

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-310

CORRESPONDENCE

MESSAGE CONFIRMATION

01/18/02 18:57

DATE	TIME	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
01/18	18:40	09'54"	8015838135	•CALLING	30	OK 0000

flu call @ 5:33 pm

APPEARS THIS WAY
ON ORIGINAL



Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 18, 2002

To: John Smith	From: Samuel Wu
Company: Watson Labs.-Utah	Division of Metabolic and Endocrine Drug Products
Fax number: 801-583-8135	Fax number: (301) 443-9282
Phone number: 801-588-6377	Phone number: 301-827-6416

Subject: Approvable Letters for Alora

Total no. of pages including cover: 29

Comments: DMED cover letter
DRUDP cover letter
PI/PPI

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

04/05/02 16:34
ID=DMEDP-CDER-FDA

NO.	MODE	BOX	GROUP
319	TX		

DATE	TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
04/05	16:33	01'20"	8015838135	004/004	OK		0000

Called Sherry Petrie
@ 2:45 pm
801-588-6633

APPEARS THIS WAY
ON ORIGINAL



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2002

To: Dorothy A. Frank

From: Samuel Y. Wu

Company: Watson Laboratories

Division of Metabolic and Endocrine
Drug Products

Fax number: 801-583-8135

Fax number: 301-443-9282

Phone number: 801-588-6200

Phone number: 301-827-6416

Subject: NDA 21-310; Alora (estradiol transdermal system)
Approval

Total no. of pages including cover: 4

Comments:

The labeling (package insert and patient package insert) will be included in the fax from DRUDP.

Document to be mailed:

YES

NO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2002

To: Dorothy A. Frank	From: Samuel Y. Wu
Company: Watson Laboratories	Division of Metabolic and Endocrine Drug Products
Fax number: 801-583-8135	Fax number: 301-443-9282
Phone number: 801-588-6200	Phone number: 301-827-6416

Subject: NDA 21-310; Alora (estradiol transdermal system)
Approval

Total no. of pages including cover: 4

Comments:

The labeling (package insert and patient package insert) will be included in the fax from DRUDP.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at DIVISION'S PHONE NUMBER. Thank you.



WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

DUPLICATE

February 5, 2002



Division of Metabolic and
Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

Response to Approvable Letter

AL
N 000 ~~BA~~
ORIG AMENDMENT

RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to Approvable Letter

Watson submits the enclosed information in response to FDA's approvable letter dated January 18, 2002, requesting revisions to the labeling for Alora. For both the package insert and the patient insert, we have included a copy of our proposed version, with the changes indicated.

The enclosed version, with the exception of minor typographical corrections, includes all of FDA's requested revisions, as well as all of the requested additional information.

We have modified Table 3 (vasomotor symptom reduction), in accordance with your request. The supporting efficacy data are enclosed, on a CD. Further explanatory text for these changes follows:

As per the Statistical Analysis Plan for this study, efficacy was assessed in terms of the mean % reduction in frequency of moderate/severe hot flushes from baseline. The values reported in the previously proposed labeling were calculated from the mean data for the non-LOCF data presented in Table 21 of the Clinical Trial Report (NDA #20-655, Section 8, Volume VI, page 0085). However, the LOCF data should have been reported to correspond with the existing approved labeling for Alora.

The mean changes in frequency of moderate/severe hot flushes (LOCF data) are reported in Appendix C.4.12 of the Clinical Trial Report (NDA #20-655, Section 8, Volume XII, pages 0046-0051) and the amended table is shown in the enclosed package insert.

We believe this submission meets the labeling recommendations of the Agency for this product.



Regarding your request for additional safety and effectiveness information, there is no additional information pertaining to safety or effectiveness. Other than the study that was the subject of this NDA, there are no additional studies.

Please note that your approvable letter omitted the 0.1 mg/day strength; please include this strength in the prevention of osteoporosis indication when approval is issued.

We look forward to your prompt response. If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377.

Best Regards,

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

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, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Watson Laboratories, Inc.	DATE OF SUBMISSION February 5, 2002
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-310

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Estradiol Transdermal System (EMTDS)	PROPRIETARY NAME (trade name) IF ANY Alora® Estradiol Transdermal System	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Estra-1,3,5 (10)-triene-3, 17-diol	CODE NAME (If any) None	
DOSAGE FORM: Transdermal System	STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day	ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

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 A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

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

REASON FOR SUBMISSION Response to Approvable Letter

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.

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

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

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21CFR 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(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

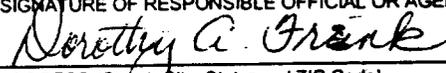
CERTIFICATION

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 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 review 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 Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	DATE February 5, 2002
ADDRESS (Street, City, State, and ZIP Code) 417 Wakara Way Salt Lake City, Utah, 84108		TELEPHONE NUMBER (801) 588-6200

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
 CBER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

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.

ORIGINAL



A Subsidiary of Watson Pharmaceuticals, Inc.

