

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204017Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 57731

MEETING MINUTES

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

Dear Ms. Deebo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG200-15 (LNG/EE) Transdermal Contraceptive Delivery System.

We also refer to your submission dated August 15, 2011, requesting a meeting with the Division which was scheduled for October 24, 2011. Further, we refer to your electronic mail dated October 21, 2011, requesting that the scheduled meeting be cancelled based on the preliminary responses that were conveyed to you on October 20, 2011.

A copy of the official minutes is enclosed for your information.

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

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

SPONSOR'S QUESTIONS AND THE DIVISION'S RESPONSE

Non-Clinical Question

1. *Agile has developed a literature search strategy to identify reports in the literature to support our 505(b)(2) submission. Will published literature supportive of preclinical information on LNG/EE be sufficient to satisfy a 505(b)(2) submission?*

Division Response:

Yes. The Sponsor should include copies of all published literature reports it intends to rely upon for approval of the proposed product in its 505(b)(2) application.

The Division notes the Sponsor's intention to reference FDA's previous findings of safety and effectiveness for ethinyl estradiol and levonorgestrel "in the public domain" based on nonclinical data submitted in support of (b) (4). This statement suggests that the Sponsor is proposing to reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries for support of safety and/or efficacy. A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug.

If the Sponsor intends to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, it must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). The Sponsor should establish a "bridge" (e.g., via comparative bioavailability data) between its proposed drug product and each listed drug upon which it proposes to rely to demonstrate that such reliance is scientifically justified. If the Sponsor intends to rely on literature or other studies for which it has no right of reference but that are necessary for approval, the Sponsor also must establish that reliance on the studies described in the literature is scientifically appropriate.

If the Sponsor intends to rely on FDA's previous finding of safety and/or effectiveness for a listed drug(s) or published literature that describes a listed drug(s), it should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically

equivalent product were approved before the Sponsor's application is submitted, such that the Sponsor's proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, the Division may refuse to file the Sponsor's application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Sponsors considering the submission of an application through the 505(b)(2) pathway should consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>)).

Clinical Questions

- The NDA for AG200-15 in electronic Common Technical Document (eCTD) format will contain a Clinical Overview (2.5), a Summary of Clinical Efficacy (2.7.3) and a Summary of Clinical Safety (2.7.4), but no separate Integrated Summary of Safety (ISS) or Integrated Summary of Efficacy (ISE). Agile proposes that separate ISS and ISE will not be required for this submission as the active ingredients in this combined hormonal contraceptive are established, well-characterized drugs that have an acceptable safety profile and a long history of use in the United States. Additionally, the ISS and ISE do not add any more value to the data and analyses that will be presented in Sections 2.73 and 2.74 of the application. Does FDA agree with this proposal?*

Division Response:

No. Integrated Summaries of Safety and Efficacy should be submitted as required by 21 CFR 314.50.

- Agile proposes*

(b) (4)
(b) (4)

Division Response:

The general plan appears reasonable; however, it is premature to discuss details prior to submission of the NDA. Postmarketing requirements and commitments will be discussed as part of the approval process, if the NDA is approved.

- Agile plans to include only those case report forms [CRFs] that are typically included in an NDA submission, for deaths, and discontinuations due to adverse events and for serious adverse events. Will this be acceptable to the Agency?*

Division Response:

No. In addition to the CRFs proposed, the NDA submission needs to include the narratives and CRFs for all pregnancies and all the Pregnancy Follow-up Forms. The Division also requests that the Sponsor submit the Data Safety Monitoring Board (DSMB) meeting minutes, if applicable. It would also be helpful for the Sponsor to conduct and submit the results of a Standardized MedDRA Query (SMQ) for venous thromboembolism in the phase 3 database.

5. *Agile plans to submit data sets for the following studies in the NDA submission: two phase 3 studies (ATI-CL 12, ATI-CL 13), four pharmacokinetic studies (ATI-CL10, ATI-CL14, ATI-CL15 and ATI-CL16) and one dose finding, pharmacodynamic /pharmacokinetic study (ATI-CL11). Since data for the older, Phase 1/2 studies are not available in electronic format and uses an older formulation of the product, does FDA agree that no other clinical data sets will be required?*

Division Response:

The Division agrees that datasets for older phase 1/2 studies will not be required but asks that the Sponsor provide all the available clinical study reports for the phase 1/2 clinical studies.

