

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204017Orig1s000

OTHER ACTION LETTERS



NDA 204017

COMPLETE RESPONSE

Agile Therapeutics, Inc.
Attention: Mark B. Carroll
Vice President, Regulatory Affairs and Quality Assurance
101 Poor Farm Road, 3rd Floor
Princeton, NJ 08540

Dear Mr. Carroll:

Please refer to your New Drug Application (NDA) dated April 12, 2012, received April 13, 2012, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for levonorgestrel/ethinyl estradiol 120/30 mcg/day transdermal contraceptive delivery system.

We acknowledge receipt of your amendment dated June 26, 2017, which constituted a complete response to our February 13, 2013, action letter.

We also acknowledge receipt of your amendment dated December 1, 2017, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Drug Product

Adhesion of your transdermal system to skin is critical for the safe and effective use of the drug product. We relayed our concerns with the adhesion performance of your product in the February 13, 2013, Complete Response Letter. Significant adhesion problems remain based on quality issues discussed in this section and findings from your most recent clinical study, ATI-CL23 discussed in the CLINICAL section below.

As noted in our information request dated November 7, 2017, the goal of quality adhesion testing is to assure that future batches of drug product are comparable to batches that have adequate in vivo adhesion. Based on our review of the manufacturing process and in-process controls, we

determined that the in-process adhesion data for the clinical and commercial-scale intermediates were not comparable, and that there was a high frequency of invalid results.

In addition, the proposed finished product specification lacks a validated test and appropriate acceptance criteria for Part Tack. The current adhesion test, TP074, is highly variable, subjective, and results in uninterpretable data with non-comparable profiles between batches.

Therefore, we have identified the following drug product quality deficiencies:

1. You have not demonstrated that the in-process adhesion and tack tests are suitable for ensuring the quality and the in vivo adhesion of the commercial-scale product.
2. 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.

Facility Inspections

3. During a recent inspection of the Corium International Inc. (FEI 3003693015) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection.

CLINICAL

In your clinical trial (ATI-CL23), 11.3% of patches result in less than 75% of adherence during the 7-day wear cycle and over half of subjects reported at least one complete patch detachment during the study. In this context, your Pearl Index was higher than expected for a combined hormonal contraceptive product, rates of subject discontinuation were above 50% and unscheduled bleeding (cycle control) on treatment was over 40%. It is unclear whether these findings were a result of inadequate adhesion of your product, application site tolerability issues, unscheduled bleeding or other issues.

Regarding efficacy, we identified twelve additional on-treatment pregnancies in Study ATI-CL23, which resulted in a Pearl Index of 5.83 (95% CI 4.45-7.21), with a significant number of the FDA-adjudicated pregnancies occurring in women who had delays in applying patches. We are concerned about the implications of these findings for real-world use, and the extent to which the significant withdrawal and drop-out rates may have impacted the reliability of the results.

The serious risks with your product, including thromboembolic events, appear to be similar to those seen with other combined hormonal contraceptives.

In summary, based on the adhesion problems seen in your clinical trial and described in the product quality section, you have not demonstrated that your drug product has the in vivo adhesion properties requisite for its safe and effective use. The extent to which these adhesion issues affected efficacy, unscheduled bleeding and high subject discontinuation rates is unclear.

Given that the main advantage of your combined hormonal contraceptive product would be a more convenient dosing schedule, we are unable to conclude that the reduced efficacy outweighs the risks and uncertainties described above.

Recommendations to Address the Deficiencies:

Drug Product

1. Assess whether the unacceptable in vivo adhesion properties observed in your clinical trial are the result of the current design and formulation of the drug product, or are due to some other factor(s).
2. Develop and validate in-process tests for tack and adhesion. Justify the acceptable ranges using results obtained during the manufacture of drug product batches with acceptable in vivo adhesion properties.
3. Develop and validate tests for part tack and adhesion for release and stability on the finished drug product. Justify the acceptable ranges using results obtained from finished drug product batches with acceptable in vivo adhesion properties.

Facility Inspections

4. Satisfactory resolution of the objectionable conditions observed at the manufacturing facility (FEI 3003693015) for this NDA is required.

