

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204017Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Memorandum** DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** February 12, 2020

**From:** Mark R. Seggel, Ph.D.  
Application Technical Lead  
Office of New Drug Products  
Branch 4/DNDP II

**Through:** Moo-Jhong Rhee, Ph.D.  
Chief, Branch V  
Office of New Drug Products  
Branch 4/DNDP II

**To:** OPQ IQA #4 for NDA 204017  
TWIRLA (levonorgestrel and ethinyl estradiol) transdermal system

**Subject:** Final Recommendation - APPROVAL

**Summary:**

The OPQ Integrated Quality Assessment (IQA) dated November 1, 2019, recommended a Complete Response for the resubmission of 505(b)(2) NDA 204017. It was noted that labeling (prescribing information (PI), container/carton) negotiations had not been completed and the labeling did not comply with the requirements under 21 CFR 201. The NDA was otherwise complete and adequate from the ONDP perspective.

Deficiencies in the proposed labeling included use of incorrect nomenclature. Throughout labeling the product was referred to as a “(b) (4).” Per USP <1151> Dosage Forms, the correct term is “transdermal system.” Formatting of the product title and established name were also incorrect. Sections 3, Dosage Form and Strength, Section 11, Description, and Section 16, How Supplied / Storage and Handling, were incomplete or lacked clarity. The description of product adhesion in Section 14 Clinical Studies, also lacked completeness and clarity. See Caroline Strasinger’s labeling review in Chapter IV, Labeling, of IQA # 4 for details.

Recommended revisions to the prescribing information and to the container (pouch) and carton labels were conveyed to the applicant.

The revised pouch and carton labels submitted January 17, 2020 (sn 0072) adequately incorporate all ONDP and DMEPA recommendations (see Attachment 1 of this Addendum).

Sample carton, sample pouch and sample pack (carton of 6 cartons of three transdermal systems) labels are comparable to trade labels, but include the statement, "Professional Sample: Not For Resale."

Revised prescribing information was submitted on February 12, 2020. As revised, the PI is adequate from the OPQ perspective. Relevant text is captured in Attachment 1. Note that information about replacement TDS has been added to Section 16. Also note that the only accepted use of "patch" in the labeling is in relation to the directions for use which refer to the "patch change day."

**Additional Comments:**

**Release-Rate:** During internal labeling discussions, questions were raised about how the stated strength (120 mcg LNG / day and 30 mcg EE / day) of the drug product was calculated. A request for residual drug data was sent on December 10, 2019. In their December 13, 2019 response (sn 0069), Agile noted that the product was designed to minimize residual drug. They stated that residual levonorgestrel and ethinyl estradiol were not measured post-wear. Rather, the average amount of drug delivered (a derived value based on exposure data relative to exposure from oral contraceptives) over the seven-day wear period was subtracted from the loading dose. In order to accurately assess the residual drug content and strength of Twirla, a post-marketing commitment (PMC) was developed in collaboration with DBRUP:

**PMC-3785-2**

A clinical study in a minimum of 25 women to accurately assess the residual drug content and strength of Twirla. This study will evaluate Twirla worn by study subjects and analyze the ethinyl estradiol (EE) and levonorgestrel (LNG) content after the prescribed wear and monitor adhesion over the entire wear period.

**Milestones:**

Draft Protocol Submission: 06/2020

Final Protocol Submission: 09/2020

Study Completion: 06/2021

Final Report Submission: 09/2021

Agile acknowledged agreement via email on February 6, 2020. Note that the rather long timeline is because commercial product will not be immediately available.

**Facility Status:** All manufacturing facilities continue to have acceptable CGMP status (see Attachment 2, Facility Status Report as of 02/10/2020).

#####

**Recommendation:**

This NDA is now recommended for **Approval** from the OPQ perspective.

**Application Technical Lead Signature:**

Mark R. Seggel, Ph.D.,  
CMC Lead (acting)

*{see digital signature page}*

**ATTACHMENTS**

**Attachment 1. Labeling**

**Attachment 2. Facility Status Report**

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## Prescribing Information (as submitted February 12, 2020)

### Highlights

#### **TWIRLA (levonorgestrel and ethinyl estradiol) transdermal system**

**Initial U.S. Approval: 1968 (norgestrel and ethinyl estradiol)**

#### -----DOSAGE FORM AND STRENGTH-----

Transdermal system: 120 mcg/day levonorgestrel (LNG) and 30 mcg/day ethinyl estradiol (EE) (3)

### Full Prescribing Information

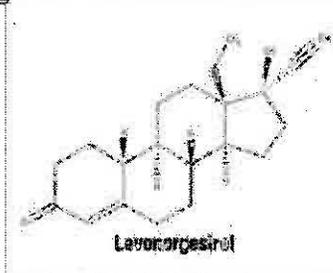
#### **3 DOSAGE FORMS AND STRENGTHS**

TWIRLA (120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol) transdermal system is a circular beige colored product with the name and strength etched on the backing membrane.

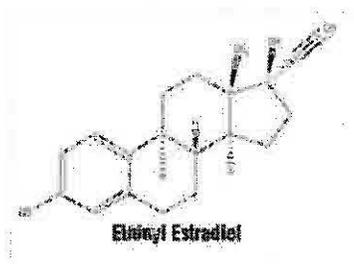
#### **11 DESCRIPTION**

TWIRLA (levonorgestrel and ethinyl estradiol) transdermal system (TDS) contains 2.60 mg levonorgestrel (LNG) (17 $\alpha$ )-(-) [13-ethyl-17-hydroxy-18, 19-dinorpregn-4-en-20-yn-3-one], a progestin, and 2.30 mg ethinyl estradiol (EE), [(17 $\alpha$ )-19-norpregna-1, 3, 5(10)-trien-20-yne-3, 17-diol] an estrogen (Figure 2).

**Figure 2. Structural Formulas**



Molecular Formula: C<sub>21</sub>H<sub>34</sub>O<sub>2</sub>  
Molecular Weight: 312.45



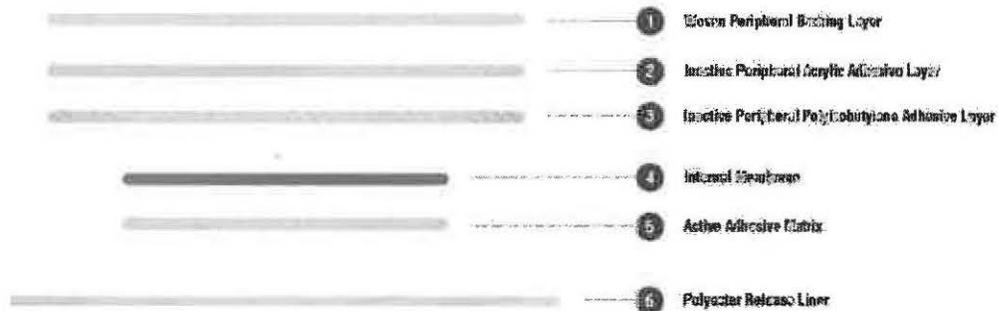
Molecular Formula: C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>  
Molecular Weight: 296.41

TWIRLA is designed to provide daily exposure of 120 mcg LNG and 30 mcg EE. TWIRLA is a matrix type TDS consisting of a 15 cm<sup>2</sup> active adhesive laminate center, surrounded by a peripheral inactive adhesive laminate. The entire area of TWIRLA is 28 cm<sup>2</sup>.

TWIRLA consists of 5 layers and a release liner which is removed and discarded prior to application. The two innermost layers contain the active ingredients (LNG and EE), as well as inactive components. Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a woven peripheral backing layer, which is etched with "TWIRLA Levonorgestrel 120 mcg/day Ethinyl Estradiol 30 mcg/day"; (2) an

inactive peripheral acrylic adhesive layer; (3) an inactive peripheral polyisobutylene adhesive layer; (4) an internal membrane to separate the active adhesive matrix from the inactive adhesive laminate; (5) the active adhesive matrix (Figure 3).

**Figure 3: Schematic Depiction of the AG200-15 TDS**



The inactive components are acrylic adhesives, capric acid, copovidone, crospovidone, dimethyl sulfoxide, ethyl lactate, lauryl lactate, polybutene, polyester internal membrane, polyester release liner, polyisobutylene adhesives, and woven polyester backing membrane. TWIRLA is not made with latex.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

TWIRLA (levonorgestrel and ethinyl estradiol) transdermal system is a beige 28 cm<sup>2</sup> round product etched with “TWIRLA Levonorgestrel 120 mcg/day Ethinyl Estradiol 30 mcg/day” and supplied as:

- a carton of 3 identical TDS, each TDS is packaged in an individual pouch. NDC 71671-100-03
- as a single TDS provided for replacement as needed. NDC 71671-100-01

### 16.2 Storage Conditions and Disposal

Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store in original unopened pouch.

Used TDS still contain some active hormones. To discard, fold the sticky sides of the TDS together, place in a sturdy container, preferably with a child-resistant cap, and place this container in the trash. Used TDS should not be flushed down the toilet. See [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for more information about disposal of medicines.

## 14 CLINICAL STUDIES

### Adhesion

Based on a Phase I study in 78 subjects wearing one TWIRLA on the lower abdomen for 7 days, 77 systems applied (98.7%) exhibited 75% or greater surface area adhesion at all

timepoints evaluated (every 24 hours) throughout the wear period. In the Phase 3 trial, 5.0% of all transdermal systems worn during the year-long trial (55,900 transdermal systems) fully detached. Subject-reported adhesion was generally better for the abdomen as compared to the upper torso and buttock. Full detachment rates were higher for transdermal systems exposed to water as compared to transdermal systems with no water exposure.

**Attachment 2. Facility Status Report**

Time run: 2/10/2010 9:12:03 AM

(b) (4)

Plant Overall Manufacturing Inspection Recommendation or Approval	Inspection Requested	Inspection Completed	Plant/DA Alerts	Plant Phone
	0	1	No	No

(b) (4)

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
-----

/s/  
-----

MARK R SEGCEL  
02/12/2020 05:22:38 PM

## RECOMMENDATION

<input type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input checked="" type="checkbox"/> Complete Response

**NDA 204017**  
**Twirla (levonorgestrel and ethinyl estradiol)**  
**Transdermal System**  
**Assessment #4**

<b>Drug Product Name</b>	Levonorgestrel and Ethinyl Estradiol Transdermal System
<b>Dosage Form</b>	Transdermal System (patch)
<b>Strength</b>	120/30 mcg/day, 7-day
<b>Route of Administration</b>	Transdermal
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Agile Therapeutics, Inc.
<b>US agent, if applicable</b>	-

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission (0058)	05/16/19	Multidiscipline
Amendment (0060)	07/17/19	Drug Product; Manufacturing
Amendment (0063)	08/20/19	Manufacturing
Labeling / Container-Carton (0064)*	10/15/19	Not reviewed*

\* Response to DMEPA comments. Will be evaluated from the Drug Product CMC perspective when labeling negotiations resume.

### QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
<b>Drug Substance</b>	Joe Leginus	Donna Christner
<b>Drug Product</b>	Caroline Strasinger	Moo-Jhong Rhee
<b>Manufacturing (Process)</b>	James Norman	Yubing Tang
<b>Manufacturing (Facilities)</b>	Laurie Nelson	Vidya Pai
<b>Microbiology</b>	-	-
<b>Biopharmaceutics</b>	Bryan Ericksen	Vidual Kolhatkar
<b>Laboratory (OTR)</b>	Not Applicable	-
<b>Environmental</b>	Jim Laurenson	Scott Furness

<b>Regulatory Business Process Manager</b>	Marquita Burnett
<b>Application Technical Lead</b>	Mark Seggel

## EXECUTIVE SUMMARY

### IQA NDA Assessment Guide Reference

#### I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

In its present form, Agile Therapeutics' resubmission of 505(b)(2) New Drug Application #204017 for Twirla (levonorgestrel and ethinyl estradiol) Transdermal System is not ready for approval.

Labeling negotiations have not been completed and there is no agreement on the content and format of the final product labeling. The proposed product labeling currently does not comply with the requirements for labels and labeling in 21 CFR 201.

Sufficient information and supporting data have been provided in accordance with 21CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. Adequate *in vivo* adhesion of the drug product has been demonstrated. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The claim for a categorical exclusion from an EA under 21 CFR 25.31(b) is acceptable with the proposed mitigation strategy (labeling statements).

#### II. SUMMARY OF QUALITY ASSESSMENTS

**Background:** NDA 204017 was originally submitted on April 13, 2012. A Complete Response Letter (CRL) was issued on February 13, 2013. Clinical and Product Quality deficiencies were noted. A response to the CRL was submitted on June 24, 2013, but it was considered incomplete. A new clinical study, ATI-CL23, was conducted to address the clinical deficiencies. The results of this study, along with revised chemistry, manufacturing and controls information were provided in the June 26, 2017 resubmission. On December 21, 2017 a second Complete Response letter was issued. There appeared to be a significant problem with *in vivo* adhesion, which was considered likely to adversely impact the safe and efficacious use of the product. Tests for ensuring acceptable quality, and, in particular, tack and adhesion, of drug product intermediates and the finished drug products were also inadequate. The product manufacturing facility, Corium, was found to be not ready for commercial manufacturing.

Following formal Dispute Resolution negotiations, it was agreed that demonstration of adequate *in vivo* adhesion in a comparative study would be sufficient to address this critical issue. The results of ATI-CL26, a pilot non-comparative adhesion study, and of comparative *in vivo* adhesion study ATI-

CL25 were provided in the May 19, 2019 resubmission. Both *in vivo* adhesion studies were conducted with batch #38449. This batch was manufactured December 15, 2017 using the intended commercial-scale process and revised controls.

An Advisory Committee meeting is scheduled for October 30, 2019 to consider whether the potential benefit of Twirla outweighs the safety risks. Twirla appears to have a relatively high Pearl Index (PI; estimated pregnancy rate per 100 women-years) compared to other approved forms of contraception.

#### A. Product Overview

<b>Proposed Indication(s) including Intended Patient Population</b>	TWIRLA is a weekly low-dose estrogen (EE) / progestin (LNG) combination hormonal contraceptive (CHC) transdermal patch indicated for use by women to prevent pregnancy.
<b>Duration of Treatment</b>	TWIRLA is used in a 28-day (four-week) cycle. A new patch is applied to the abdomen, buttock, or upper torso (excluding the breasts) each week for three consecutive weeks (21 total days). No patch is worn in week four (the patch-free week). Use to be continued for as long as contraception is desired.
<b>Maximum Daily Dose</b>	120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol, over 7-day period of use.
<b>Alternative Methods of Administration</b>	For topical application only.