6. *Agile plans to submit data sets in the traditional SAS Transport files. We do not plan to submit a Study Data Tabulation Model (SDTM) in the NDA. Upon review of the additional detail attached, does FDA agree with not receiving a SDTM?*

Division Response:

The Agency does not require submission in SDTM, but the Division strongly encourages the Sponsor to do so if possible. The Division also strongly recommends that both SDTM and ADaM datasets be provided. This will facilitate review and likely reduce the queries for customized datasets. For more information about data standard and format, please refer to the FDA website

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>).

If the Sponsor chooses not to submit datasets in CDISC format, the Sponsor should observe the principle of the CDISC standard. Further, the analysis datasets should include all the variables needed for the statistical analyses without requiring merging with other datasets or deriving any additional variables. Such variables include the efficacy endpoints and treatment groups, as well as all necessary covariates, such as age, weight, BMI, etc.

In addition to the datasets, programs for efficacy analyses should also be included with the submission. These programs should be sufficient to allow the Division to reproduce the results in the submission.

7. *Because earlier studies (studies 1-9) used a different formulation than the formulation that will be the subject of the marketing application, Agile plans to reference studies 1-9 in the Pharmaceutical Development Report. A table of safety data from studies 1-9 will be included in the Clinical Overview. Does FDA agree with this approach?*

Division Response:

From a CMC standpoint, information on all formulations used throughout the development of this product should be included in the Pharmaceutical Development Sections of Modules 2 and 3. Provide a table listing formulations used for each trial.

With respect to clinical pharmacology studies, earlier studies (Studies 1-9) should be reported in the relevant clinical sections. See also response to Question 5.

CMC Question

8. *Consistent with other marketed contraceptive products, Agile is planning to ask for a categorical exclusion on an Environmental Assessment. Does FDA agree?*

Division Response:

It would be acceptable to request a categorical exclusion from preparation of an Environmental Assessment. Please refer to the *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998)* <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm> to determine what information would need to be provided to support the categorical exclusion request.

Labeling Question

9. *The product labeling will be based largely on class labeling for oral contraceptives and data specific from the clinical studies on AG 200-15 and will be referenced as such in the annotated label. Is this strategy acceptable?*

Division Response:

Yes. The content, although not the non-PLR format, of the only approved transdermal contraceptive patch should also guide the development of the label for the proposed product (e.g., provide information about placement, replacement, adhesion and disposal of the patch).

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page

that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

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Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

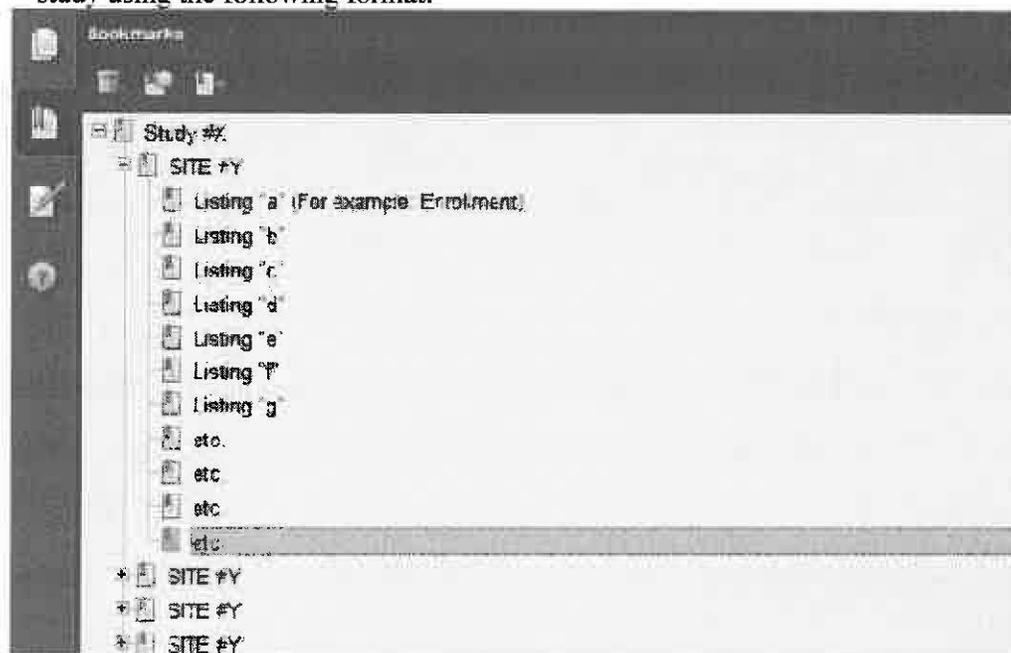
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment I, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

INITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

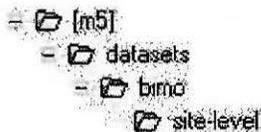
Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

LISA M SOULE
11/10/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 57,731

Agile Therapeutics
Attention: Lisa Flood, BSN
Associate Director, Regulatory Affairs and Clinical Operations
366 Wall Street
Princeton, NJ 08540-1517

Dear Ms. Flood:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG200-15 (transdermal contraceptive delivery system containing ethinyl estradiol and levonorgestrel).

We also refer to the meeting between representatives of your firm and the FDA on September 22, 2008. The purpose of the meeting was to discuss the adequacy of the nonclinical data, completed phase 1 and phase 2 studies, and to evaluate the proposed phase 3 plan.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.D.
Reproductive Clinical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 22, 2008

TIME: 1:00 PM to 2:30 PM

LOCATION: 10903 New Hampshire Avenue, Building 22, Room 1313

APPLICATION: IND 57,731

DRUG NAME: AG200-15 (transdermal contraceptive delivery system containing ethinyl estradiol and levonorgestrel)

TYPE OF MEETING: Type B Meeting

MEETING CHAIR: Lisa Soule, M.D.

MEETING RECORDER: Pamela Lucarelli

FDA ATTENDEES: (Title and Office/Division)

Scott Monroe, M.D., Director, Division of Reproductive and Urologic Products (DRUP)
Lisa Soule, M.D., Clinical Team Leader, DRUP
Daniel Davis, M.D., Medical Officer, DRUP
Jennifer Mercier, Chief, Project Management Staff, DRUP
Krishan Raheja, Ph.D., Pharmacology Reviewer, DRUP
Hae Young Ahn, Ph.D., Deputy Director, Division of Clinical Pharmacology (DCP) III,
Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Doanh Tran, R.Ph., Ph.D., Acting Team Leader, DCP III, OCP, OTS
Hyunjin Kim, Pharm.D., M.S., Clinical Pharmacology Reviewer, DCP III, OCP, OTS
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing
Assessment (DPA) II, Office of New Drug Quality Assessment (ONDQA), Office of
Pharmaceutical Sciences (OPS)
Kate Dwyer, Ph.D., Statistical Reviewer, DB III, Division of Biometrics III (OB III)
Pamela Lucarelli, Regulatory Health Project Manager, DRUP

EXTERNAL CONSTITUENT ATTENDEES:

Thom Rossi, Ph.D., President and CEO, Agile Therapeutics
Marie Foegh, M.D., Chief Medical Officer, VP Research and Development
Greg Arnold, Ph.D., Vice President, Manufacturing
Gary Shangold, M.D., Medical/Regulatory Consultant
Arkady Rubin, Ph.D., Biostatistician/Clinical Consultant
Robert Osterberg, R.Ph., Ph.D., Toxicology/Regulatory Consultant
Lisa Flood, BSN, Associate Director Regulatory Affairs and Clinical Operations

BACKGROUND:

AG200-15 is being developed for the prevention of pregnancy in women who elect to use a transdermal contraceptive delivery system (TCDS) as a method of contraception. AG200-15 is a thin transdermal system that gives systemic exposure, as measured by area under the curve (AUC), to levonorgestrel (LNG) and ethinyl estradiol (EE). The overall patch size is (b) (4) with an active matrix core area of 15 cm². The TCDS is applied and replaced every seven days for three weeks, followed by a one-week "patch-free" period.