Clinical

5. Assess whether the unacceptable in vivo adhesion properties are the result of the current design and formulation of the drug product, or are due to some other factor(s) and how this may contribute to efficacy, cycle control and safety of your product. Address the implications of the delays in applying the patch seen in your trial and the high withdrawal and dropout rates. If the unacceptable adhesion is due to the design and formulation of the drug product, we recommend that you design a new transdermal system and conduct another clinical trial with the new transdermal system in the US population.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

PROPRIETARY NAME

Please refer to correspondence dated, September 11, 2017 which addresses the proposed proprietary name, Twirla (levonorgestrel/ethinyl estradiol) transdermal delivery System, 120/30 mcg/day. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and

clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a

complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

AUDREY L GASSMAN
12/21/2017



NDA 204017

ACKNOWLEDGE INCOMPLETE RESPONSE

Agile Therapeutics, Inc.
Attention: Gracelyn Deebo
Sr. Vice President, Regulatory Affairs
101 Poor Farm Road
Princeton, NJ 08540

Dear Ms. Deebo:

We acknowledge receipt of your June 24, 2013, submission to your new drug application (NDA) for Twirla (levonorgestrel and ethinyl estradiol) transdermal delivery system.

For the reasons explained below, we do not consider this submission to be a complete response to our February 13, 2013, action letter. We will not start the review clock until we receive a complete response.

CLINICAL

In our Complete Response letter, we informed you that the two phase 3 studies submitted in your NDA failed to demonstrate acceptable evidence of efficacy. In addition, our review identified substantial problems with study conduct, including low completion rates, and issues with subject follow-up and data collection that limit conclusions and limit our confidence in the study results. One of the deficiencies in the Complete Response letter explicitly stated that you will need to conduct a new phase 3 trial before your NDA may be approved. We do not consider it possible to rely only upon the studies that we have already reviewed to provide adequate evidence of efficacy for your product.

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

With regard to your response to Product Quality Deficiencies 1 and 4:

It is the current policy of the FDA that all transdermal systems be labeled with identifying information including, at a minimum, the name of the product and the strength. Therefore your proposal to seek approval for the product without an identifying label is not acceptable.

With regard to your response to Product Quality Deficiency 2:

The acceptance criterion and justification of the acceptance criterion remain a review issue for cold flow, however at this time, it is noted that the cold flow specification provided on June 24, 2013 appears as:

Cold Flow¹

TP103

1. Qualitative Assessment 1: The system can be easily removed from the pouch such that the removal does not alter the physical appearance of the pouch.
2. Qualitative Assessment 2: After removal of the release liner, minimal adhesive remains on the release liner and minimal adhesive stringing or balling is observed beyond the perimeter of the patch.
3. NMT (b) (4) %

Qualitative Assessment 1 should read:

“The system can be easily removed from the pouch such that the removal does not alter the physical appearance of the transdermal system.”

With regard to your response to Product Quality Deficiency 3:

Justification of the specification for excipient assay remains a review issue. We acknowledge the additional *in vitro* information provided; however, from a cursory review of the information, it appears that the age of the system (utilizing samples from stability studies) is being used to justify the bounds of each excipient acceptance criterion. Because the penetration enhancers work in association with each other, the combined effect of minimum and maximum amounts of all (b) (4) penetration enhancers should be assessed.

With regard to your response to Product Quality Deficiencies 5-8 and Additional CMC and Biopharmaceutics Comments:

A cursory review of these responses was performed and we have no additional information to communicate at this time; however, the adequacy of these deficiencies remains a review issue for any future Complete Response submission.

PATH FORWARD

In our Complete Response Letter, we stated that under 21 CFR 314.102(d), you may request a meeting or telephone conference to discuss what steps you need to take before your application may be approved. We note that you did not request such a meeting and instead submitted your June 24, 2013, document without first soliciting feedback from FDA regarding your approach. We strongly recommend that you request a meeting with us prior to another submission so that you can fully understand our concerns described in the Complete Response letter, including our concerns with your completed phase 3 studies and our rationale for the need for a new phase 3 trial. You could consider including information from your June 24, 2013, submission as part of the meeting briefing package together with specific questions to FDA.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

HYLTON V JOFFE
07/17/2013



NDA 204017

COMPLETE RESPONSE

Agile Therapeutics, Inc.
Attention: Marie Foegh, M.D., Dr. Sc.
Chief Medical Officer & Vice President, Clinical and Research & Development
101 Poor Farm Road
Princeton, NJ 08540

Dear Dr. Foegh:

Please refer to your New Drug Application (NDA) dated April 12, 2012, received April 13, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Twirla (levonorgestrel and ethinyl estradiol) transdermal system for the prevention of pregnancy in women who elect to use a transdermal system as a method of contraception.