January 25, 2002

N 0002
NEW CORRESP

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857



**RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to Approvable Letter**

In response to FDA's approvable letter dated January 18, 2002, Watson is notifying the Division that we intend to file an amendment to the NDA.

If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377.

Best Regards,

A handwritten signature in cursive script that reads 'Dorothy A. Frank'.

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Watson Laboratories, Inc.	DATE OF SUBMISSION January 25, 2002
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-310

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Estradiol Transdermal System (EMTDS)	PROPRIETARY NAME (trade name) IF ANY Alora® Estradiol Transdermal System	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Estra-1,3,5 (10)-triene-3, 17-diol	CODE NAME (If any) None	
DOSAGE FORM: Transdermal System	STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day	ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

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 A PENDING APPLICATION RESUBMISSION PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

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

REASON FOR SUBMISSION Intent to Amend NDA

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.

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

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(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Intnet to Amend NDA

CERTIFICATION

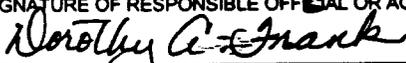
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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 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 Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	DATE January 25, 2002
ADDRESS (Street, City, State, and ZIP Code) 417 Wakara Way Salt Lake City, Utah 84108		TELEPHONE NUMBER (801) 588-6200

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
 CBER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

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.

ORIGINAL



WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

16 January, 2002

Dr. Solomon Sobel, Director
Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-45
5600 Fishers Lane
Rockville, MD 20857

N 000 C
NEW CORRESP

RE: NDA 21-310: Alora[®] Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dr. Sobel:

Based upon our telephone conversations of January 11, 14, 15 and 16 with the Regulatory Project Managers at DMEDP and DRUDP, Watson understands that the package insert for Alora will have further changes requested by FDA, in addition to those requested in the approvable letter of November 16, 2001. It is also our understanding that the statement to be added to the new insert regarding Adhesion, which Watson provided at FDA's request, has proved to be difficult to review within the user fee goal date. To facilitate FDA's approval of the new indication and size within the goal date, Watson makes the following proposal regarding these issues:

1. Watson will accept all of FDA's requested changes to the insert for the Alora product.
2. The statement regarding Adhesion is not particular to the new indication, and is being added at DRUDP's request, to make the labeling conform to the Division's current information requirements. Since the review of this statement appears to be the single issue delaying approval, Watson will withdraw the proposed Adhesion statement from the insert. Watson will also commit to submitting a proposed Adhesion statement, with a detailed supporting rationale, based on the clinical data previously submitted in supplement S003 to NDA 20-655. Watson will submit this in a supplemental NDA within 30 calendar days of receiving an approval letter for the new indication.

There is no reason to delay the approval of the new indication for this product because of questions over adhesion data. The product has been used safely so far without any statements in the insert regarding adhesion. We realize that the Division wants the insert to contain a statement regarding adhesion, and will commit to providing one quickly.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Regulatory Affairs



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Watson Laboratories, Inc.	DATE OF SUBMISSION January 16, 2002
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-310	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Estradiol Transdermal System (EMTDS)	PROPRIETARY NAME (trade name) IF ANY Alora® Estradiol Transdermal System
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Estra-1,3,5 (10)-triene-3, 17-diol	CODE NAME (If any) None
DOSAGE FORM: Transdermal System	STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day
ROUTE OF ADMINISTRATION: Transdermal	

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

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 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 801)	
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 A PENDING APPLICATION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> EFFICACY SUPPLEMENT
	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OR 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 Proposal for Labeling		

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)

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(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Proposal for Labeling

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 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 Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	DATE January 16, 2002
ADDRESS (Street, City, State, and ZIP Code) 417 Wakara Way Salt Lake City, Utah, 84108		TELEPHONE NUMBER (801) 588-6200

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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.



WATSON
Laboratories, Inc.

ORIGINAL

A Subsidiary of Watson Pharmaceuticals, Inc.

January 14, 2002

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

NOV 0006
NEW CORRESP

**RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day,
0.075 mg/day and 0.1 mg/day
Response to request for information**

In response to a request for clarifying information, made by Ms. Dornette Spell-LeSane on January 10 of this year, Watson is providing the following information:

The adhesion data for Alora was contained in supplement S003 to NDA 20-655, submitted September 3, 1998 and approved November 24, 1998. The Clinical Report number in that supplement is E97005. This information is the basis of the Adhesion section of the package insert.

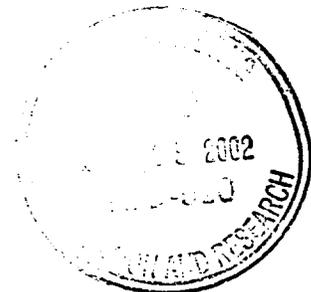
If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Watson Laboratories, Inc.	DATE OF SUBMISSION January 14, 2002
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-310

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Estradiol Transdermal System (EMTDS)	PROPRIETARY NAME (trade name) IF ANY Alora® Estradiol Transdermal System	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Estra-1,3,5 (10)-triene-3, 17-diol	CODE NAME (If any) None	
DOSAGE FORM: Transdermal System	STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day	ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

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 A PENDING APPLICATION RESUBMISSION PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

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

REASON FOR SUBMISSION Response to Request for Information

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.