MEETING OBJECTIVES:

The objective of the meeting is to discuss the following:

- The adequacy of the phase 1 and 2 studies performed and data acquired thus far to proceed to the proposed phase 3 study and to support a future NDA for AG200-15.
- The acceptability of the proposed phase 3 development plan for AG200-15 and of the draft phase 3 study protocol.
- The adequacy of the current nonclinical data for supporting a future NDA for AG200-15.
- The adequacy of the proposed chemistry, manufacturing, and controls (CMC) information for an NDA submission for AG200-15.

DISCUSSION POINTS:

The Sponsor's questions are presented below in *italics*, followed by the Division's responses in normal text. Additional discussion held during the meeting is summarized below in **bold** text.

1. *Does the Division concur that the existing nonclinical safety studies for LNG and EE are sufficient to support a future NDA submission for EE and LNG for the prevention of pregnancy?*

Division Response:

Yes. There are no safety concerns regarding LNG and EE, as these ingredients have been used extensively for the same indication as for the proposed formulation.

2. *Does the Division agree that no additional nonclinical safety studies need to be conducted on lauryl lactate, ethyl lactate, and capric acid in order to support a future NDA for the prevention of pregnancy?*

Division Response:

No. There is a safety concern about capric acid, which is one of the three excipients in the proposed patch formulation. The Pharmacology/Toxicology review of the Sponsor's submissions of March 29, 1999 (SS# 003) and April 21, 1999 (SS# 004) determined that lauryl lactate and ethyl lactate are safe for use as found in the proposed patch formulation,

but the information on capric acid was not adequate. More information should be submitted regarding its chronic dermal safety and mutagenic potential.

If this information is not available in the literature, the Sponsor will need to conduct these studies.

Additional Discussion at the Meeting:

The Sponsor noted that capric acid, (b) (4) has been the subject of skin irritation studies, which show a concentration-dependent irritative effect. It has been shown to be a moderate irritant, but never a primary skin irritant. There are reportedly no structural alerts for mutagenicity. The (b) (4) is contained in three approved drugs, (b) (4)

(b) (4) It is also a direct food additive, presumably having met the minimum toxicity evaluation required by the Center for Food Safety and Nutrition. The Sponsor further noted the consideration that a topically applied substance must be both an irritant and a mutagen to be a likely carcinogen.

The Sponsor agreed to provide the cited references for review by the Division. The Division's primary concern is for dermal, not systemic, toxicity.

The Sponsor also noted that it had not asked the Division about the DMSO contained in the drug product, believing that it is covered by and meets the limits stated in the ICH Q3 guidance (b) (6)

Post-Meeting Comment:

The Division does not need any studies for DMSO.

3. *Does the Division agree that the PK profile of AG200-15 will be adequately characterized by the current PK data and by the proposed PK study with the to-be-marketed AG200-15 product?*

Division Response:

No. The Division recommends that the Sponsor conduct the following studies prior to initiation of the phase 3 studies:

- 1) A relative bioavailability (BA) study comparing the to-be-marketed formulation of the transdermal contraceptive delivery system (TCDS; i.e., AG200-15) and an oral contraceptive (OC) product
- 2) A study to assess the effect of different application sites on the pharmacokinetics (PK) of AG200-15, if phase 3 studies will allow application of AG200-15 to more than one body site (e.g., abdomen, buttock, upper arm)

In addition, the Division recommends modifying the proposed PK study for the TCDS to add additional seven-day intensive PK measurements following the fourth and sixth applications (i.e., the first and third applications during the second cycle) of the TCDS, in addition to the proposed intensive PK measurement following the first patch application. This would help to assess the carryover effect between cycles and the accumulation within each cycle.

Finally, the NDA should include one or more PK study(ies) assessing the PK profiles of the to-be-marketed formulation of the TCDS under different external conditions (e.g., sauna,

exercise, cold water).