We acknowledge receipt of your amendments dated April 19, June 1, July 10, 16, and 18, August 3, 10, 15, 16, and 31, October 17, 19, and 31, November 29, December 4 and 12, 2012; January 11, 16, 17, 18, and 29, 2013.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. The two phase 3 studies submitted in this NDA failed to demonstrate acceptable evidence of efficacy. The Pearl Index in the larger 13-cycle study (ATI-CL12) was 7.50 with an upper bound of the 95% confidence interval of 9.97. The Pearl Index in the smaller 6-cycle study (ATI-CL13) was 8.19 with an upper bound of the 95% confidence interval of 16.19. Our calculations are based on pregnancies identified as on-treatment. These Pearl Indices and the upper bounds of their associated 95% confidence intervals are substantially higher than that seen in the registration trials for any of the approved hormonal contraceptives. You attribute these findings to inclusion of subjects in your trials who are more representative of women in the United States who would use the product, if approved. We encourage and value clinical trials that include generalizable populations. However, several of your assertions with regard to generalizability are not supported by the available data. In addition, we have identified substantial problems with study conduct, including low completion rates and issues with subject follow-up and data collection that limit conclusions and our confidence in the study results. We also have no evidence that your product will have a better safety profile than other combination hormonal contraceptives to justify accepting the higher Pearl Indices.

In order to address this deficiency, you will need to conduct a new pre-approval phase 3 study in a representative sample of women in the United States who are seeking hormonal contraception. This study will need to demonstrate an acceptable Pearl Index and upper bound of the 95% confidence interval. We recommend that the study duration be 13 cycles. The study should use your proposed to-be-marketed product after you have adequately addressed the product quality deficiencies (see below) that may have impacted the efficacy findings in your completed studies. We also recommend that you conduct further analyses of Study ATI-CL12 to identify possible explanations for some of the observed findings, such as the clustering of pregnancies at five clinic sites, the impact of incentives for subjects to remain in the study, and the adequacy of investigator training. These exploratory analyses will not be sufficient to address our concerns but may yield useful information that can be incorporated into the design of your new study.

The new study should be conducted with rigor and close oversight to ensure that the following issues identified in the current submission are minimized or addressed in a timely manner:

- High rates of premature withdrawal from the study and loss to follow-up
- Subject non-compliance with drug use, study visits and study procedures such as daily diary completion, sonograms to date pregnancies, and providing accurate follow-up contact information.
- Fairly high number of cycles excluded from the efficacy analysis because no intercourse occurred or in which back-up contraception was used
- Missing data, conflicting data, illegible data, and poor follow-up, which made it difficult to accurately determine the date of conception and the date of last patch use in many of the pregnancies
- Discrepancies in reporting of serious adverse events and lack of adequate information about diagnostic workups, which made it difficult to make a meaningful determination as to whether the event might have been drug-related.
- Subject concerns about patch adhesion, application site reactions and acceptability of the patch
- Investigator inexperience with the conduct of contraceptive studies
- Rapid study enrollment, which may have contributed to selection of many subjects who were not committed to completing the trial or using study medication
- Rapid completion of the final study reports that may have resulted in a poor quality submission containing numerous errors and inconsistencies

PRODUCT QUALITY

1. (b) (4) controls are not adequate. Establish an (b) (4) test at release of the product (release specification) for identifying bad/compromised transdermal systems (TDS) after (b) (4) laser etching until more data can be generated supporting that the laser controls adequately control the etching process.

2. The specification is not adequate as presented in your submission. The current specification provided in the NDA does not contain a test for cold flow or shear as requested and discussed in our Information Request letters and your October 17, 2012, response. Additionally, acceptance criteria for several tests are not adequate, have not been adequately updated as previously requested, or have not been adequately justified. You need to update the specification and acceptance criteria accordingly.
3. The justification for the specifications is not adequate. Justify the upper and lower bounds of the acceptance criteria for the excipient assay with either *in vivo* or *in vitro* skin permeation data. We acknowledge the additional information provided on October 17, 2012; [REDACTED] (b) (4)

[REDACTED]

Given the importance of the permeation enhancers in drug delivery and the manufacturing and stability variability potential discussed in your NDA and in your submission received October 17, 2012, the bounds of the acceptance criteria cannot be adequately justified based on statistical analyses. Further justification is needed.
4. Identify the strength of the product [REDACTED] (b) (4) levonorgestrel and [REDACTED] (b) (4) ethinyl estradiol (or equivalent presentation of language and units). Additionally, the identifying label on the backing membrane of the drug product (each patch) must, at a minimum, include the name of the product and the strength. This is consistent with FDA's current policy regarding the identifying label for all transdermal drug delivery systems.
5. Impurities have not been adequately characterized. You need to test for [REDACTED] (b) (4) in the final product and provide acceptance criteria for these [REDACTED] (b) (4) (if toxicologically relevant levels are detected in the final drug product) or justify why a test for [REDACTED] (b) (4) is not needed.
6. Update the post-approval stability protocol with new tests added to the specification.
7. Your application referenced the Drug Master File (DMF) [REDACTED] (b) (4). This DMF was found inadequate to support your submission. An information request letter was sent to the DMF holder on March 14, 2012. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date that the DMF holder amended their DMF to address the deficiencies.
8. 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 two 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, you are proposing a new laser etching process to be used for the identifying label on the commercial product. The impact of the etch was not assessed during clinical trials. 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, include comparative performance (*in vitro* or *in vivo*) data and stability data to support the proposed shelf life. Validation studies will need to be conducted on the new equipment. Inspection requests may be resubmitted upon receipt of your Complete Response submission.