Twirla (levonorgestrel and ethinyl estradiol) Transdermal System, referred to as AG200-15, is a circular patch designed to deliver 120 mcg/day levonorgestrel (LNG) and 30 mcg/day ethinyl estradiol (EE) over a period of 7 days. The patch has an overall diameter of approximately 6 cm (2.35 inches) and surface area of ca. 28 cm<sup>2</sup>. The active adhesive matrix has an area of ca. 15 cm<sup>2</sup>. The active components are incorporated into a non-crosslinked acrylic adhesive matrix. Four skin permeation enhancers are included to facilitate penetration of the actives through the skin.

Ortho Evra, a Combined Hormonal Contraceptive (CHC) transdermal system (patch) delivering 0.035 mg EE and 0.15 mg norelgestromin per day for 7 days has been discontinued by Janssen Pharmaceuticals, but a generic equivalent, Xulane, is available.

Combined oral contraceptives (COC) are available containing 0.03 mg EE and 0.15 mg LNG. Other available COCs contain 0.02 mg EE and 0.09 mg LNG. Nuvaring is a vaginal ring containing EE and etonorgestrel which

releases on average 0.12 mg/day of etonogestrel and 0.015 mg/day of ethinyl estradiol over a period of 3 weeks.

Agile Therapeutics opines that, "Transdermal drug delivery systems offer significant advantages over more conventional oral or parenteral dosage forms. First, the administration of the drug is noninvasive. Second, the release is controlled over time with the potential to reduce the incidence and/or severity of side effects. Third, first pass metabolism is eliminated increasing the amount of parent drug(s) available systemically to produce a therapeutic response. Finally, better compliance may result in increased efficacy."

Adhesion of Twirla (levonorgestrel and ethinyl estradiol) Transdermal System to skin is critical to the safe and effective use of the drug product. Also critical to the safe and effective use of Twirla is the controlled release of the active ingredients. Adequate control of impurities derived from the adhesives system must be maintained.

## **B. Quality Assessment Overview**

The chemistry, manufacturing and controls (CMC) of Twirla (levonorgestrel and ethinyl estradiol) Transdermal System was previously reviewed and found inadequate by Dr. Caroline Strasinger (see Chemistry Review #1, January 14, 2013, and Review #2, February 12, 2013, and memos dated August 3, 2012 and January 15, 2013). The June 26, 2017 resubmission was also found inadequate from the CMC perspective (see Quality Assessment #3, December 13, 2017). In May 19, 2019, this application was resubmitted with the results of ATI-CL26, a pilot non-comparative adhesion study and a comparative *in vivo* adhesion study, ATI-CL25, which are the subject of the current review.

### **Drug Substance: Adequate**

Levonorgestrel and ethinyl estradiol are widely used active ingredients in contraceptive drug products. The chemistry, manufacturing and controls (CMC) of these drug substances are documented in (b) (4) Drug Master Files (DMFs) (b) (4) respectively. Both DMFs remain adequate to support use of the drug substances in the drug product.

This NDA is recommended for APPROVAL from the drug substance perspective. See Chapter I, Drug Substance, for details.

### **Drug Product: Adequate**

Twirla (levonorgestrel and ethinyl estradiol) transdermal system consists a polyester peripheral backing layer, a peripheral acrylic adhesive layer, a

peripheral polyisobutylene (PIB) adhesive layer, a polyester active matrix backing, the active matrix adhesive (containing LNG, EE (b) (4), and a polyester release liner. (b) (4)

DMSO, ethyl lactate, caproic acid and lauryl lactate.

The December 21, 2017 Complete Response Letter noted that, “the finished drug product specification is not adequate to ensure the quality, tack and adhesion of the drug product at release and on stability. The current in vitro adhesion test does not ensure adequate in vivo adhesion properties requisite for the safe and efficacious use of the drug product.”

The current ONDP Drug Product assessment focuses on part tack and adhesion tests methods and acceptance criteria, and on in vivo adhesion. The adhesion test then in place, TP074, was found to be highly variable, subjective, and resulted in uninterpretable data with non-comparable profiles between batches.

Based on Agency recommendations, the adhesion test method was revised and validated. Overall, the revised part tack and adhesion tests represent significant improvements over the previous methods. Although based on very limited data, the proposed acceptance criteria are acceptable. Part tack and adhesion results should be considered when evaluating stability and any future manufacturing changes.

Although the in vivo adhesion performance remains questionable given the high percent of failure in the “real world” adhesion study ATI-CL23 as discussed in the previous review cycle, the results from ATI-CL25, a pivotal comparative in vivo adhesion study versus Xulane allows for an adequate recommendation from the quality adhesion perspective.

The change in PIB adhesive type / grade from (b) (4) was evaluated. This change did not adversely impact finished product performance. The change from clinical scale manufacturing to commercial scale manufacturing, and minor changes to the commercial scale process, have been shown to have little to no effect on product performance.

NDA 204017 is recommended for APPROVAL from the drug product perspective. An expiration dating period of 24 months is granted when stored at 20° to 25°C (68° to 77°F).

See Chapter II, Drug Product, and Chapter VIII, Quality *In Vivo* Adhesion Assessment, for details.

### **Environmental Assessment: Adequate**

The claimed categorical exclusions for EE and LNG under 21 CFR 25.31(b) are appropriate for the expected introduction concentrations into the aquatic environment (EIC<sub>aq</sub>) which are well below 1 part per billion (ppb). While a statement of no extraordinary circumstances (21 CFR 25.15(a)) was included with the claims, there is a certain environmental risk associated with disposal of used product, which contain significant amounts of residual LNG and EE. The proposed mitigation strategy is based on providing clear disposal instructions in the labeling. The claimed categorical exclusion is acceptable based on the proposed mitigation strategy (see Quality Assessment #3, December 13, 2017 for details).

### **Labeling: Inadequate**

The May 16, 2019 resubmission included draft prescribing information (PI), pouch labels and carton labels. The applicant has also developed a new replacement carton and replacement pouch containing one patch to be made available to patients who experience a patch adhesion failure.

Deficiencies related to the product title, nomenclature, established name, dosage form, and product description (Section 3) have been identified. Numerous deficiencies with Section 11 Description and Section 16 How Supplied / Storage and Handling have also been identified. Deficiencies with the pouch and carton label have been identified. Revisions to the discussion of in vivo adhesion under Section 14 are proposed.

DMEPA provided comments regarding the labeling to the applicant on October 1, 2019. Revised container and carton labels were submitted on October 15, 2019. The revised labels have not been formally reviewed from the ONDP perspective, however the labels obviously remain deficient as documented in this Quality Assessment.

See Chapter IV, Labeling, for details and recommended revisions to be communicated to the applicant when labeling negotiations resume.

From the ONDP review perspective, the current labeling is deficient and the application is NOT READY FOR APPROVAL.

As noted above, to mitigate environmental risk, product labeling (prescribing information, labels and patient instructions) is expected to include directions to discard used product in the trash (solid waste) (b) (4). (b) (4) see Quality Assessment #3, December 13, 2017 for details). The DMEPA labeling review team was advised of this issue. The ONDP Environmental Assessment Team should be consulted during

final labeling negotiations to ensure implementation of the mitigation strategy is complete.

**Manufacturing: Adequate**

(b) (4)

As revised, the application is now ADEQUATE from the Process review perspective. See Chapter Va, Process, for details.

**Facilities:** During the previous inspection of the drug product manufacturing facility, Corium, it was determined that the facility was not ready for commercial manufacturing. This was reflected in the December 21, 2017 Complete Response Letter.

Re-inspection of Corium was completed September 20, 2019. The manufacturer has adequately addressed all issues identified during the previous pre-approval inspection. All other facilities have acceptable CGMP status. See Chapter Vb, Facilities, for details.

An 'Overall Manufacturing Inspection Recommendation' of APPROVE was issued on September 25, 2019.

Note: Although CDRH-OC had previously (see Quality Assessment #3) recommended a medical device GMP inspection of Agile Therapeutics to assess compliance with Quality System Requirements under 21 CFR 820, it was subsequently determined that an evaluation was not necessary (see the September 25, 2019 Submission Manufacturing Status report for NDA-204017-orig-1-resub-60 in Panorama).

#### **Biopharmaceutics: Adequate**

The in vitro release method and acceptance criteria were previously reviewed and approved. Refer to the January 3, 2013 Biopharmaceutics review and to the November 15, 2017 Biopharmaceutics review (IQA #3, December 13, 2017) for details.

The current assessment focused on comparison of product (batch 38449) manufactured at commercial-scale using the commercial process and used in pivotal adhesion study ATI-CL25, and a commercial-scale development batch (37620) which had previously been bridged to clinical process lots (see 3.2.P.2 in the June 26, 2017 resubmission).

The in vitro release profiles of batches 38449 and 37620 met the f2 similarity requirements for both LNG and EE, adequately bridging the change in process (and in grade of PIB).

The application remains ADEQUATE from the Biopharmaceutics perspective (see Chapter VI of this Quality Assessment).

#### **Microbiology: Adequate**

Risk for microbial contamination of this non-aqueous formulation is low. Testing per USP <51> indicates that the formulation inhibits microbial growth. Microbial limits testing is not required for batch release and stability testing of the finished product (see Chemistry Review #1).

**CDRH: Adequate**

As a drug-device combination product, Twirla (levonorgestrel and ethinyl estradiol) Transdermal System is subject to the requirements under 21 CFR Part 4. CDRH Office of Compliance was previously consulted to assess conformance to medical device GMPs under 21 CFR 820. CDRH-OC has determined that conformance with the applicable Quality System Requirements under 21 CFR 820 has been adequately documented. See Quality Assessment #3 for details.

Note that current practice for the review of transdermal drug delivery systems such as Twirla does not require a separate CDRH-ODE consult.

### C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Identity	• CGMPs	L		Acceptable	
Appearance - Patch	• Raw materials • Mfg. process • Mfg. equipment, site and scale	M	Established mfg. conditions (b) (4) controls; AQLs	Acceptable	
Appearance - Pouch	• Raw materials • Mfg. process • Mfg. equipment, site and scale	L		Acceptable	
Assay	• Raw materials • Mfg. process • Mfg. equipment, site and scale	M	(b) (4)	Acceptable	
Content Uniformity	• Raw materials • Mfg. process • Mfg. equipment, site and scale	M	As above	Acceptable	Low LNG and EE drug content
Degradation Products	• Process conditions • Storage	L		Acceptable	
Solid State Form	• Raw materials • Mfg. process	L		Acceptable	(b) (4)
Drug Release / Skin Permeation / Dose dumping	• Raw materials • Mfg. process • Mfg. equipment, site and scale • CCS	M	(b) (4)	Acceptable	
Microbial Limits	• Raw materials • Mfg. environment • CCS	L		Acceptable	Non-aqueous system Microbial limits testing waived (b) (4)
Permeation Enhancer Assay	• Mfg process conditions • Mfg. equipment, site and scale	M	Process conditions	Acceptable	Critical to bioavailability (b) (4)
Adhesion, Shear, Tack, and Cold Flow	• Raw materials • Process • Mfg. equipment, site and scale	H (Note a)	Established mfg. process parameters: (b) (4)	Acceptable	(Note b)
Release Liner Removal Force	• Raw materials • Process • Mfg. equipment, site and scale	L		Acceptable	

Pouch integrity	Mfg. process conditions	L		Acceptable	
-----------------	-------------------------	---	--	------------	--

Note a: Per Chapter II of this IQA, Methods from Cycle #1 and #2 were invalid. Results were meaningless and not reproducible primarily because product was measured as a whole unit.

Note b: Method revisions have improved reproducibility and meaningfulness as now each part (active and periphery) are measured separately. Data is limited for the new acceptance criterion in the resubmission, so the risk is M.

**D. List of Deficiencies for Complete Response**

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

Not applicable.

2. Drug Substance Deficiencies

Not applicable.

3. Drug Product Deficiencies

Not applicable.

4. Labeling Deficiencies

Not applicable. Recommended revisions to the labeling as outlined in IQA Chapter IV, Labeling, will be conveyed to the applicant if and when clinical deficiencies are resolved and labeling negotiations resume.

5. Manufacturing Deficiencies

Not applicable.

6. Biopharmaceutics Deficiencies

Not applicable.

7. Microbiology Deficiencies

Not applicable.

8. Other Deficiencies (Specify discipline, such as Environmental)

Not applicable.

*Application Technical Lead Name and Date:*

Mark R. Seggel, Ph.D.  
Acting CMC Lead  
OPQ/ONDP/DNDPII/NDPBV

*{see electronic signature page}*

# QUALITY ASSESSMENT DATA SHEET

## IQA NDA Assessment Guide Reference

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Ethinyl Estradiol	Adequate	27-JUL-2017 (J. Leginus)	
	II		Levonorgestrel	Adequate	27-JUL-2017 (J. Leginus)	

See Review #3, 12/13/2017, for list of Type III and Type IV DMFs.

#### B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
Original IND and associated submissions (01/19/1999 to present)	IND 57731	EE and LNG Controlled Release Film, Agile Therapeutics

### 2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	Final	Study ATI-CL25 supports non-inferiority of in vivo adhesion to reference. Additional non-comparative analysis indicates adequate adhesion.	08/14/19	C. Wang, M. Shen, Y. Tsong
Pharmacology / Toxicology	Final	Revised limits for impurities are acceptable.	11/21/17	M. Summan
CDRH-ODE	na			
CDRH-OC	Final	See IQA #3		
Clinical	na			
Other	na			

## **CHAPTERS: Primary Quality Assessment**

Chapter I: Drug Substance

Chapter II: Drug Product

Chapter III: Environmental Analysis (*See IQA #3*)

Chapter IV: Labeling

Chapter Va: Process

Chapter Vb: Facilities

Chapter VI: Biopharmaceutics

Chapter VII: Microbiology (*See Chemistry Review #1*)

Chapter VIII: Additional Quality Discipline - Quality *In Vivo* Adhesion Assessment

Attachment I: Submission Manufacturing Status Report



Mark  
Seggel

Digitally signed by Mark Seggel

Date: 11/01/2019 02:25:08PM

GUID: 507572b5000036176969356148025bae

**BIOPHARMACEUTICS****Product Background:**

The current submission is for the approval of Twirla (levonorgestrel/ethinyl estradiol 120/30 mcg/day) transdermal contraceptive delivery system, also known as AG200-15. Twirla is indicated for prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

**NDA:** 204017-ORIG-1-RESUB-60

**Drug Product Name / Strength:** Twirla (levonorgestrel/ethinyl estradiol) / 120/30 mcg/day

**Route of Administration:** Transdermal

**Applicant Name:** Agile Therapeutics Inc.

***Review Summary: Adequate***

The in vitro release method and acceptance criteria were previously reviewed and approved. Refer to the January 3, 2013 Biopharmaceutics review by Dr. Tapash Ghosh and November 14, 2017 Biopharmaceutics review by Dr. Peng Duan.