The Division recommends that the Sponsor submit study protocols for review by the Division before initiating these studies.

Additional Discussion at the Meeting:

The Sponsor agreed to do the studies requested by the Division, but proposed to do the relative BA and the application site studies in parallel with the phase 3 program, rather than prior to phase 3. The Sponsor believes that AG200-15 will deliver about $(b) (4)$ $\mu\text{g/day}$ of EE and $(b) (4)$ $\mu\text{g/day}$ of LNG. (b) (4)

Additionally, Study ATI-CL11 showed that mean C_{trough} values for the AG200-15 patch were approximately 31% higher than for the AG200 patch. (b) (4)

The Sponsor agreed to conduct a relative BA study using an oral contraceptive comparator, and the Division agreed that this could be done in parallel with phase 3. The Division's primary clinical concern is with the EE levels; however, if either hormone's levels in the PK study differed from that expected, this could be problematic for the phase 3 work (i.e., safety concerns if EE is higher than anticipated; efficacy concerns if LNG is lower than expected). The Sponsor is encouraged to target the patch exposure toward that of a lower-EE OC; the Division is more concerned about safety issues arising with higher estrogen exposure than with attempting to improve the bleeding profile by increasing estrogen exposure. The Division is also interested in the variability of the PK data, and findings of significant outliers in the exposure data would be a review issue.

Regarding application sites, the Sponsor expects that absorption from the abdomen will be up to $(b) (4)$ % less than from the buttock and that the buttock is likely to be bioequivalent (BE) to the upper torso and arm. The Sponsor believes that, even using a buttock application, the EE exposure will be less than that of a $(b) (4)$ μg OC. The Division did not agree to include the site-specific PK assessment within the phase 3 trial.

The Sponsor asked how many cycles per application site were needed. The Division requested an acceptable number of subjects using the application sites providing the highest and lowest exposure, so that safety and efficacy could be bracketed. Full safety evaluation will likely entail a large post-marketing study, similar to EURAS.

Post-Meeting Comment:

The Division agrees that the Sponsor may conduct the application site study in parallel to the phase 3 studies. As discussed at the meeting, there should be sufficient subjects in the phase 3 studies to allow evaluation of safety and efficacy of the various application sites should the PK differ among the application sites. Subjects in the phase 3 studies should be instructed to use the same application site throughout a 21-day patch cycle, and to document in the patient diary the application site used for a given cycle.

The Sponsor agreed to add the additional PK measurements to the Sponsor's proposed PK study as requested by the Division, and to conduct the external conditions study.

4. *Does the Agency agree that these studies are sufficient*

(b) (4)

(b) (4)

Division Response:

Labeling will be discussed during the NDA review cycle, and will depend upon the results of the studies submitted with the NDA.

5. *Does the Division agree that a single pivotal study will be adequate to support a NDA submission for AG200-15?*

Division Response:

No. The Division requests that the Sponsor conduct two clinical safety and efficacy trials. One should be 12 months in duration, and should enroll sufficient subjects to provide 10,000 cycles of exposure, with at least 200 subjects completing one year (13 cycles) of exposure. The other study, which could be a six-month trial, should utilize an oral contraceptive comparator containing 30 µg of ethinyl estradiol (EE) and 150 µg of levonorgestrel (LNG) in order to better compare the exposure, common adverse events, and bleeding profiles for the patch and the oral product. The Division requests that 200 subjects per arm be randomized in this trial.

The Division also requests that pharmacokinetic data be collected in both trials on all subjects. This will help identify whether there is marked inter- or intra-subject variability. Specifically, the Division requests the collection of EE and LNG levels at steady state at two points in each trial (Months 3 and 6 in the six-month trial and Months 6 and 12 in the 12-month trial).

Additional Discussion at the Meeting:

The Division suggested a 30 µg EE/150 µg LNG comparator so that safety and PK data could be compared to an OC product providing higher exposure than the AG200-15. The comparator product could not be used to help fulfill the 10,000 cycle requirement of exposure to the patch.