ADDITIONAL COMMENTS

The following comments are not approvability issues, but should be addressed in the Complete Response submission.

Clinical

1. Ensure that a future study enrolls a sufficiently large and diverse population from the United States so that efficacy can be assessed in the following subgroups, for which the current submission suggests possible discrepancies in efficacy:
 - a. Racial/ethnic subgroups (White, African-American, Hispanic)
 - b. Subjects categorized by site of patch application (buttock, abdomen, upper torso)
2. We do not require that you include an active comparator in the future study.
3. We do not require you to assess drug levels in an attempt to measure drug compliance. However, if you choose to do so, this information may be useful to investigators in counseling subjects who do not appear to be using the product correctly.
4. Enroll a sufficient number of women who are truly naïve users of hormonal contraception, and provide clear and accurate data on previous use that allows naïve users (never before used hormonal contraception) to be distinguished from prior users who have not used hormonal contraception within a specified time period before their enrollment.
5. Should a sizeable percent of women with possible pregnancy and/or adverse events be lost-to-follow-up, this would be a significant review issue. Similarly, “false positive” HCG results are expected to be rare and should be further evaluated (e.g., confirmation by a urine pregnancy test, repeat quantitative serum testing, and ultrasound examinations). Should there be a number of such cases, particularly where further follow-up was not done, this would be a significant review issue.
6. Discrepancies between the Investigator and Sponsor interpretations of a pregnancy should be carefully delineated.
7. In your new study, a better scoring system for patch adherence should be devised and data should not be dependent on only observation at site visits; data about patch adherence should also be recorded in the subject diary, as it is likely to provide data that is more accurate and representative of the entire treatment period.

8. For your new study, we request that the study report adhere to the Mishell et al. recommendations (Contraception, 2007, 75: 4-15) for the primary analysis of the bleeding profile, rather than using an 84-day reference period. For the various parameters of bleeding and/or spotting, provide the mean, median, and range of observed days of bleeding, spotting, and bleeding plus spotting within each 28-day reference period.
9. In your new study, provide summary information on the outcome of all on-treatment pregnancies, including neonatal condition in the case of live-born infants.
10. If you intend to rely on safety or efficacy data from Study ATI-CL12, conduct an external audit of the data submitted in the final study report, and include the findings of the audit in your Complete Response Submission.

