGED TO (TESTOSTERONE BUCCAL SYSTEM) MUCOADHESIVE. PLEASE MAKE A NOTE OF IT.
(on 12-JUN-2003 by R. AGARWAL ())

FDA Contacts: E. DEGUIA (HFD-580) 301-827-4260 , Project Manager
R. AGARWAL , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 19-JUN-2003 by S. ADAMS (HFD-322) 301-827-9051

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CSN OAI Status: NONE
Estab. Comment: [redacted] ADDRESS FOR THIS SITE IS [redacted] AND IS DIFFERENT FROM WHAT IS LISTED IN THE EES. HOWEVER, THE CFN # [redacted] FOR BOTH THE ADDRESSES IS SAME. PLEASE CHECK. (on 27-AUG-2002 by R. AGARWAL ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-SEP-2002			[redacted]	AGARWALR
OC RECOMMENDATION	17-SEP-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 9614848
MIPHARM SPA
VIA BERNARDO QUARANTA BERNARDO 12
MILANO, , IT

DMF No: [redacted] AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: NEC OAI Status: NONE
Estab. Comment: DRUG PRODUCT IS MANUFACTURED, TESTED, RELEASED AND PACKAGED BY MIPHARM S.P.A, VIA BERNARDO QUARANTA BERNARDO, 12, 1I-20141 MILANO, ITALY. CFN # FOR THIS SITE IS NOT PROVIDED.
DOSAGE FORM OF THE DRUG PRODUCT IS "BUCCAL BIOADHESIVE" AND ACCORDING TO THE APPLICANT "IT IS IN THE PHARMACEUTICAL FORM OF A TABLET".
THE CHEMIST IS INTERESTED IN PARTICIPATING IN THE INSPECTION OF

DRUG PRODUCT MANUFACTURING SITE IN ITALY.
(on 28-AUG-2002 by R. AGARWAL ())
THE ESTABLISHED DOSAGE FORM IS:
STRIANT (TESTOSTERONE BUCCAL SYSTEM) MUCOADHESIVE (on 28-MAY-2003 by J. D AMBROGIO (HFD-322) 301-827-9049)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-SEP-2002				AGARWALR
SUBMITTED TO DO	17-SEP-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	19-SEP-2002	GMP			ADAMSS
INSPECTION SCHEDULED	10-JUN-2003		18-JUN-2003		IRIVERA
INSPECTION SCHEDULED	11-JUN-2003		18-JUN-2003		ADAMSS
INSPECTION PERFORMED	19-JUN-2003		19-JUN-2003		ADAMSS
DO RECOMMENDATION	19-JUN-2003			ACCEPTABLE INSPECTION	ADAMSS
BASED ON REVIEW OF 483 AND IVNESTIGATOR'S RECOMMENDATION. FIRM'S COMMITMENT TO CORRECT ISSUES SITED ON 483. AWAITING EIR AND FIRM'S RESPONSE					
OC RECOMMENDATION	19-JUN-2003			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

NDA FILEABILITY CHECKLIST

NDA Number: 21-543 **Applicant:** Columbia Laboratories Inc.
100 North Village Avenue, Suite 32
Rockville Centre, NY 11570

Stamp Date: 08-AUG-2002 (see note below)
Drug Name: **Trade name (testosterone) buccal bioadhesive**
Container closure: [redacted] blister
Strength: 30 mg
Route of Administration: Buccal

Note: Application was deemed incomplete when received because the required user fee was not paid. Fee was received on 19-AUG-2002.

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes _x__ No ____)

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		Drug product manufacturing site will be ready for inspection in April 2003.
6	Has an environmental assessment report or categorical exclusion been provided?	x		
7	Does the section contain controls for the drug substance?	x		DMF [redacted] contains all the relevant information
8	Does the section contain controls for the drug product?	x		
9	Has stability data and analysis been provided to support the requested expiration date?	x		Applicant proposes a 2 years of expiration date. Real time stability data supports [redacted] expiration date.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		Applicant will be asked to summarize the investigational formulation in tabular form showing the study number, batches used and their components.
14	Is there a Methods Validation package?	x		
15	Is a separate microbiological section included?		x	Not applicable

This application **meets the filing requirement** from the CMC point of view. This application is adequate to review from the CMC stand point.

Review Chemist: Rajiv Agarwal, Ph.D date: 11-OCT-2002

Team Leader: Moo-Jhong Rhee, Ph.D date: 11-OCT-2002

cc:
Original NDA 21-543
HFD-580/ NDA 21-543/Division File
HFD-580/Chem/RAgarwal/MRhee
HFD-580/PM/EDeguia

Have all DMF References been Identified? YES

DMF Number	Holder	Description	LOA	Status
		Testosterone drug substance	Included	
			Included	
			Included	
			Included	
			Included	

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/s/

Rajiv Agarwal
10/11/02 09:35:04 AM
CHEMIST

Moo-Jhong Rhee
10/11/02 11:43:08 AM
CHEMIST
I concur