6. *Does the Division concur with this approach to defining and evaluation pregnancies?*

Division Response:

Yes, the Division agrees with the definition of "in-treatment" pregnancies as those with an estimated date of conception (EDC) from the date of first patch application through day 14 after the last patch removal, and agrees with the plan to provide both the Pearl Index and life table analyses.

7. *Does the Division concur with this method for determining the EDC?*

Division Response:

The Division recommends that ultrasound dating be obtained (as early as possible) for all pregnancies, as this is the most accurate method to determine the EDC. The date of the first positive pregnancy test may be helpful, but the quantitative β -hCG level is not accurate for EDC determination. EDC based on pelvic and/or abdominal examination is acceptable if no ultrasound data are available. Finally, diary information and investigator estimation of EDC are sometimes needed if no other useful information is available. In the case of uncertain or conflicting data, the Division may determine that a pregnancy occurred "in-treatment."

8. *Does the Division concur that the proposed study design will be sufficient to support an NDA submission for the Agile TCDS for the prevention of pregnancy?*

Division Response:

No, see response to Question 5. Submit the protocols for the phase 3 trials for review prior to initiating the studies. The Division has the following general comments based on the overview of the proposed study provided in the meeting package:

- The primary efficacy analysis should be based on the calculation of pregnancy rate using the Pearl Index and life table analyses based on women aged 18 to 35 years and excluding all cycles in which other birth control methods (including condoms) were used (the pregnancy intent-to-treat [ITT] population). However, pregnancies conceived during cycles in which other birth control methods were used should be included.
- Eliminate the exclusion criterion based on BMI. The Division emphasizes the need for safety data on hormonal contraceptives used by heavier women. If there is concern that heavier women may have a higher rate of pregnancy, it would be acceptable to define the pregnancy ITT population to include only women below a specified BMI. If approved, the labeled indication would note that the reported efficacy results apply only to women below that BMI.
- Eliminate the exclusion criterion for (b) (4). If this is retained, it will also be included in labeling.
- Concerning evaluation of cycle control, the Division considers that "early withdrawal flow" is unscheduled bleeding/spotting and not a part of "withdrawal flow."

Additional Discussion at the Meeting:

The Sponsor noted concern about safety and efficacy issues if heavier subjects are enrolled, and is concerned that the proportion of heavy subjects will be even greater than what is representative of the target population, since most other contraceptive trials impose BMI restrictions. The Division noted that it currently recommends against such BMI exclusions and will recommend restrictive labeling if such exclusion criteria are used. The Sponsor proposed including heavier women in only the OC comparator study; the Division found this potentially adequate to address the need for safety data, provided that the sample size was increased from the currently recommended 200/arm. The Sponsor will make a proposal for the Division's consideration. The Sponsor will also consider stratifying enrollment by weight, to ensure that the study population does not exceed the general population in the distribution of heavier women.

9. *Will a safety database of approximately 1350 subjects treated with the TCDS containing LNG/EE be sufficient to support an NDA submission for the prevention of pregnancy?*

Division Response:

The larger database as recommended in response to Question 5 should be sufficient to support an NDA submission.

10. *Given that there were no dermal safety issues in an aggregate of 346 women in varying and repetitive use situations, does the Division also concur that the human dermal safety study requirement has been satisfied and is sufficient to support an NDA submission?*

Division Response:

No. The following studies will be needed:

- A formal dermal safety study; this may be done in a subset of subjects in one of the phase 3 studies.
- A cold flow study to determine that active drug does not leak from the contraceptive patch onto the skin.

Additional Discussion at the Meeting:

The Sponsor has not done a distinct dermal safety study, but noted that Study 10 did include a formal evaluation of skin irritation weekly. Study 11 also provided data on skin irritation through adverse event reports. EE and LNG are not known to be phototoxins or photosensitizers. The Sponsor will review the absorption spectrum to evaluate the potential for these adverse effects. The Division asked for summary data for all subjects for whom skin irritation data has been collected, organized by formulation and dose to which they were exposed. Based on review of this data, and the capric acid toxicology literature to be submitted, the Division will readdress this request. The Division requested that the phase 3 protocol require skin inspections at each clinical visit, and that investigator's observations should be captured on a case report form (CRF) specifically intended to record the status of the application site. CRFs should be submitted for review along with the protocols, as should the diary used to capture medication compliance and bleeding data.

The Sponsor noted that the patch is a matrix system, not a reservoir; therefore, cold flow is not likely to be a clinical concern. The Sponsor will evaluate cold flow as requested in the response to Question 16.

11. *Does the division concur that evaluation of coagulation profile in the Phase III study as described in the draft study protocol is acceptable and is sufficient to support an NDA submission?*

Division Response:

A coagulation study is not required by the Division, and the Division has no recommendation as to the coagulation parameters to be evaluated if the Sponsor decides to conduct such a study.

12. *Does the Division concur with this regulatory pathway [505(b)(2)]?*

Division Response:

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003 response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

If the Sponsor intends to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, the Sponsor must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). The Sponsor should establish a "bridge" (e.g., via comparative bioavailability data) between the proposed drug product and each listed drug upon which the Sponsor proposes to rely in order to demonstrate that such reliance is scientifically justified. If the Sponsor intends to rely on literature or other studies for which it has no right of reference, but that are necessary for approval, the Sponsor also must establish that reliance on the studies described in the literature is scientifically appropriate.

The Sponsor should clarify what aspects of the submission would be supported by the 505(b)(2) pathway.

Additional Discussion at the Meeting:

The Sponsor asked if the Division could provide guidance on the adequacy of referenced literature to support the NDA. This would be reviewed by the Division as part of the NDA review.

13. *Does the Division concur clinical studies in females less than 18 years of age are not required?*

Division Response:

Although the Division recommends that the trials permit enrollment of women under the age of 18 years, it is not required.

Post-Meeting Comment:

As part of the NDA submission, the Sponsor should request a waiver for required pediatric trials. Pediatric studies for oral contraceptives are typically waived for premenarcheal females, and fulfilled through extrapolation from the adult trials for postmenarcheal females under age 18.

14. Does the FDA agree that the raw materials are suitable for the Phase 3 product and an NDA submission?

Division Response:

From a CMC standpoint, the raw materials appear to be suitable. Please identify the function of each excipient in the formulation. See the response to Question 2 for input from the Pharmacology/Toxicology reviewer.

15. Does the FDA agree that the test attributes and specification rationales are appropriate for Phase 3? In particular, the testing for (b) (4) is performed from samples collected during (b) (4). Is the plan to use three sample points for the drug release test acceptable?

Division Response:

Overall, the test attributes and specifications appear to be adequate for phase 3, with the following exceptions:

- Add a specification for (b) (4) in the dosage form
- Assay specifications should be set at (b) (4) % both at release and on stability (b) (4)
- In addition to the (b) (4) (b) (4)

For drug release, the Division agrees that testing at the current sampling times during the phase 3 trials is appropriate. Upon submission of the NDA, the Sponsor could request a reduction of the sampling time points, but this is a review issue and a final determination will be made at that time.

Additional Discussion at the Meeting:

The Sponsor requested assay specification of (b) (4) %. The Division would accept this now, but at the time of NDA submission, the Sponsor would need to provide data showing that the (b) (4) % specification is effective, or expiry might be affected.

16. Does the FDA agree that the stability plan with the proposed test attributes, storage conditions and intervals is acceptable to support Phase 3, an NDA submission and potential expiration date of 24 months?

Division Response:

Overall, the stability plan appears to be appropriate, with the following exceptions:

- Add a 6 month time point for the stability studies performed at accelerated conditions (40°C/75% RH).
- Add a specification for (b) (4) in the dosage form
- Expiry is an NDA review issue and will be set based upon evaluation of the submitted stability data.
- The dosage form should be monitored for the impact of the phenomena of "cold flow" on stability.

17. Does the FDA agree with the process development of [REDACTED] (b) (4) for the manufacturing process?

Division Response:

The process development [REDACTED] (b) (4) plans for the manufacturing process appear to be adequate.

Linked Applications

Sponsor Name

Drug Name

IND 57731

(b) (4)

(ETHINYL/ESTRADIOL/LEVONORGESTR
EL

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

/s/

LISA M SOULE

10/22/2008