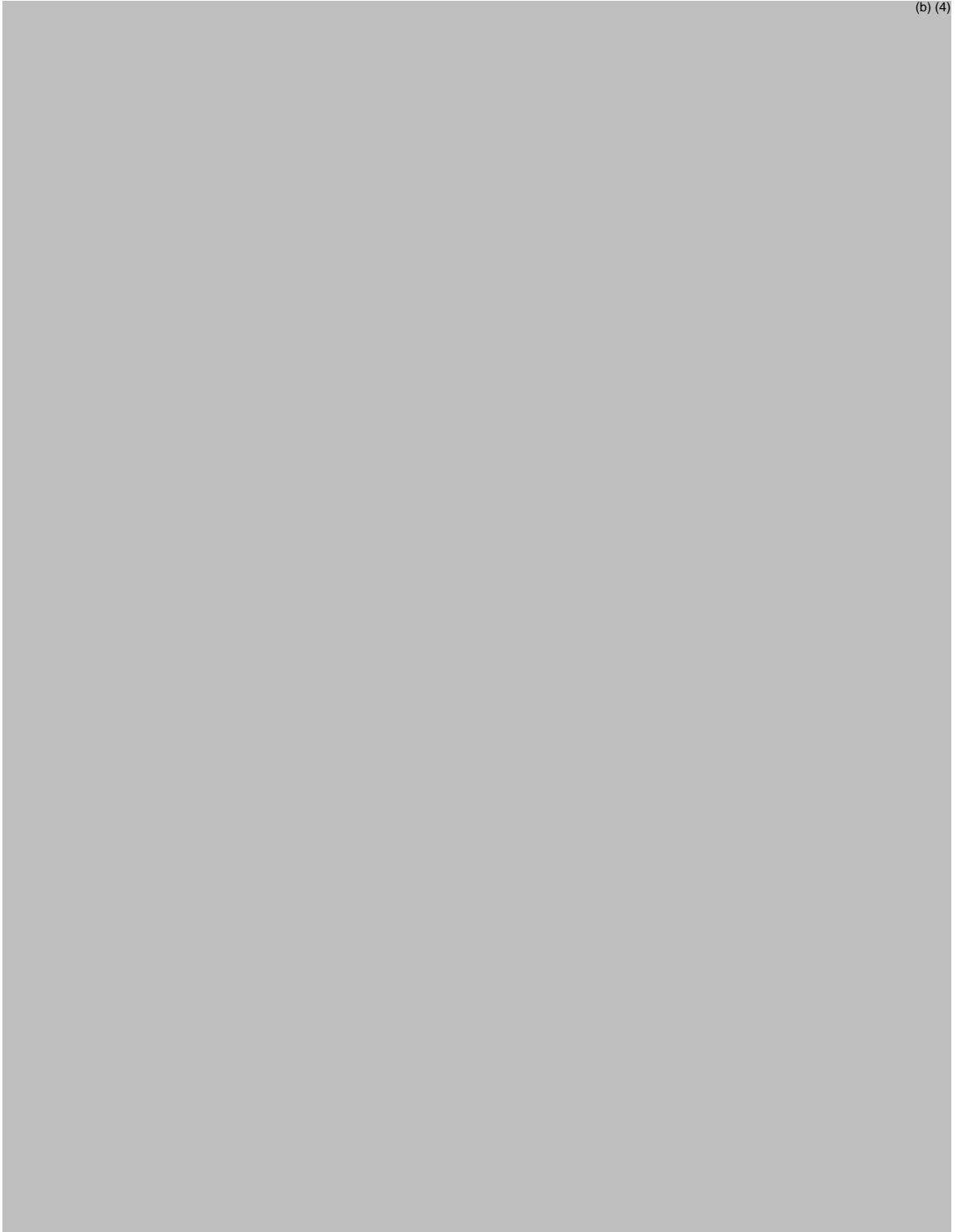
Chemistry, Manufacturing and Controls

1. You provided an assessment of skin adhesion characteristics in the October 17, 2012, submission entitled “Summary of Reasons for Unscheduled Patch Change by Subject Self-Assessment Safety Population” (Clinical/Statistical Report: Table 14.3.7_4.1). Amend this assessment to include “Partly Detached” and “Accidentally Pulled Off.”
 - The categories “Patch Fall Off,” “Partly Detached” and “Accidentally Pulled Off” are all adhesive concerns that could result in inadequate delivery of therapy and should be included in the adhesive assessment. When these categories are included, the percent of transdermal systems experiencing adhesive issues range from 5.0-9.7% with an average of 6.8%.
2. We conducted a Methods Validation of methods TP011 (Release Liner Peel Force), TP078 (Determination of Shear), TP074 (Part Adhesion), and AM79 (Excipient Determination) and provide the following comments for your consideration in your Analytical Method Development:
 - Corium Test Procedure Determination of Shear Adhesion (Doc # TP078 Effective NOV 30 2010 Rev 04 DCR # 10475) 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 Determining Adhesive Peel Strength at (b) (4) (Doc # TP074 Effective AUG 06 2010 Rev 05 DCR # 10317)

(b) (4)



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



Biopharmaceutics:

1. Adjust the *in vitro* drug release criterion at the 72 hour time point from No Less Than (NLT) (b)(4)% to NLT (b)(4)% for both ethinyl estradiol and levonorgestrel.

Clinical Pharmacology:

1. Address whether the product quality deficiencies described above may have impacted the findings in your clinical pharmacology studies. You may need to repeat some of your clinical pharmacology studies if the existing data are unreliable due to product quality.
2. We identified potential carry-over effects of both ethinyl estradiol and levonorgestrel between adjacent treatment cycles (in Study ATI-CL14) and adjacent periods (in Study ATI-CL15 and ATI-CL16). This may also impact reliability of the study results. If the product quality deficiencies can be adequately addressed, provide a revised analysis that corrects for/compensates for this potential carry-over effect. If you are unable to adequately address carry-over with the available data, provide a proposal for how you will obtain reliable clinical pharmacology data.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

HYLTON V JOFFE
02/13/2013