Three commercial scale batches were submitted in 2017: 36099, 36172, and 37620. One commercial scale batch, 38449, was submitted in 2019, manufactured with a slightly modified process and used in the pivotal adhesion study #ATI-CL25. The target zone temperatures and air flow parameters changed since 2017. The Applicant submitted in vitro release data and calculated similarity factor  $f_2$  comparing batches 37620 and 38449. The  $f_2$  value was above 50, indicating similarity. These results adequately bridge the change (b) (4).

**List Submissions being reviewed (table):**

05/14/2019	NDA 204017/Sequence 0058/Response to Complete Response Letter
08/20/2019	NDA 204017/Sequence 0063/Response to Information Request

**Highlight Key Outstanding Issues from Last Cycle:**

Biopharmaceutics was adequate in the last cycle. There were no biopharmaceutics deficiencies in the Complete Response Letter.



## QUALITY ASSESSMENT



### Concise Description Outstanding Issues Remaining:

None

### *Bridging of Formulations*

#### Reviewer's Assessment:

There was a slight modification in process for the commercial scale batch submitted in 2019, batch 38449. (b) (4)

(b) (4)

(b) (4)

(b) (4) See 08/21/2019

Process review by James J. Norman, Ph.D., pp. 7-11. Comparative in vitro release data was requested to support the proposed process change. On August 12, 2019, the following information request was communicated to the Applicant :

1. Submit comparative in vitro release data to support the proposed change (b) (4). Submit complete in vitro release data (individual, mean, SD, profiles) for pre-change and post-change batch(es), and appropriate statistical testing (e.g., the f2 equation) for comparing in vitro drug release profiles. The response should also include batch number(s), manufacturing date(s) and test date(s).

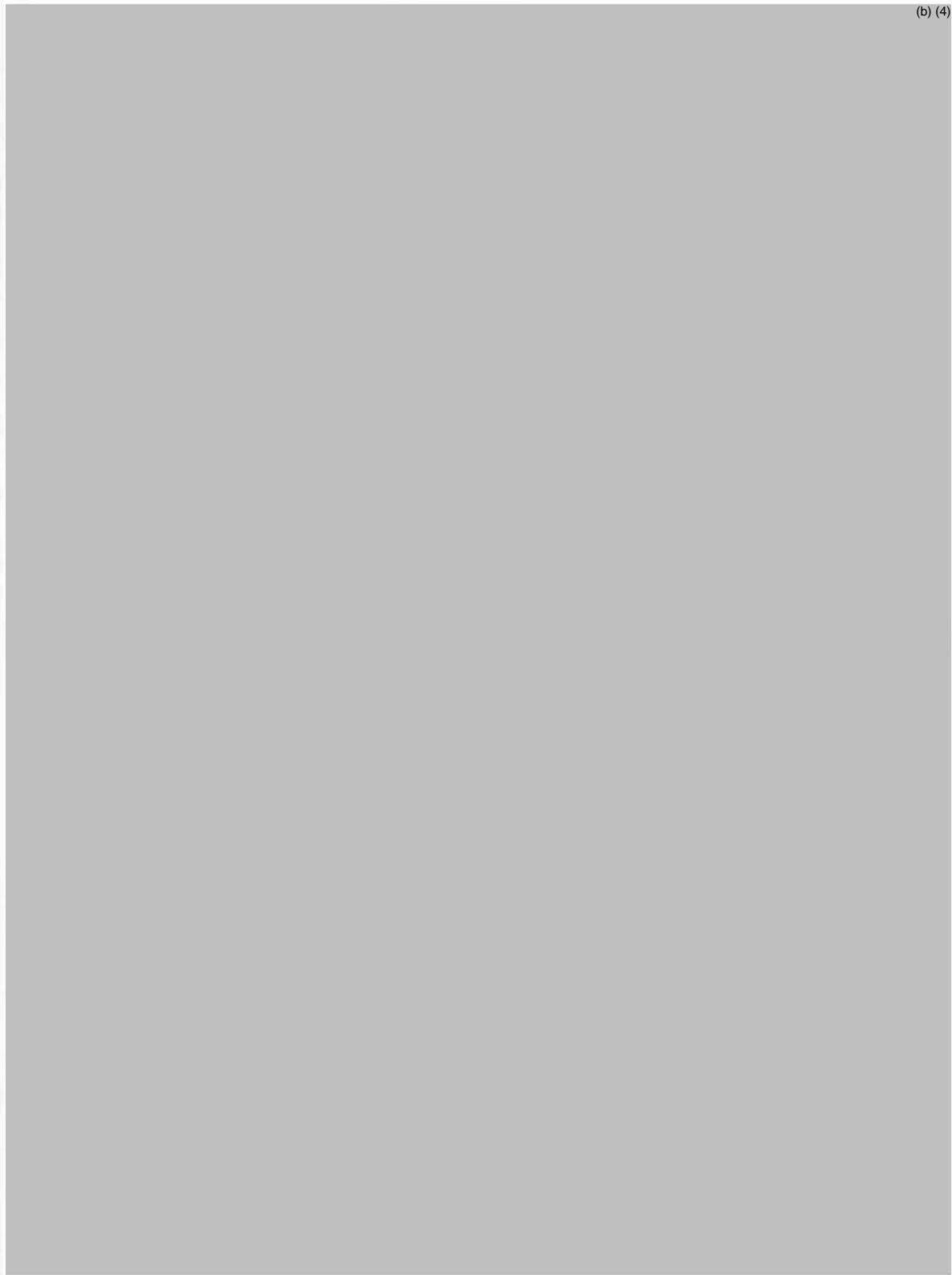
On August 20, 2019 (Sequence 0063), the Applicant responded:

<\\cdsesub1\evsprod\nda204017\0063\m1\us\111-info-amend\vir-response-12-aug-2019.pdf>

In vitro release data were submitted for four batches, including 37620 (pre-change batch) and 38449 (post-change batch). The f2 comparison between these batches was 77 for ethinyl estradiol and 83 for levonorgestrel. The reviewer repeated the f2 calculations and agreed with the results of 77 and 83, respectively. Since this value is above 50, the in vitro release profiles were similar. Profiles are shown in the two figures below:



# QUALITY ASSESSMENT



(b) (4)



## QUALITY ASSESSMENT



Note that the 72 hour time point is no longer required, and the current acceptance criteria include not less than (b)<sub>(4)</sub>% dissolution at the 96 hour time point.

These results adequately bridge the change in process.

***Primary Biopharmaceutics Reviewer Name:***

Bryan Ericksen, Ph.D.

***Secondary Reviewer Name:***

Vidula Kolhatkar, Ph.D.



**Bryan  
Ericksen**

Digitally signed by Bryan Ericksen  
Date: 9/30/2019 05:09:19PM  
GUID: 59285fba002134adea4d6f405770a2b2



**Vidula  
Kolhatkar**

Digitally signed by Vidula Kolhatkar  
Date: 10/08/2019 11:09:02AM  
GUID: 5424aeae00c3274f93e50573f7ca407e

# CHAPTER IV: LABELING

## 1.0 PRESCRIBING INFORMATION

### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TWIRLA® safely and effectively. See full prescribing information for TWIRLA.

TWIRLA (levonorgestrel and /ethinyl estradiol) (b) (4)-transdermal system (b) (4)

Initial U.S. Approval:

**WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS**  
*See full prescribing information for complete boxed warning.*

- TWIRLA is contraindicated in women over 35 years old who smoke. (4)
- Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. (5.1)

**INDICATIONS AND USAGE**

TWIRLA is a (b) (4) combination (b) (4)

**Limitation of Use:** (b) (4)

**DOSAGE AND ADMINISTRATION** (b) (4)

- (b) (4)
- (b) (4)
- (b) (4)
- Do not cut or alter the patch in any way. (2.1)

**DOSAGE FORM AND STRENGTH**

Transdermal system: 120 mcg/day levonorgestrel (LNG) and 30 mcg/day ethinyl estradiol (EE). (3)

<b>CONTRAINDICATIONS</b>		
Item	Information Provided in the NDA	Assessor's Comments
<b>Product Title in Highlights</b>		
Proprietary name	TWIRLA	ADEQUATE
Established name(s)	(levonorgestrel/ethinyl estradiol) (b) (4)	INADEQUATE  (levonorgestrel and ethinyl estradiol) transdermal system

Route(s) of administration	(b) (4)	INADEQUATE  Remove (b) (4) (b) (4)
<b>Dosage Forms and Strengths Heading in Highlights</b>		
Summary of the dosage form(s) and strength(s) in metric system.	Transdermal system: 120 mcg/day levonorgestrel (LNG) and 30 mcg/day ethinyl estradiol (EE).	ADEQUATE
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE AND ADMINISTRATION section</b>		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	"Patch" is used throughout the label and labeling.	<p>Comment to Applicant: Per USP &lt;1151&gt; Dosage Forms, "patch" is not a preferred term. (b) (4)</p> <p>(b) (4)</p> <p>of your product throughout the PI and the Carton Container as appropriate.</p>

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

#### 3 DOSAGE FORMS AND STRENGTHS

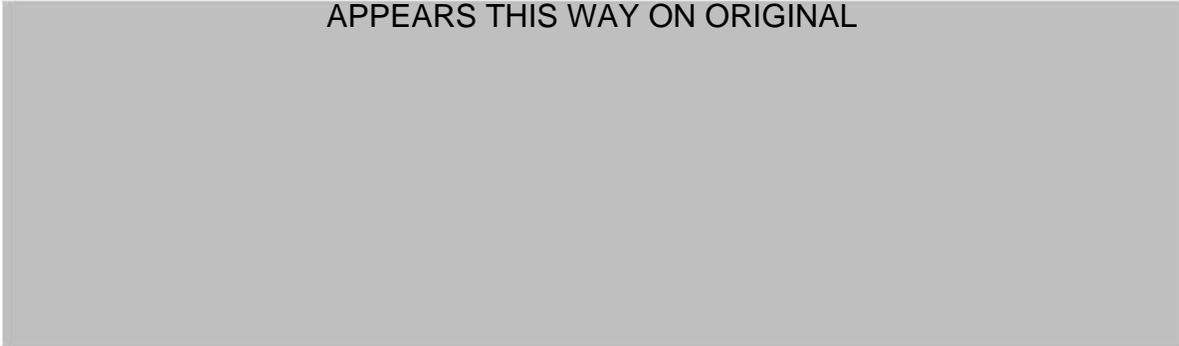
TWIRLA (120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol) transdermal (b) (4)-system is a circular beige colored product with the name and strength etched on the backing membrane. (b) (4)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
<b>DOSAGE FORMS AND STRENGTHS section</b>		
Available dosage form(s)	Transdermal delivery system	INADEQUATE Transdermal system
Strength(s) in metric system	120mcg/day and 30 mcg/day	ADEQUATE
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Not included	INADEQUATE a circular beige colored product with the name and strength etched on the backing membrane.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

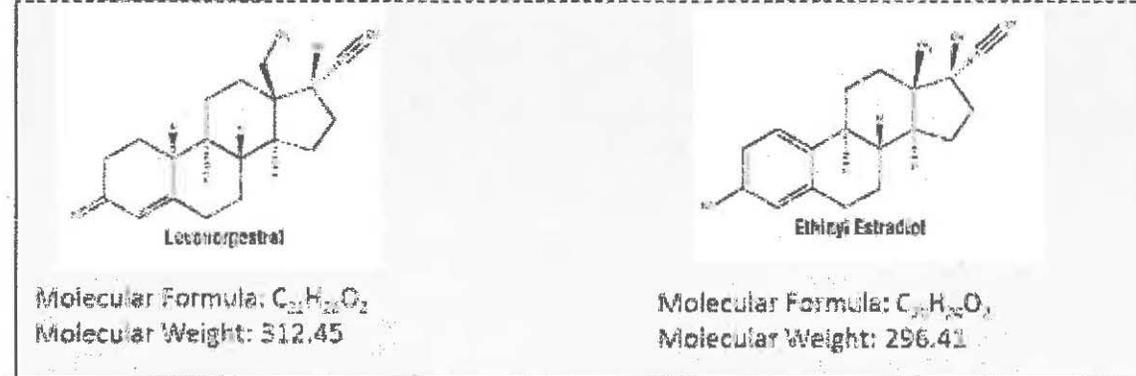
**1.2.3 Section 11 (DESCRIPTION)**

APPEARS THIS WAY ON ORIGINAL



**11 DESCRIPTION**

TWIRLA (levonorgestrel and ethinyl estradiol) (b) (4) transdermal system contains 2.60 mg levonorgestrel (LNG) (17 $\alpha$ )-(-) [13-ethyl-17hydroxy-18, 19-dinorpregn-4-en-20-yn-3-one], a (b) (4) (progesterin (b) (4) and 2.30 mg ethinyl estradiol (EE), [(17 $\alpha$ )-19-norpregna-1, 3, 5(10)-trien-20-yne-3, 17-diol] an estrogen.

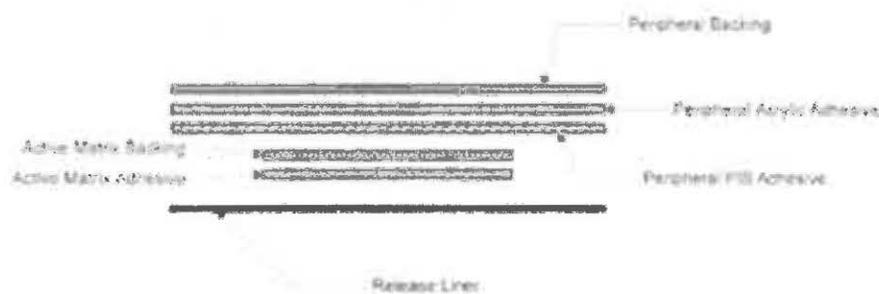


TWIRLA is designed to provide daily exposure of 120 mcg LNG and 30 mcg EE. (b) (4) TWIRLA is a matrix type transdermal system (b) (4) consisting of a 15 cm<sup>2</sup> (b) (4) active adhesive (b) (4) laminate (b) (4) center (b) (4) surrounded by a peripheral inactive adhesive laminate (b) (4)

The (b) (4) entire (b) (4) area of TWIRLA is 28 cm<sup>2</sup>. (b) (4)

TWIRLA (b) (4) consists (b) (4) of 5 layers and a release liner (which is removed and discarded (b) (4) prior to application). Proceeding from the outer surface toward the surface adhering to the skin, the layers are (1) a woven peripheral backing layer, which is etched with "TWIRLA Levonorgestrel 120 mcg/day Ethinyl Estradiol 30 mcg/day"; (2) an inactive peripheral acrylic adhesive layer; (3) an inactive peripheral polyisobutylene adhesive layer; (4) an internal membrane to separate the active adhesive matrix from the inactive adhesive laminate; (5) the active adhesive matrix.

Figure 1: Schematic Depiction of the TWIRLA Transdermal Patch System



(b) (4) TWIRLA is not made with contains no latex.



Item	Information Provided in the NDA	Assessor's Comments
<b>DESCRIPTION section</b>		
Proprietary and established name(s)	(b) (4)	INADEQUATE  TWIRLA (levonorgestrel and ethinyl estradiol) transdermal system
Dosage form(s) and route(s) of administration	(b) (4)	INADEQUATE  transdermal system
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	polyester release liner, woven polyester (b) (4) adhesives, polyester backing, polyisobutylene adhesives, copovidone, polybutene, crospovidone, lauryl lactate, dimethyl sulfoxide, capric acid, and ethyl lactate	INADEQUATE  List in alphabetical order
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Statement of being sterile (if applicable)	N/A	
Pharmacological/therapeutic class	(b) (4)	INADEQUATE LNG, a progestin EE, an estrogen
Chemical name, structural formula, molecular weight	Chemical names and structures provided	INADEQUATE Include molecular formula and molecular weight of each active ingredient
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Size of system and brief description of layers provided	INADEQUATE Request inclusion of a schematic and rewording of drug product description. See edits above.

**Section 11 (DESCRIPTION) Continued**

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	(b) (4)	INADEQUATE (b) (4) Overlay is not a desired term

**1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments
<b>HOW SUPPLIED/STORAGE AND HANDLING section</b>		
Available dosage form(s)	(b) (4)	INADEQUATE Transdermal system
Strength(s) in metric system	is available in one strength of 120 mcg/day LNG and 30 mcg/day EE	ADEQUATE
Available units (e.g., bottles of 100 tablets)	(b) (4)	INADEQUATE Carton of 3 transdermal systems, each transdermal system is packaged in an individual pouch.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	INADEQUATE Remove (b) (4) and replace with system
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

**Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)**

Item	Information Provided in the NDA	Assessor's Comments
------	---------------------------------	---------------------

<p>Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)</p>	<p>(b) (4)</p>	<p>INADEQUATE (b) (4)</p>
<p>If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."</p>	<p>N/A</p>	<p>Modify to "Store in original unopened pouch."</p>
<p>Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.</p>	<p>Store at room temperature 25°C (77°F); excursions permitted to 15-30°C (59-86°F).</p>	<p>INADEQUATE Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted 15°C to 30°C (59 to 86°F) [see USP Controlled Room Temperature].</p>
<p>Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."</p>	<p>TWIRLA (b) (4) is included in section 11</p>	<p>INADEQUATE TWIRLA is not made with latex</p>
<p>Include information about child-resistant packaging</p>	<p>(b) (4)</p>	<p>INADEQUATE (edit for clarity) Used transdermal systems still contain some active hormones. To discard, fold the sticky sides of the transdermal system together, place in a sturdy container, preferably with a child-resistant cap, and place this container in the trash. Used transdermal systems</p>

	not be flushed down the toilet. See <a href="http://www.fda.gov/drugdisposal">www.fda.gov/drugdisposal</a> for more information about disposal of medicines.	should not be flushed down the toilet. See <a href="http://www.fda.gov/drugdisposal">www.fda.gov/drugdisposal</a> for more information about disposal of medicines.
--	--	---

### 1.2.5 Other Sections of Labeling

*In Section 14 the following edits regarding in vivo adhesion should be communicated to the applicant:*



### 1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
<b>Manufacturing Information After Section 17</b>		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	<p>Located after IFU</p> <p>Manufactured by: Corium International, Inc. 4558 50<sup>th</sup> Street, SE Grand Rapids, MI 49512</p> <p>Manufactured for: Agile Therapeutics, Inc. 101 Poor Farm Rd. Princeton, NJ 08540</p>	<p>INADEQUATE</p> <p>Move location of information to after Section 17 and before IFU.</p>

## 2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling: INADEQUATE

All portions of the PI should be revised as indicated in the screen shots above. A summary of deficiencies are listed below in *"ITEMS FOR ADDITIONAL ASSESSMENT."*

## 3.0 CARTON AND CONTAINER LABELING

### 3.1 Container Label

(b) (4)

### 3.2 Carton Labeling

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Twirla  (b) (4)	INADEQUATE  Revise to:  Twirla  (levonorgestrel and ethinyl estradiol) transdermal system  120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol
Dosage strength	120/30 mcg/day	120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol  Also revise contains so that LNG amount appears first and EE appears second
Route of administration	Transdermal Use Only	ADEQUATE
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Pouch: (b) (4)  Carton: (b) (4) 3 transdermal systems	INADEQUATE  Pouch: Revise to "1 transdermal system"  Carton: remove "1 Month Therapy"
"Rx only" displayed on the principal display	Present	ADEQUATE
NDC number	Present	ADEQUATE
Lot number and expiration date	Present	ADEQUATE

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 25°C (77°F); excursions permitted to 15-30°C (59-86°F).	INADEQUATE Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted 15°C to 30°C (59 to 86°F)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Present	ADEQUATE

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Mfd. For: Agile Therapeutics, INC. Princeton, NJ 08540 Mfd. By: Corium International Grand Rapids, MI 49512	ADEQUATE
Medication Guide (if applicable)	N/A	Revise (b) (4) to "Recommended Dosage: See prescribing information".
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	polyester release liner, woven polyester (b) (4) adhesives, polyester backing, polyisobutylene adhesives, copovidone, polybutene, crosopovidone, lauryl lactate, dimethyl sulfoxide, capric acid, and ethyl lactate	INADEQUATE List in alphabetical order

**Assessment of Carton and Container Labeling: *INADEQUATE***

The above review comments apply to all configurations (pouch, carton, overpack) and trade, physician's sample, and replacement pouch. Consistent with USP <1151> all uses of the word "(b) (4)" should be removed or changed to "transdermal system."

## ITEMS FOR ADDITIONAL ASSESSMENT

### General

- Per USP <1151> Dosage Forms, “(b) (4)” is not a preferred term. Replace all uses of the word “(b) (4)” with, “system”, “transdermal system” or the name of your product throughout the PI and all configurations of the Carton and Container as appropriate.
- The established name should not include a slash (/) revise all uses of the established name throughout the PI, and all configuration of the carton and container to:  
(levonorgestrel and ethinyl estradiol) transdermal system

*In addition to the General deficiencies above which apply to all components of the Label and Labeling, the below deficiencies specific to each section should be communicated to the applicant.*

### PI – Section 3

- Include a description of the identifying characteristics of the dosage forms

### PI – Section 11

- List inactive ingredients in alphabetical order
- Correct the therapeutic class of levonorgestrel to progestin and add therapeutic class for ethinyl estradiol, estrogen
- Add molecular weight and molecular formula for each of the active ingredients
- Revise the description of the drug product and include a schematic for clarity
- Remove “(b) (4)” and “(b) (4)” as they are promotional
- Remove the use of the descriptive word “(b) (4)” to describe the backing membrane

### PI – Section 16

- Revise description of available units to “Carton of 3 transdermal systems, each transdermal system is packaged in an individual pouch.”
- Remove duplicative storage conditions (Do not store in the refrigerator or freezer) and application instructions covered in other sections of the label (b) (4)
- Modify negative storage conditions to affirmative storage conditions “Store in original unopened pouch.”

- **Modify storage conditions to “Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted 15°C to 30°C (59 to 86°F) [see USP Controlled Room Temperature].”**
- **Modify disposal information for clarity “Used transdermal systems still contain some active hormones. To discard, fold the sticky sides of the transdermal system together, place in a sturdy container, preferably with a child-resistant cap, and place this container in the trash. Used transdermal systems should not be flushed down the toilet. See [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for more information about disposal of medicines.”**

#### **PI-Section 14**

- **Modify in vivo adhesion information for accuracy and clarity**

#### **Container (Pouch) and Carton**

**Comments below apply to all configurations (pouch, carton, overpack) and trade, physician’s sample, and replacement counts unless otherwise noted:**

- **Revise Proprietary, Established Name, and Strength to appear as below and assure size of font is compliant with CFR requirements:**  
     **Twirla**  
     **(levonorgestrel and ethinyl estradiol) transdermal system**  
     **120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol**
- **Revise total drug content statement to reflect order of established name (Levonorgestrel first, ethinyl estradiol second).**
- **Revise Net Contents for Pouch to “1 transdermal system” and remove “(b) (4).”**
- **Remove “(b) (4)” from Net Contents of Carton.**
- **Revise storage conditions to read “Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted 15°C to 30°C (59 to 86°F).”**
- **Revise the statement “(b) (4)” to “Recommended Dosage: See prescribing information”.**
- **List inactive ingredients in alphabetical order.**

**Overall Assessment and Recommendation:**

The Label and Labeling of NDA 204017 are inadequate due to the deficiencies noted above for all sections of the PI and the Carton and Container labels.

**This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted above are satisfactorily resolved.**

*Primary Labeling Assessor Name and Date:*

*Caroline Strasinger, Ph.D. 04-OCT-2019  
OPQ, ONDP, DNDP II, BV*

*Secondary Reviewer Name and Date (and Secondary Summary, as needed):*

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is *not* deemed ready for approval as of this review.

*Moo-Jhong Rhee, Ph.D. 04-OCT-2019  
Chief, Branch V  
DNDP II/ONDP*



**Caroline  
Strasinger**

Digitally signed by Caroline Strasinger  
Date: 10/04/2019 03:15:03PM  
GUID: 5051dfdd000013b995075b4d54108ed8



**Moo Jhong  
Rhee**

Digitally signed by Moo Jhong Rhee  
Date: 10/04/2019 03:21:26PM  
GUID: 502d0913000029f9798ca689a802fa55

## CHAPTER VIII: ADDITIONAL QUALITY DISCIPLINE

### Quality in Vivo Adhesion Assessment

<b>Product Information</b>	
<b>NDA Number</b>	204017
<b>Assessment Cycle Number</b>	3
<b>Drug Product (DP) Name / Strength</b>	Twirla Levonorgestrel (LNG) and Ethinyl Estradiol (EE), Transdermal System, 120/30 mcg/day
<b>Route of Administration</b>	Transdermal
<b>Drug Product Manufacturer</b>	Agile
<b>Proposed Indication</b>	Contraception

**Assessment Recommendation: Adequate**

**Assessment Summary:**

Document(s) Assessed	Date Received
Resubmission (0058)	16-MAY-2019
IR Response (0060)	17-JUL-2019

In November of 2017 OPQ recommended Complete Response (CR) to the Office of New Drugs with respect to adhesion performance. The recommendation was based on the review of the adhesion data from the clinical efficacy study ATI-CL23, which included daily assessment of adhesion by the subject throughout the year long efficacy trial. The Applicant Filed a Formal Dispute Resolution Request (FDRR) on June 6, 2018 contesting the CR recommendation. The Appeal was denied by ODE III on July 19, 2018, and then again by OND on October 4, 2018. However, in the OND Appeal Denied Letter the following path forward related specifically to adhesion of this product was provided to the Applicant:

*...if AG200-15 can demonstrate generally similar adhesion performance to Xulane, this would support the conclusion of adequate adhesion of AG200-15 and suggest that the results of the ATI-CL23 are those that might be seen with an adequately performing patch in the context of a clinical trial.*

Previous in vivo adhesion deficiencies noted in the Complete Response letter issued on 21-DEC-2017 have been satisfactorily resolved in part due to the path identified in the OND Appeal Denied Letter and as summarized below in **Key Issues from Last Cycle and Their Resolution**.

**Key Issues from Last Cycle and Their Resolution:**

- **The product did not demonstrate adequate in-vivo adhesion performance in ATI-CL23 (11.3% of TDS resulted in less than 75% adherence, and 14.7% of all cycles used 4 or more TDS during the cycle).**
  - The Applicant conducted ATI-CL25 (Non-inferiority to Xulane) and ATI-CL26 (single arm pilot study) to support the adhesion of the product.
  - The Office of Biostatistics Review (7-AUG-2019) concludes AG200-15 (Twirla) is non-inferior to Xulane and that the probability that a randomly selected AG200-15 maintains at least 75% adhesion throughout its entire wear period (0.99 with its 95% lower confidence limit of 0.95).

**Concise Description of Outstanding Issues:**

None

CQAs For Review Cycle #3	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 3	Comments
<i>in-vivo</i> adhesion	H	Adhesion is critical for efficacy and safety. The product did not demonstrate adequate in-vivo adhesion in ATI-CL23 (11.3% of TDS resulted in less than 75% adherence, and 14.7% of all cycles used 4 or more TDS during the cycle).	H	Adhesion is critical for efficacy and safety. No drug product changes (e.g. reformulation) were made that would impact adhesion performance since the previous failed study. The clinical trial design appears to be the main contributor to the different adhesion outcome. The product exhibited at least 70% surface area adherence for the duration of wear in ATI-CL25 and is non-inferior to Xulane.

## **Conclusion and Recommendation:**

**From a quality perspective, the formulation and product design of the drug product used in clinical study ATI-CL25 have demonstrated adequate *in-vivo* adherence for the prescribed 7-day wear period. From the OPQ perspective, recommendation of APPROVAL is made to the Office of New Drugs for adherence of AG200-15 (i.e. Twirla).**

**Background:** The purpose of this review is to assess the *in-vivo* adherence performance of Twirla (levonorgestrel and ethinyl estradiol) transdermal system (also described as AG200-15) based on new information and studies performed after the previous CR. In November of 2017 OPQ recommended Complete Response to the Office of New Drugs with respect to adherence. The recommendation was based on the review of the adherence data from the clinical efficacy study ATI-CL23, which included daily assessment of adherence by the subject throughout the year long trial, with no restrictions on movement or wear. A study design such as this provided a realistic wear perspective and the resultant data showed **10-20% of all users required four or more TDS per cycle to maintain therapy per labeled instructions. The proposed labeling stated “if the (b) (4) does not stick completely, (b) (4).”**

**Therefore, the reviewer felt this point was the most indicative data of the true adherence failure of the product as this unequivocally accounted for any and all re-adhering capability of the product per the labeled use. This product was proposed to be packaged in cartons of three, and therefore, it could be expected that 10-20% of all users would be forced to seek replacement product in order to maintain prescribed wear and subsequently contraception. Additional analyses were also conducted including the statistical analysis applied to more formal in-patient adherence study designs, which also concluded adherence was not adequate. Refer to the Office of Biostatistics Review dated 29-NOV-2017 by Chao Wang and the Drug Product Review for In Vivo Adherence dated 16-NOV-2017 by Caroline Strasinger for more detail.**

As alluded to, the *in-vivo* adherence of a transdermal system can also be evaluated in a more formal in-patient setting. This controlled environment, while not representative of the normal wear environment and routine daily activities of a patient, has been utilized previously for many NDA products, particularly in situations in which an at home efficacy study is not conducted or most commonly in the setting of ANDA applications. Although the OND Level Appeal (Dispute Resolution) ultimately agreed

*...with the Division that the adherence results in the ATI-CL23 study raise concerns. In particular, the relatively high proportion of patches, especially early in the trial, that detached (not meeting the Division's expectation, as set in the Type C meeting responses<sup>16</sup>, that detachment should be infrequent), the frequency with which more than 3 patches per cycle were needed, and the failure of AG200-15 to demonstrate that at least 90% of the patches had at least 75% of the surface area adhered for the duration of wear (overall 11.3% of patches had <75% adherence) and that more than 90% of patches had adequate (at least 75%) adherence for the 7-day wear period are all*

*troubling findings, and raise the potential for poorer contraceptive effectiveness due to adhesion issues.<sup>1</sup>*

A path forward was provided to the applicant to conduct a more formal in clinic wear study. Specifically,

*...if AG200-15 can demonstrate generally similar adhesion performance to Xulane, this would support the conclusion of adequate adhesion of AG200-15 and suggest that the results of the ATI-CL23 are those that might be seen with an adequately performing patch in the context of a clinical trial.*

As such the applicant has conducted ATI-CL25, a comparative non-inferiority (NI) study of AG200-15 to Xulane (Ethinyl Estradiol and Norelgestromin) and ATI-CL26, a single arm AG200-15 pilot study to inform population size for the NI study. The Applicant refers to the drug product as "patch" and AG200-15 for ATI-CL25 and ATI-CL26. Patch is synonymous with the terms transdermal system (TDS), system, and drug product; all listed terms (patch, TDS, system, drug product) and AG200-15 refer to the active drug product, Twirla (levonorgestrel and ethinyl estradiol) transdermal system unless otherwise noted as Xulane.

#### **Adhesion Study Design**

ATI-CL26 was a single-dose, open-label, 7-day adhesion study of AG200-15. All TDS were applied by site personnel to the subjects' lower abdomen. Subjects remained at the study site for the duration of the study and the systems were removed by study site personnel after 168 hours (7 days) of wear. Adhesion was evaluated by trained site personnel on the standard 5-point scale every 24 hours and assessors were blinded to the previous days score. Subjects were allowed to conduct activities associated with daily living including once daily showering (<10 minutes) though strenuous exercise and sexual activity were not permitted during wear. Subjects were instructed not to attempt to re-adhere partially detached products, and no overlays, tapes, or coverings were permitted during the study. Prior to application the site was wiped three times with a warm water washcloth, and lightly patted dry with a soft towel and the TDS applied above or below the undergarment line and held in place with the hand for 10 seconds. The study was designed to be a descriptive adhesion trial with approximately 30 subjects.

ATI-CL25 was a randomized, open label, single dose, two treatment comparative crossover adhesion study of AG200-15 and Xulane (Ethinyl Estradiol and Norelgestromin) Transdermal System. Similar to ATI-CL26 subjects remained in clinic, were permitted to shower, instructed not to attempt to re-adhere partially detached products, and the application site was the lower abdomen. Site personnel applied the product and evaluated each system. For ATI-CL25, a photograph of the applied system was taken at every time point. The study was designed to be a comparative Non-Inferiority adhesion trial with approximately 80 subjects. On page 18-19 (of 41) of the Clinical Study Report, the Applicant states:

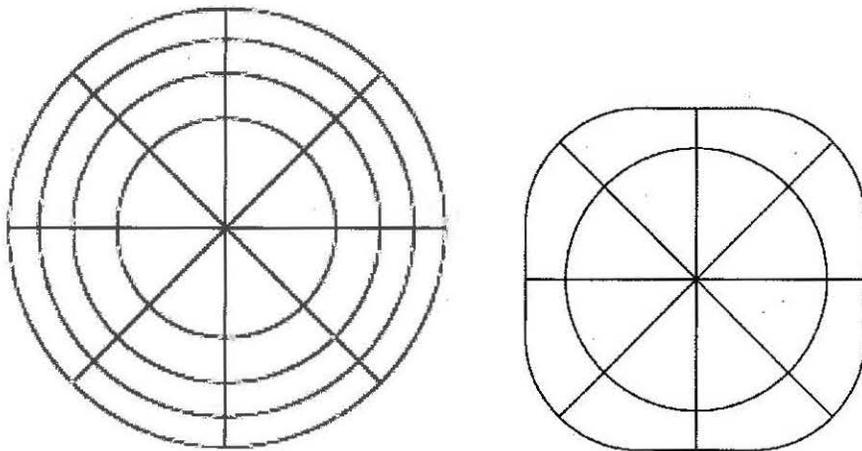
---

<sup>1</sup> OND Appeal Denied letter dated 4-OCT-2018

*...all patches were applied in this tightly controlled setting with careful attention to the initial application. This is important in a NI trial that is ascertaining patch performance as the key outcome of interest. A trial with variability in patch application that shows NI would otherwise be challenging to meaningfully interpret. Therefore, efforts were made to tightly manage consistency of patch application and patch care during the study.*

#### **Adhesion Assessments (by Site Personnel)**

Adhesion was evaluated for both studies by trained study personnel. The adhesion evaluation was divided into three personnel descriptions; tracers, graders, and calculators. Tracers were provided with a transparency that contained a diagram with 32 pre-printed equally sized sectors for the AG200-15 and 16 pre-printed equally sized sectors for the Xulane product (Figure 1).



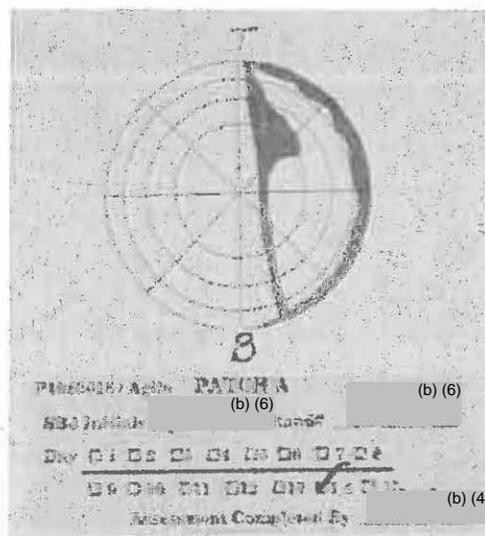
**Figure 1: Transparency for AG200-15 (surface area 28 cm<sup>2</sup>) and Xulane (surface area 14 cm<sup>2</sup>) respectively.**

Tracers were blinded to any previous tracings so as not to bias the process. According to Study Procedure P1980518, tracers held the transparent diagram over the applied product insuring that no pressure was created by the hand holding or by the hand performing tracings. Lifted areas were marked in red using permanent marker on the transparent diagrams. If wrinkles were observed, an assessment was done to determine presence or absence of contact with the skin (if contact with the skin was observed then areas were not marked, if contact with the skin was lost, areas were marked on the transparency). Each transparency was then photocopied (and scanned) and provided to the qualified grader.

A grader performed the visual assessment of lifted areas for each sector and recorded the percentage of lifting onto the provided source worksheet. For example, if Sector #1 is 50% lifted, 50% was recorded in the source worksheet. If sector #2 was fully adhered, 0% was recorded in the source worksheet and if Sector #3 was completely detached, 100% was recorded in the sector. Percentage of lift was assessed in 10% increments. According to procedure, the grader was blinded to previous scores and a grader could not serve as a calculator.

A calculator entered the percentage of lifting for each sector into the MS Excel worksheet. The MS Excel worksheet was designed to perform the calculation of the percent of adhered areas and corresponding adherence score. After all "% lift" assessments had been entered, the person performing the entry recorded the % adherence and the 5-Point Adhesion Score onto the source worksheet. In an IR response dated 17-JUL-2019, the Applicant provided the MS Excel calculation file for each of the products which verified the calculation properly accounts for the different number of segments and surface area of the product.

An example of the transparency and a photograph can be seen below (this timepoint translated to 84.06 % adherence). Each subject's image at each time point is included in Section 5.3.5.1 under study ATI-CL25.



### Reviewer's Assessment:

The applicant's clinical study design was appropriate for a formal or in-patient week-long study to assess adherence. To minimize subjectivity in estimating percent adherence the applicant elected to use a transparency to trace over the unadhered parts. The applicant states the transparency was used in a manner to minimize any pressure being placed on the system during assessment. In addition, photographs of the product at each timepoint and of the transparency have been provided.

The Xulane product is smaller than the Twirla product and as such the Applicant elected to use a 16 segment transparency for Xulane and a 32 segment transparency for Twirla.

Only the abdomen was assessed in the study, which was the agreed to site of application during the Dispute Resolution. Notable, in the previous review, the abdomen was the site of the best adherence.

In conclusion, the study design and calculation of percent adherence is adequate. An inspection of the clinical site was conducted to verify the integrity of the trial; no 483 was issued.

## Applicant's Summary of Adhesion Data

The applicant provided summary statistics for ATI-CL26 (N=30). Although the Applicant focused on Mean Score, the distributions were provided as seen in Table 14.2.3 below. (Reviewer Note: Mean score is only used in non-inferiority analysis). There were 24 screening failures for ATI-CL26 with the primary reason being indicated as Failed Inclusion/Exclusion Criteria (The Clinical Inspection Report August 8, 2019 found no issue with the conduct of the clinical trials; no 483 was issued). No photographs were taken during this study. Although the transparencies were used, only 5-point scale scores were reported (not actual % adherence). Only two scores of 2 (i.e. total surface area adherence was between 50% and 74%) were reported and both returned to a score of 1 at the next assessment time point.

Table 14.2.3  
Frequency Distribution of Adhesion Scores by Evaluation TimePoint  
ITT Population

Time Point	N	AG200-15 adhesion scores (Observed)					AG200-15 adhesion scores (Worst Score Carried Forward)				
		0 n(%)	1 n(%)	2 n(%)	3 n(%)	4 n(%)	0 n(%)	1 n(%)	2 n(%)	3 n(%)	4 n(%)
24 hours	30	30(100.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	30(100.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
48 hours	30	29(96.7%)	1(3.3%)	0(0.0%)	0(0.0%)	0(0.0%)	29(96.7%)	1(3.3%)	0(0.0%)	0(0.0%)	0(0.0%)
72 hours	30	28(93.3%)	1(3.3%)	0(0.0%)	0(0.0%)	1(3.3%)	29(96.7%)	1(3.3%)	0(0.0%)	0(0.0%)	0(0.0%)
96 hours	30	28(93.3%)	1(3.3%)	0(0.0%)	0(0.0%)	1(3.3%)	29(96.7%)	1(3.3%)	0(0.0%)	0(0.0%)	0(0.0%)
120 hours	30	29(96.7%)	0(0.0%)	1(3.3%)	0(0.0%)	0(0.0%)	29(96.7%)	0(0.0%)	1(3.3%)	0(0.0%)	0(0.0%)
144 hours	30	27(90.0%)	2(6.7%)	1(3.3%)	0(0.0%)	0(0.0%)	27(90.0%)	1(3.3%)	2(6.7%)	0(0.0%)	0(0.0%)
168 hours	30	26(86.7%)	4(13.3%)	0(0.0%)	0(0.0%)	0(0.0%)	25(83.3%)	3(10.0%)	2(6.7%)	0(0.0%)	0(0.0%)
Overall	210	199(94.8%)	9(4.3%)	2(1.0%)	0(0.0%)	0(0.0%)	198(94.3%)	7(3.3%)	5(2.4%)	0(0.0%)	0(0.0%)

Note: Worst adhesion score carried forward = a highest adhesion score assessed at any time point after the baseline is used for subsequent time points until a higher score is assessed.

For ATI-CL25 the applicant prespecified that AG200-15 was to be considered noninferior to Xulane if the upper bound of the one-sided confidence interval on the mean difference in adhesion of less than 0.15 was achieved. This was done in accordance with the Draft Guidance for Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs. The mean difference in adhesion scores between AG200-15 and Xulane was -0.24, demonstrating noninferiority (p value <0.0001). A score of 2 or greater was observed in one AG200-15 subject and in 11 Xulane subjects. Worst score carried forward is utilized in the mean difference analysis and is also reflected below in the Table 5 Frequency Time Point

Table 4. Primary Study Endpoint: Test of Non-Inferiority

	AG200-15 (N=78)	Xulane (N=77)	Mean Difference (N=77)
Mean (SD)	0.14 (0.28)	0.39 (0.40)	-0.24 (0.46)
95% 1-sided CI	--	--	-0.16
Test of non-inferiority, P value	--	--	< 0.0001

Reference: Table 14.2.5.2

**Table 5. Summary of Adhesion Scores – Frequency by Time Point**

Score	AG200-15 (N=78); n (%)								Xulane (N=77); n (%)							
	0h	24h	48h	72h	96h	120h	144h	168h	0h	24h	48h	72h	96h	120h	144h	168h
0	78 (100)	77 (98.7)	75 (96.2)	72 (92.3)	68 (87.2)	63 (80.8)	60 (76.9)	58 (74.4)	77 (100)	72 (93.5)	69 (89.6)	64 (83.1)	51 (66.2)	38 (49.4)	34 (44.2)	29 (37.7)
1	0	1 (1.3)	3 (3.8)	6 (7.7)	9 (11.5)	14 (17.9)	17 (21.8)	19 (24.4)	0	5 (6.5)	7 (9.1)	12 (15.6)	24 (31.2)	35 (45.5)	35 (45.5)	37 (48.1)
2	0	0	0	0	1 (1.3)	1 (1.3)	1 (1.3)	1 (1.3)	0	0	1 (1.3)	1 (1.3)	2 (2.6)	4 (5.2)	8 (10.4)	11 (14.3)
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	0	0.013	0.038	0.077	0.141	0.205	0.244	0.269	0	0.065	0.117	0.182	0.364	0.558	0.662	0.766

Reference: Listing 16.2.5.1

Note: 5-Point Adhesion Scale: 0 = ≥ 90% adhered (essentially no lift off the skin); 1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin); 2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin); 3 = > 0% to < 50% adhered (not detached, but more than half of the patch lifting off the skin without falling off); 4 = 0% adhered (patch detached; completely off the skin)

According to the applicant, both Xulane and AG200-15 exhibited greater than 95% of systems with at least 75% adherence (scores of 0 and 1). This statement is based on individual timepoints (i.e. 7 days per product applied) not total systems applied (or number of subjects). When viewing the results on a per system or subject basis, 98.8% of all AG200-15 maintained 75% or greater adhesion throughout the duration of wear and 85.8% of Xulane TDS maintained 75% or greater adhesion throughout the duration of wear (At the final time point 93.5% of subjects wearing Xulane exhibited 75% or greater adhesion).

### Summary of the Office of Biostatistics Assessment

A statistical consult was requested by the Office of Pharmaceutical Quality to assess the *in vivo* adhesion data of ATI-CL25 and ATI-CL26. Refer to the Biostatistics Consult Review by Chao Wang dated 14-AUG-19 for full details.

In summary, per the OND Appeal Denied letter dated 4-OCT-2018, the adhesion of AG200-15 could be demonstrated if it was shown to be non-inferior to Xulane. The Office of Biostatistics confirmed that assuming normal distribution the 95% upper confidence limit for the mean paired adhesion score difference is -0.16, which is less than the NI margin of 0.15 (hypothesis tests and margin defined by the Adhesion Guidance for ANDAs), and therefore AG200-15 is Non-inferior to Xulane.

Because AG200-15 is proposed for an NDA and not an ANDA, it was still important to assess the data from the adhesion study in a manner consistent with new drugs (i.e. not in a non-inferiority study to a non-bioequivalent product). In general, this is to assess the probability of a TDS maintaining at least 70-75% adhesion during the entire wear period.

Product	Sample size	Number of successes	Estimated probability	Jeffery 95% LCL	SOC 95% LCL
AG200-15	78	77	0.99	0.95	0.95
Xulane	77	66	0.86	0.78	0.78

Table 5: Summary of the probability that a randomly selected TDS maintains at least 75% adhesion for its entire wear period.

Product	Sample size	Number of successes	Estimated probability	Jeffery 95% LCL	SOC 95% LCL
AG200-15	78	77	0.99	0.95	0.95
Xulane	77	71	0.92	0.86	0.86

Table 6: Summary of the probability that a randomly selected TDS maintains at least 70% adhesion for its entire wear period.

The analysis indicates that the probability of a randomly selected AG200-15 maintains at least 75% adhesion throughout its entire wear period in a controlled setting is estimated to be 0.99 and the 95% lower confidence limit (LCL) is 0.95. The same analysis was applied to the smaller single arm study (ATI-CL26) and the probability is estimated to be 0.98 with an LCL of 0.83. The smaller 95% LCL is likely due to the smaller sample size.

Sample size	Number of successes	Estimated probability	Jeffery 95% LCL	SOC 95% LCL
30	28	0.93	0.83	0.83

Table 7: Summary of the probability that a randomly selected TDS maintains at least 75% adhesion for its entire wear period for Study ATI-CL26.

### Reviewer's Assessment:

The Office of Biostatistics Assessment confirms AG200-15 has demonstrated non-inferiority to Xulane. **Notable, demonstration of non-inferiority, particularly to a non-bioequivalent product, is not standard practice for demonstration of adhesion for an NDA.**

The adhesion of AG200-15 was also assessed per our current practices when studying the adhesion of transdermal systems in a controlled study (and not in a non-inferiority comparison to another product). The data from the controlled in-patient (formal study ATI-CL25), indicates the AG200-15 exhibits adequate adhesion. Specifically, AG200-15 passes the statistical hypothesis test at the 95% lower confidence limit. This hypothesis test loosely translates that we are 95% confident that at least 95% of all AG200-15 systems manufactured will exhibit a surface area adherence of at least 70% (or 75%) for the duration of wear (i.e. 7-days). Using the one arm study, ATI-CL26, we are 95% confident that at least 83% of all AG200-15 systems manufactured will exhibit a surface area adherence of 75% for the duration of wear. Though the product studied in ATI-CL25 and ATI-CL26 was the same, the decrease (95% of systems to 83% of systems) is likely due to the smaller sample size of ATI-CL26.

Although the product has not been reformulated, and the previous adhesion study (ATI-CL23) resulted in the below major conclusions, it is likely the starkly different outcomes are due to the trial design differences (a controlled in-patient versus an outpatient real world setting).

- 11.3% of all systems will result in less than 75% of the product surface area adhering during the seven day wear period and at least 5% will completely fall off.
- The abdomen has better adhesion as compared to the torso and buttock. Still, 11.6% of the most experienced patients (Cycle 13 patients) experienced a poorly adhering product (<75% of the surface area adhered) to the abdomen during the last month (Cycle 13) of use. The same population's adhesion experience at other application sites was 17.7% (torso) and 15.0% (buttock).
- 10-20% of all users will require four or more TDS per cycle to maintain therapy per labeled instructions. 14.7% of all cycles studied (N=18,841) required the use of four or more TDS.

This last point is the single most indicative point of inadequate adhesion for this product as this unequivocally accounts for any and all re-adhering capability of the product per the labeled use. This product is proposed to be packaged in cartons of three, therefore, it can be expected that 10-20% of all users will be forced to seek replacement product in order to maintain prescribed wear and subsequently contraception.

### **Additional Analysis**

Though not used in formal analysis, subjects in ATI-CL25 were also given a questionnaire regarding their wear preferences and experience. The results are provided in Appendix 16.1.11 however, of note, Question 3 was "Based on your experience wearing the patch, would you consider using it for your birth control?"

	<b>Yes</b>	<b>Maybe</b>	<b>No</b>
AG200-15 (n = 79)	35	21	23
Xulane (n = 79)	50	13	16
	<b>Yes to Both</b>	<b>Maybe to Both</b>	<b>No to Both</b>
(n = 79)	32	7	12
Percentage	42%	9%	15%

Notably, more women said yes to Xulane than AG200-15 and further, of the 35 that said yes to AG200-15, 32 also said yes to Xulane. The reason most identified for not choosing AG200-15 for use as birth control was related to size of the system, and the reason most identified as a reason to choose AG200-15 was that it stuck well to skin, though the percentage of subjects who stated Xulane stuck well was similar.

4/5. Why did you answer YES/NO to question 3? (circle all the reasons below)

- 1) The size of the patch
- 2) The shape of the patch
- 3) The thickness of the patch
- 4) The color of the patch
- 5) The material the patch is made of
- 6) The patch did/did not stick well to my skin
- 7) The patch was easy/hard to remove after 7 days
- 8) Y/N Sticky material left on my skin after I remove the patch

If "YES"		(1) Size	(2) Shape	(3) Thickness	(4) Color	(5) Material	(6) Sticks	(7) Remove	(8) Residue
n = 85	Overall	52 61%	24 28%	23 27%	16 19%	25 29%	56 66%	33 39%	20 24%
n = 34	AG200-15	14 41%	7 21%	10 29%	6 18%	10 29%	23 68%	14 41%	6 18%
n = 49	Xulane	38 78%	17 35%	13 27%	10 20%	15 31%	33 67%	19 39%	14 29%

If "NO"		(1) Size	(2) Shape	(3) Thickness	(4) Color	(5) Material	(6) Sticks	(7) Remove	(8) Residue
n = 39	Overall	19 49%	5 13%	4 10%	1 3%	6 15%	13 33%	0 0%	9 23%
n = 23	AG200-15	14 61%	3 13%	2 9%	0 0%	3 13%	6 26%	0 0%	6 26%
n = 16	Xulane	5 31%	2 13%	2 13%	1 6%	3 19%	7 44%	0 0%	3 19%

### Reviewer's Assessment:

It is interesting to note that despite the Applicant implying AG200-15 has better adhesion than Xulane, more women still would choose to use Xulane as a form of birth control than AG200-15 (50 versus 35 subjects), and further that the vast majority of the women who stated they would use AG200-15 said they would also use Xulane (32 of 35). It can thus be hypothesized that the population most likely to use AG200-15 upon approval would be those already inclined to use a TDS for contraception (i.e. current Xulane users who still may prefer to use Xulane over AG200-15 given the size variation) and thus would likely not provide a significantly new or better option for contraception (from the patient usability perspective).

### Quality Control of the Product

The quality control methods of the drug product release and stability specification (adhesion, tack, peel from release liner, shear and cold flow) are used to ensure the adhesive character of the TDS is consistent batch to batch and throughout its shelf life. Although the majority of these tests do not correlate to *in-vivo* adhesion performance, when tests and acceptance criteria are appropriately established, they do provide a level of quality assurance of current and future

batches. Per the OPQ Drug Product Review in this cycle, the applicant has now established an adequate specification. Ultimately the goal of quality adhesion testing is to assure that future batches are comparable to those batches which were tested and exhibited adequate *in-vivo* adhesion. Refer to the OPQ Drug Product Review for more information.

**Overall Recommendation:**

Despite the starkly different study outcomes between ATI-CL23 and ATI-CL25, the OND Appeal Denied letter stated that if the AG200-15 could demonstrate “generally similar adhesion performance to Xulane, this would support the conclusion of adequate adhesion of AG200-15.”

Therefore, because AG200-15 demonstrated non-inferiority to Xulane and because AG200-15 (under the study conditions of ATI-CL25) demonstrated that a randomly selected TDS could maintain 70% surface area adhesion at the 95% Lower Confidence Limit, OPQ recommends APPROVAL to the Office of New Drugs for adhesion of AG200-15 (i.e. Twirla).

Caroline Strasinger, Ph.D.  
OPQ/ONDP/ DNDP II  
Chair, Transdermal Drug Working Group  
13-AUG-2019



**Caroline  
Strasinger**

Digitally signed by Caroline Strasinger  
Date: 8/14/2019 10:51:01AM  
GUID: 5051dfdd000013b995075b4d54108ed8



**Moo Jhong  
Rhee**

Digitally signed by Moo Jhong Rhee  
Date: 8/14/2019 11:21:12AM  
GUID: 502d0913000029f9798ca689a802fa55

**NDA 204017  
ADDENDUM**

**Twirla (levonorgestrel, ethinyl estradiol) Transdermal  
System**

**Agile Therapeutics, Inc.**

**Caroline Strasinger, Ph.D.  
Branch IV  
DNDQA II/ONDQA**

**CMC Review of NDA 204017  
For the Division of Reproductive and Urological Products**

# Chemistry Review Data Sheet

1. NDA 204017  
2. REVIEW #: #2  
3. REVIEW DATE: 11-FEB-2013  
4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Quality Review #1 15-JAN-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

26-MAR-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Agile Therapeutics, Inc.  
Address: 101 poor Farm Road  
Princeton, NJ 08540  
Representative: Marie Foegh, M.D.  
Telephone: 609-683-1880

# The Chemistry Review for NDA 204017

## The Executive Summary

### I. Synopsis of Addendum

This Addendum updates the Office of Compliance recommendation from Pending to Acceptable. An additional comment for the Complete Response (CR) Letter is also discussed below. An updated EES report and an email from the Inspector can be found in Appendix 1 and 2 respectively.

### II. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the ONDQA perspective, this NDA is recommended for **COMPLETE RESPONSE**.

The Applicant has not provided sufficient information on raw material controls, manufacturing processes and process controls, and specifications for assuring consistent product quality of the drug product. The applicant has not provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the proposed expiration dating period. The identifying label on the drug product backing membrane is insufficient to assure the product can be appropriately identified during use.

The Office of Compliance has issued an "**ACCEPTABLE**" overall recommendation on all the manufacturing facilities.

Labels and Labeling were not reviewed in this review cycle.

**Please communicate the following additional item in the CR Letter. This item is in addition to those discussed in the Quality Review dated 14-JAN-2013:**

**During the facility inspection, it was noted that different equipment was used for the manufacture of clinical trial supplies as compared to that proposed for the commercial product. Provide a tabulated comparison of the <sup>(b) (4)</sup> processes and equipment. Address whether the new equipment is of a different design or operating principle. If it is a scale-up of the equipment, address whether this can change the product performance. Also, a new laser etching process has been submitted in the original application which was not assessed in clinical trial material. In order to support this change, provide data to demonstrate that the new process will not adversely impact the performance of the product. At a minimum, this should include comparative performance (in vitro or in vivo) data and stability data to support the proposed shelf life. We remind you that validation studies will need to be conducted on the new equipment and that inspection requests may be resubmitted upon receipt of your CR.**

Reviewer Notes:

***Office of Compliance Recommendation***

The Office of Compliance issued an overall "ACCEPTABLE" recommendation for all facilities involved in the manufacture and testing of the drug product on 11-FEB-2013. See Appendix 1 for the updated EES report.

Based on correspondence with the inspector for the drug product manufacturing site, Corium Manufacturing Group, (refer to Appendix 2) the following additional CR Letter item should be communicated to the Applicant.

**During the facility inspection, it was noted that different equipment was used for the manufacture of clinical trial supplies as compared to that proposed for the commercial product. Provide a tabulated comparison of the (b) (4) processes and equipment. Address whether the new equipment is of a different design or operating principle. If it is a scale-up of the equipment, address whether this can change the product performance. Also, a new laser etching process has been submitted in the original application which was not assessed in clinical trial material. In order to support this change, provide data to demonstrate that the new process will not adversely impact the performance of the product. At a minimum, this should include comparative performance (in vitro or in vivo) data and stability data to support the proposed shelf life. We remind you that validation studies will need to be conducted on the new equipment and that inspection requests may be resubmitted upon receipt of your CR.**

APPENDIX 1: EES report

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Application: NDA 204917/030 Action Goal:  
 Stamp Date: 13-APR-2012 District Goal: 15-DEC-2012  
 Regulatory: 13-FEB-2013  
 Applicant: AGILE Brand Name: AG200-15, Transdermal contraceptive patch  
 101 POOR FARM RD Etab. Name:  
 PRINCETON, NJ 08540 Generic Name:  
 Priority: 3 Product Number, Dosage Form, Ingredient, Strengths:  
 Org. Code: 580 001. PATCH, LEVONORGESTREL, 2.0MG/PATCH  
 001. PATCH, ETHINYL ESTRADIOL, 2.0MG/PATCH  
 Application Comment: THIS NDA PROVIDES FOR A TRANSDERMAL CONTRACEPTIVE DELIVERY SYSTEM FOR USE BY WOMEN TO PREVENT PREGNANCY (on 24-APR-2012 by R. MCKNIGHT, 3017961765)  
 FDA Contacts: R. MCKNIGHT Project Manager 3017961765  
 C. STRASINSER Review Chemist (HFD-800) 3017963776  
 D. CHRISTNER Team Leader 3017961341  
 Overall Recommendation: ACCEPTABLE on 11-FEB-2013 by T. SHARP D 3017963265

Establishment: CFN: (b) (4) FEE: (b) (4)  
 (b) (4)  
 DMF No: (b) (4) AADA:  
 Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE PACKAGER  
 DRUG SUBSTANCE RELEASE TESTER  
 Establishment Comment: DRUG SUBSTANCE MANUFACTURING, PACKAGING, AND RELEASE (b) (4)  
 Profile: NON-STERILE API BY CHEMICAL SYNTHESIS CAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO CD	(b) (4)				MCKN/SHTR
CD RECOMMENDATION				ACCEPTABLE BASED ON PROFILE	(b) (4)

Establishment: CFN: [REDACTED] FEB: 3033692105

CORNUM MANUFACTURING GROUP

4568 53TH ST SE  
GRAND RAPIDS, MI 495125401

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT MANUFACTURING, PACKAGING  
(on 24-APR-2012 by R. MCKNIGHT / 3033692105)  
Profile: TRANSDERMAL PATCH

OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	25-APR-2012				MCKNIGHTR
SUBMITTED TO OC	25-APR-2012	10-000 Letter			SMTHDE
ASSIGNED INSPECTION TO IB	10-MAY-2012	GMP Inspection			DOMBROWSKR
OC RECOMMENDATION	11-DEC-2012			WITHHOLD FIRM NOT READY	DOMBROWSKR
Comment					
SUBMITTED TO OC	24-JAN-2013	Product Specific			SAFAA JAZR
Comment					
ASSIGNED INSPECTION TO IB	25-JAN-2013	Product Specific			DOMBROWSKR
Comment					
OC RECOMMENDATION	09-FEB-2013			ACCEPTABLE INSPECTION	DOMBROWSKR
Comment					
OC RECOMMENDATION	11-FEB-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SHARPT

Establishment: CFN: [REDACTED] (b) (4) FEB: [REDACTED] (b) (4)

[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: OUTSIDE TEST LAB FACILITY USED BY CORNUM FOR SELECT EXPIMENTAL MATERIAL/DRUG SUBSTANCE TESTING (b) (4)

Profile: [REDACTED] OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				MCKNIGHTR
OC RECOMMENDATION				ACCEPTABLE BASED ON PROFILE	(b) (4)

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: OUTSIDE TESTING FACILITY USED BY CORPILM FOR SELECT EXPERIMENTAL MATERIAL/DRUG SUBSTANCE TESTING (b) (4)

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				MCKNIGHTR
OC RECOMMENDATION				ACCEPTABLE BASED ON PROFILE	(b) (4)

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: OUTSIDE TESTING FACILITY USED BY CORPILM FOR SELECT EXPERIMENTAL MATERIAL/DRUG SUBSTANCE TESTING (b) (4)

Profile: (b) (4) OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	(b) (4)				MCKNIGHTR
OC RECOMMENDATION				ACCEPTABLE BASED ON PROFILE	(b) (4)

**APPENDIX 2: Correspondence with Inspector of the Corium Facility**

**From:** (b) (4)  
**Sent:** Monday, February 11, 2013 9:04 AM  
**To:** Strasinger, Caroline  
**Subject:** RE: Corium PAI NDA 204-017

(b) (4)

I should have the EIR done hopefully by mid-week.

(b) (4)

**From:** Strasinger, Caroline  
**Sent:** Monday, February 11, 2013 8:59 AM  
**To:** (b) (4)  
**Cc:**  
**Subject:** FW: Corium PAI NDA 204-017

Hello,

I saw that the site got recommended for approval this morning. If you are able to send me your report that will be helpful to me for finalizing my review.

(b) (4)

Thanks for your help,

Caroline

---

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

---

/s/

---

CAROLINE STRASINGER  
02/11/2013

TERRANCE W OCHELTREE  
02/12/2013



**CHEMISTRY REVIEW**



Chemistry Review Data Sheet

**NDA 204017**

**Twirla (levonorgestrel, ethinyl estradiol) Transdermal  
System**

**Agile Therapeutics, Inc.**

**Caroline Strasinger, Ph.D.**  
Review Chemist

**Office of New Drug Quality Assessment  
Division of New Drug Quality Assessment II  
Branch IV**

**CMC Review of NDA 204017  
For the Division of Reproductive and Urological Products**



# Table of Contents

<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>7</b>
<b>I. Recommendations .....</b>	<b>7</b>
A. Recommendation and Conclusion on Approvability .....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
<b>II. Summary of Chemistry Assessments.....</b>	<b>7</b>
A. Description of the Drug Product(s) and Drug Substance(s) .....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
<b>III. Administrative.....</b>	<b>9</b>
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block .....	9
<b>Chemistry Assessment.....</b>	<b>10</b>
<b>I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....</b>	<b>10</b>
S DRUG SUBSTANCE [Ethinyl Estradiol & Levonorgestrel (b) (4)] .....	10
P DRUG PRODUCT [Twirla, Transdermal System].....	13
A APPENDICES .....	83
R REGIONAL INFORMATION .....	84
<b>II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....</b>	<b>84</b>
<b>III. List Of Deficiencies To Be Communicated.....</b>	<b>85</b>



# Chemistry Review Data Sheet

1. NDA 204017
2. REVIEW #: #1
3. REVIEW DATE: December 12, 2012
4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

13-APR-2012

Amendment 0005

18-JUL-2012

Amendment 0009

16-AUG-2012

Amendment 0011

17-OCT-2012

Amendment 0013

31-OCT-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Agile Therapeutics, Inc.
Address:	101 poor Farm Road Princeton, NJ 08540
Representative:	Marie Foegh, M.D.
Telephone:	609-683-1880

8. DRUG PRODUCT NAME/CODE/TYPE:



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

- a) Proprietary Name: Twirla  
b) Non-Proprietary Name (USAN): levonorgestrel, ethinyl estradiol transdermal system  
c) Code Name/#: N/A  
d) Chem. Type/Submission Priority:  
• Chem. Type: 3  
• Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY: 0.12 mg levonorgestrel/day &  
0.030 mg ethinyl estradiol/day

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

**Ethinyl Estradiol:**

19-Norprega-1,3,5 (10)-trien-20-yne-3, 17-diol (17 $\alpha$ )

Molecular Formula: C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>

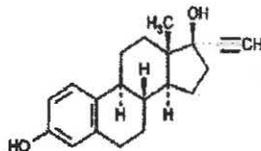
Molecular Weight: 296.41



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

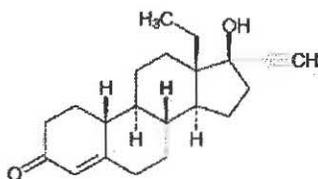


### Levonorgestrel:

(-)-13-ethyl-17-hydroxy-18-19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one

Molecular Formula: C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>

Molecular Weight: 312.44



## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Ethinyl Estradiol	3	Adequate	9/5/2012	Dr. R. Powers for ANDA (b) (4)
	II		Levonorgestrel	3	Adequate	5/30/2012	Dr. R. Powers for ANDA (b) (4)
	III		(b) (4)	3	Adequate	3/16/2002	Dr. A. Mitra for NDA (b) (4)
	III			3	Adequate	04/25/2008	Dr. A. Shaw for IND (b) (4)
	IV			3	Adequate	11/22/2012	Dr. X. Li for ANDA (b) (4)
	III			7	Not Reviewed		This DMF was not reviewed during this review cycle
	III			7	Not Reviewed		This DMF was not reviewed during this review cycle
	III			1	Deficient	3/14/2012	Deficient for administrative reasons related to



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	(b) (4)	4		N/A	the LOA
	III			4		N/A	

<sup>1</sup> 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")

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

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

### 18. STATUS:

#### ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	12/11/2012	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Acceptable	01/03/2013	Tapash Ghosh, Ph.D.
LNC	N/A		
Methods Validation	Approved with modifications	11/23/2012	Michael Trey
DMEPA	N/A		
EA	To be reviewed in next review cycle	N/A	
Microbiology	N/A		



# The Chemistry Review for NDA 204017

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 204017 for Twirla (levonorgestrel, ethinyl estradiol) transdermal system is recommended for Complete Response from the CMC perspective. The Applicant has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Applicant needs to respond adequately to the CMC issues outlined in this review. Deficiencies to be communicated to the Applicant can be found on pages 85 – 89.

An overall “PENDING” recommendation has been issued for the manufacturing and testing sites by the Office of Compliance.

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

No CMC related Phase 4 are proposed at this time.

### II. Summary of Chemistry Assessments

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

##### Drug Substance:

The drug substances, ethinyl estradiol, USP and levonorgestrel, USP, are supplied to Corium International, Inc (drug product manufacturer) by (b) (4) and are manufactured in (b) (4). The Applicant references DMF (b) (4) for information pertaining to the drug substance ethinyl estradiol (EE) and DMF (b) (4) for information pertaining to the drug substance levonorgestrel (LNG). Satisfactory Letters of Authorization (LOA) were provided to consult these DMFs in the submission. DMF (b) (4) and DMF (b) (4) were most recently reviewed by Dr. R. Powers on September 5, 2012 and May 30, 2012 respectively and both were found acceptable; no manufacturing changes have been made to the DMFs since the most recent reviews. Both drug substances are tested to compendial standard prior to release into drug product manufacture. The testing is conducted by Corium at the manufacturing site in Grand Rapids, Michigan and also at alternate analytical testing laboratory sites. Accordingly, from a Chemistry, Manufacturing, and Controls (CMC) point of view, the drug substance is deemed acceptable.

##### Drug Product:

## Executive Summary Section

Twirla is a transdermal drug delivery system (TDDS) comprised of a 15 cm<sup>2</sup> active adhesive matrix integrated with a larger peripheral adhesive system (28 cm<sup>2</sup>). The active adhesive matrix is composed of the female hormones levonorgestrel and ethinyl estradiol in an acrylic adhesive. The system is designed to release both drug substances continuously upon application to intact skin with a wear period of 1 week (7 days). The delivery of therapeutically effective levels of LNG and EE throughout the seven-day drug delivery interval is achieved through the incorporation of skin permeation enhancers (b) (4)

within the active adhesive matrix. Reliable seven-day adhesion is achieved by the peripheral adhesive system that has a flexible stretchable backing with bi-dimensional elasticity. The TDDS is manufactured at Corium International, Inc in Grand Rapids, MI.

The quality of the drug product is currently controlled by tests for appearance, assay, content uniformity, identification, related substances, excipient assay, adhesion, release liner removal force, drug release, and pouch seal strength, however during the review cycle several deficiencies regarding specification were identified and the specification table was not properly updated in this review cycle. Each carton will contain three TDDS of one strength. A single system per carton configuration is also available for use if one of the three TDDS are lost during a cycle. A 24 month expiration date has been requested for the product.

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

Twirla (levonorgestrel, ethinyl estradiol) transdermal system is a multi-laminate structure that releases LNG and EE continuously upon application to intact skin for contraception. The adhesive side of Twirla should be placed on a clean, dry area of the abdomen, buttocks or upper torso. Twirla should not be applied to the breast. The transdermal delivery system is designed for continuous wear with application of a new system each week for three weeks; the fourth week of the menstrual cycle is a "patch free week". Systems should be applied to a different site with each application. The product should be stored at room temperature.

**C. Basis for Approvability or Not-Approval Recommendation**

From the ONDQA perspective, this NDA is recommended for Complete Response.

The Applicant has not provided sufficient information on raw material controls, manufacturing processes and process controls, and specifications for assuring consistent product quality of the drug product. The applicant has not provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the proposed expiration dating period. The identifying label on the drug product backing membrane is insufficient to assure the product can be appropriately identified during use.



## CHEMISTRY REVIEW



### Executive Summary Section

Office of Compliance has issued a "PENDING" recommendation for all facilities involved.

Labels/labeling were not reviewed in this review cycle.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

ChemistName/Date: Caroline Strasinger, PhD 12-DEC-2012

ChemistryTeamLeaderName/Date: Donna Christner, PhD; 12-DEC-2012

ProjectManagerName/Date: Kerri-Ann Jennings; 12-DEC-2012

#### C. CC Block

80 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

---

*/s/*

---

CAROLINE STRASINGER  
01/14/2013

TERRANCE W OCHELTREE  
01/14/2013

### ONDQA (Biopharmaceutics) Review

<b>NDA</b>	204 - 017 (Original)
<b>Applicant:</b>	Agile Therapeutics
<b>Proposed Trade name:</b>	Twirla™
<b>Stamp Date</b>	April 13, 2012
<b>Amendment Date</b>	October 17, 2012
<b>Established Name:</b>	Levonorgestrel/ Ethinyl estradiol Transdermal system 15cm <sup>2</sup> /28cm <sup>2</sup>
<b>Dosage Form:</b>	Transdermal System
<b>Route of Administration:</b>	Topical
<b>Indication:</b>	Prevention of pregnancy
<b>Reviewer:</b>	Tapash Ghosh, Ph. D.

**Background:** AG200-15 is a transdermal contraceptive delivery system (TCDS) comprised of a 15 cm<sup>2</sup> active adhesive matrix integrated with a larger peripheral adhesive system (28 cm<sup>2</sup>). The active adhesive matrix is composed of the female hormones levonorgestrel and ethinyl estradiol in an uncross-linked acrylic adhesive matrix. Skin permeation enhancers are incorporated into the active matrix which necessitates additional supporting adhesives - the peripheral adhesive system – as a reliable approach to adhesion.

This Biopharmaceutics review addresses the *in vitro* drug release method and specifications. It also evaluated supportive *ex vivo* skin permeation study results.

#### RECOMMENDATION:

ONDQA-Biopharmaceutics has reviewed NDA 204-017 for Twirla™ (Levonorgestrel/ Ethinyl estradiol Transdermal system 15cm<sup>2</sup>/28cm<sup>2</sup>). Based on the evaluation of the overall information included in the original submission and subsequent amendments/ communications, the NDA 204-017 is acceptable from biopharmaceutics perspective (except the *in vitro* release acceptance criterion at 72 hour time) as noted below:

- The following proposed *in vitro* release method is acceptable.

#### *In Vitro* Release Method for Evaluation of Twirla™ (Levonorgestrel/ Ethinyl estradiol Transdermal system)

<b>Apparatus</b>	USP Type 5
<b>Rotation Speed</b>	75 rpm
<b>Medium Temperature</b>	32 ± 0.5 <sup>0</sup> C
<b>Dissolution Medium</b>	Deaerated 0.25% HPCD in water
<b>Dissolution Medium Volume</b>	500 mL
<b>Sampling Times</b>	2, 24 and 72 hrs

**Analytical Method :** HPLC with UV detector at 225 nm

Typical Operation Parameters	
Wavelength	(b) (4)
Flow Rate	(b) (4)
Injection Volume	(b) (4)
Column Temperature	(b) (4)
Run Time	(b) (4)
Isocratic or Gradient	(b) (4)

- The proposed *in vitro* drug release criterion at 72 hour time point as outlined below is recommended to be adjusted as per the Agency's recommendation described below in the next submission:

The Applicant's proposed Specifications for TCDS AG200-15

Test	Method	Acceptance Criteria
Drug Release Ethinyl Estradiol 2hr 24hr 72hr	(b) (4)	NMT $\frac{(b) (4)}{(4)}\%$ NLT $\frac{(b) (4)}{(4)}\%$
Drug Release Levonorgestrel 2hr 24hr 72hr	(b) (4)	NMT $\frac{(b) (4)}{(4)}\%$ NLT $\frac{(b) (4)}{(4)}\%$

The Agency's proposed Specifications for TCDS AG200-15

Test	Method	Acceptance Criteria
Drug Release Ethinyl Estradiol 2 hr 24 hr 72 hr	(b) (4)	NMT $\frac{(b) (4)}{(4)}\%$ NLT $\frac{(b) (4)}{(4)}\%$
Drug Release Levonorgestrel 2 hr 24 hr 72 hr	(b) (4)	NMT $\frac{(b) (4)}{(4)}\%$ NLT $\frac{(b) (4)}{(4)}\%$

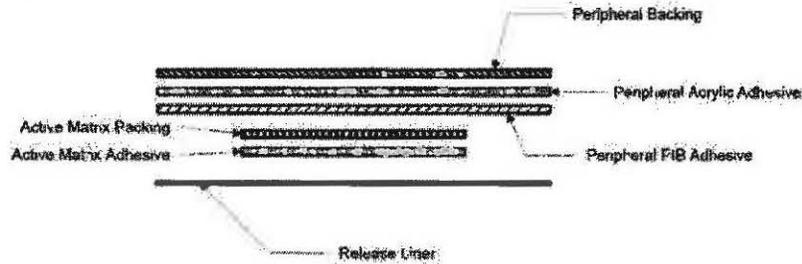
**Tapash K. Ghosh, Ph. D.**  
**Primary Biopharmaceutics Reviewer**  
**Office of New Drug Quality Assessment**

**John Z. Duan, Ph. D.**  
**Acting Biopharmaceutics Team Leader**  
**Office of New Drug Quality Assessment**

**Description of the Dosage Form (AG200-15, Transdermal Patch):** When viewed in cross-section, the AG200-15 TCDS appears as shown in Figure 1. The release liner is

(b) (4)

**Figure 1: Schematic Depiction of the AG200-15 Transdermal Patch System**



**Composition (AG200-15, Transdermal Patch):** The composition of the AG200-15 transdermal patch system, the function of each component, and the associated quality standard, are provided in Table 1.

**Table 1: Composition for AG200-15 Transdermal Patch System**

Component	Quality Standard	Function	Dry Weight (mg/Patch)	Target % (w/w)
(b) (4)				

**In Vitro Drug Release:** The dissolution test monitors drug release from the patch in an appropriate dissolution medium. Quantitation is performed by HPLC analysis. Transdermal patches are considered to be modified release drug products. Drug Release of an Ethinyl Estradiol/ Levonorgestrel (EE/LNG) Transdermal Delivery System (TDS) is determined using a 0.25% Hydroxypropyl-  $\beta$ -cyclodextrin (HPCD) water solution as the dissolution medium and a USP Type 5 dissolution apparatus using a transdermal system (b) (4). The amount of active pharmaceutical ingredient (API) released is quantified by (b) (4) high pressure liquid chromatography (HPLC), using an external standard.

**1. Dissolution Conditions:**

<b>Apparatus</b>	USP Type 5
<b>Rotation Speed</b>	75 rpm
<b>Medium Temperature</b>	32 $\pm$ 0.5 <sup>0</sup> C
<b>Dissolution Medium</b>	Deaerated 0.25% HPCD in water
<b>Dissolution Medium Volume</b>	500 mL
<b>Sampling Times</b>	2, 24 and 72 hrs

**2. Dissolution Methodology:**



### 3. Chromatographic Parameters:

Typical Operation Parameters	
Wavelength	(b) (4)
Flow Rate	
Injection Volume	
Column Temperature	
Run Time	
Isocratic or Gradient	

Upon review of the original submission, the following information request regarding release method was communicated to the applicant on 09/24/2012:

*Submit the complete report on the development and validation of the proposed in vitro drug release method (justifying choice of optimal method parameters with adequate discriminatory ability) along with the raw data (in electronic format) and the in vitro drug release profiles from the biobatches (PK and clinical) and primary stability batches supporting the proposed drug release acceptance criteria.*

*The Applicant's Response:*

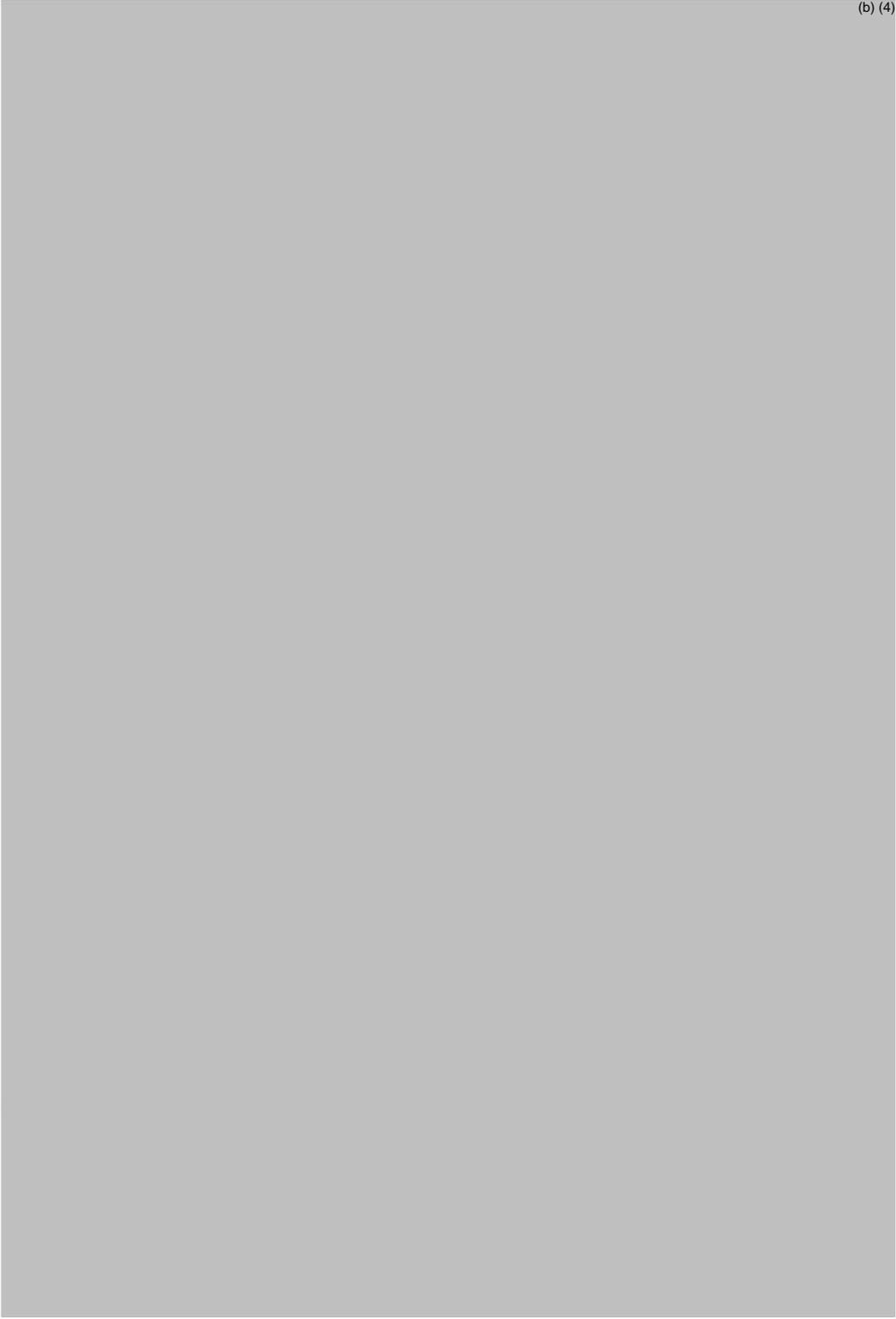


8 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

**Ex Vivo Skin Permeation:** A skin flux study was conducted on lot 29588, lot 30793, and lot 31357. Table 21 shows the age and clinical use of these lots. The skin flux data are tabulated in Table 22. No differences are seen in EE or LNG permeation between the three lots of various ages.

**Table 21: Batches Used for Skin Flux Testing**

Batch	Age at Testing	Clinical Use
29588	18 months	PK study (CL14) Phase 3 study (CL12)
30793	6 months	CL12- Phase 3 CL 13 Phase 3
31357	2 months	CL12- Phase 3 CL 15 PK Application Site



**Table 22 - Skin Flux - Lots 29588, 30793, 31357**

	<b>EE/LNG TDS Lot # 29588 (18 months)</b>	<b>EE/LNG TDS Lot # 30793 (6 months)</b>	<b>EE/LNG TDS Lot # 31357 (2 months)</b>
Ethinyl Estradiol Cumulative Amount Permeated $\mu\text{g}/\text{cm}^2/168\text{hr}$	27.90 $\pm$ 7.11	29.24 $\pm$ 2.08	24.03 $\pm$ 6.57
Levonorgestrel Cumulative Amount Permeated $\mu\text{g}/\text{cm}^2/168\text{hr}$	60.30 $\pm$ 13.03	64.89 $\pm$ 3.31	56.69 $\pm$ 11.22

Based upon these data, it was inferred that the proposed TDS system has provided an adequate level of containment of the actives and excipients so as not to influence the performance of the drug product through its intended shelf life and storage conditions.

Upon review of the original submission, the following information request regarding skin permeation study was communicated to the applicant on 09/24/2012:

*Submit the report(s) with complete data on the Skin Flux studies mentioned in Table 22.*

The Applicant responded on 10/17/2012 as follows:

The report titled "R&D Report – Comparison of In-Vitro Skin Permeation of Ethinyl Estradiol (EE) and Levonorgestrel (LNG) through Human Cadaver Skin from Three Different Lots of Ethinyl Estradiol and Levonorgestrel Transdermal System (EE/LNG TDS 15 cm<sup>2</sup>)" has been included.

**Reviewer's Comment:** *The above report was reviewed and was found satisfactory.*

---

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

---

/s/

---

TAPASH K GHOSH  
01/02/2013

JOHN Z DUAN  
01/03/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Food and Drug Administration

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis  
St. Louis, MO 63101  
Tel. (314) 539-3874

Date: November 21, 2012

To: Caroline Strasinger, Ph.D., Chemist, Office of New Drug Quality Assessment

Through: Benjamin Westenberger, Deputy Director, Division of Pharmaceutical Analysis

From: Anna Wokovich, Chemist, Division of Pharmaceutical Analysis  
Anjanette Smith, Chemist, Division of Pharmaceutical Analysis

Subject: Method Validation for NDA 204-017  
Corium Estradiol/Levonorgestrel Transdermal System  
Peel Adhesion, Release Liner, Shear, and Excipient Assay

The following methods were evaluated:

Corium Test Procedure Determining Release Liner Removal Force (Method: Doc # TP011 Effective AUG 14 2009 Rev 12 DCR # 09620)

Corium Test Procedure Determining Adhesive Peel Strength (b) (4) (Doc # TP074 Effective AUG 06 2010 Rev 05 DCR # 10317)

Corium Test Procedure Determination of Shear Adhesion (Doc # TP078 Effective NOV 30 2010 Rev 04 DCR # 10475)

Corium Test Procedure Determination of ethyl lactate, dimethylsulfoxide, (b) (4) and lauryl lactate in ethinyl estradiol / levonorgestrel TDS by (b) (4) (Doc # AM079)

The following method was evaluated and is acceptable for quality control and regulatory purposes:

Corium Test Procedure Determining Release Liner Removal Force (Method: Doc # TP011 Effective AUG 14 2009 Rev 12 DCR # 09620)

The following method was not evaluated because the method stated to use the test weight specified in the specification, but there was no specification for shear:

Corium Test Procedure Determination of Shear Adhesion (Doc # TP078 Effective NOV 30 2010 Rev 04 DCR # 10475)

The following method was evaluated and is acceptable for quality control and regulatory purposes with modification;

Corium Test Procedure Determining Adhesive Peel Strength (b) (4) (Doc # TP074 Effective AUG 06 2010 Rev 05 DCR # 10317)

The following comments are made in regard to the peel adhesion from (b) (4) method.

1.

(b) (4)

The following method was evaluated and is acceptable for quality control and regulatory purposes; however, we have the following comments:

Determination of ethyl lactate, dimethylsulfoxide, (b) (4) and lauryl lactate in ethinyl estradiol / levonorgestrel TDS by (b) (4) (AM079)

1.

(b) (4)

2.

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

---

*/s/*

---

MICHAEL L TREHY  
11/21/2012

BENJAMIN J WESTENBERGER  
11/23/2012