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

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(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Response to Request for Information

CERTIFICATION

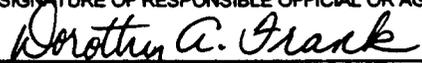
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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 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 Dorothy A. Frank, M.S., R.A.C. Executive Director, Proprietary Regulatory Affairs	DATE January 14, 2002
ADDRESS (Street, City, State, and ZIP Code) 417 Wakara Way Salt Lake City, Utah, 84108		TELEPHONE NUMBER (801) 588-6200

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
 CBER, HFM-99
 1401 Rockville Pike
 Rockville, MD 20852-1448

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.

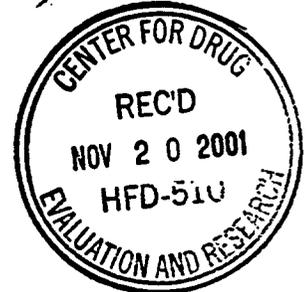


A Subsidiary of Watson Pharmaceuticals, Inc.

ORIGINAL

November 19, 2001

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857



N 000 AL
ORIG AMENDMENT

**RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Response to Approvable Letter**

In response to FDA's approvable letter dated November 16, 2001, in which revisions to the labeling for Alora were requested, Watson hereby submits the enclosed information. For both the package insert and the patient insert, we have included a copy of Watson's proposed version, with notes regarding any changes.

The enclosed version, with the exception of minor typographical errors, includes all of FDA's requested language, as well as all of the additional information requested by FDA. We believe this submission meets the labeling recommendations of the Agency for this product.

Regarding your request for additional safety and effectiveness information, there is no additional information pertaining to safety or effectiveness. Other than the study that was the subject of this NDA, there are no additional studies.

Please note that your approvable letter omitted the 0.1 mg/day strength; please include this strength in the prevention of osteoporosis indication when approval is issued.

We look forward to your prompt response. If you have any questions, please call John Smith, Regulatory Manager, at (801) 588-6377

Best Regards,

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Watson Laboratories, Inc.	DATE OF SUBMISSION November 19, 2001
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-310

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Estradiol Transdermal System (EMTDS)	PROPRIETARY NAME (trade name) IF ANY Alora® Estradiol Transdermal System	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Estra-1,3,5 (10)-triene-3, 17-diol	CODE NAME (If any) None	
DOSAGE FORM: Transdermal System	STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day	ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

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 A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

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

REASON FOR SUBMISSION Response to Approvable Letter

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.

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

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(k)(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 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 <i>Dorothy A. Frank</i>	TYPED NAME AND TITLE Dorothy A. Frank, M.S., R.A.C. Executive Director, Regulatory Affairs	DATE November 19, 2001
---	--	---------------------------

ADDRESS (Street, City, State, and ZIP Code) 417 Wakara Way Salt Lake City, Utah, 84108	TELEPHONE NUMBER (801) 588-6200
--	------------------------------------

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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

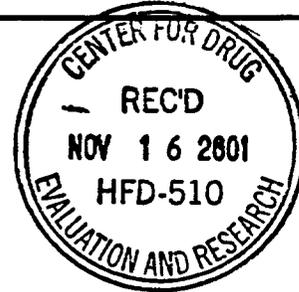


WATSON

Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

November 15, 2001



Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-45
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Response to Request for Information

Re: **NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day**

Response to Request for Information

Dear Mr. Wu:

Per your telephone conversation with John Smith on November 7, 2001, enclosed please find the requested administrative pieces for FDA's internal files to complete the "action package" for Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day. Your requests are listed below with our response, and this communication is provided by fax to your attention and will be followed by hard copy submission.

- *Please provide copies of the artwork (black and white are fine, or computer printouts) for the pouch label and carton label for the 0.025 mg size. Copies of the artwork for the .025 mg size pouch label and carton label are provided.*
- *Please confirm whether the osteoporosis clinical study was performed under the Alora IND ~~_____~~. The osteoporosis clinical study was performed under the Alora IND ~~_____~~.*
- *Please provide the dates of any end-of-phase 2 or pre-NDA meetings between FDA and Watson regarding the osteoporosis indication.*
 - End-of-phase 2 meeting on July 31, 1996 included discussion pertaining to the osteoporosis indication.
 - Teleconference on May 20, 1997 - discussion of the washout period.
 - Watson requested a pre-NDA meeting with DRUDP & also with DMEDP in April, 2000. FDA held an internal pre-meeting June 15, 2000 and determined that



a face-to-face meeting was not necessary. FDA provided comments in response to our briefing package and questions by fax on June 29, 2001.

- *Please provide a copy of Watson's request for pediatric waiver.* A copy of the pediatric waiver that was submitted in the original application is provided.
- *Are there any ongoing studies for Alora relevant to the osteoporosis indication?*
There are no ongoing studies for Alora relevant to osteoporosis indication.

If you have any questions or need any additional information, please contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Executive Director,
Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL