U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	208352/000
Drug Name:	Amphora™ Gel
Indication(s):	Prevention of Pregnancy
Applicant:	Evofem, Inc.
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Biometrics Division:	Division of Biometrics III
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Keywords: NDA review, non-inferiority, Kaplan-Meier product limit

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1 EXECUTIVE SUMMARY

The information and data in this application do not support the efficacy of Amphora™ Gel for use in the prevention of pregnancy in adults 18 years of age and older. This conclusion is based on a single multinational Phase 3 study APM001.

APM001 was a multicenter, open-label, randomized, controlled, Phase III study of repeated use of Amphora™ Gel compared to Conceptrol® Vaginal Gel as the method of contraception over seven cycles of use. In addition, Amphora™ Gel subjects continued the study for up to 13 cycles of treatment upon completion of the first seven cycles of treatment. The primary efficacy objective was to demonstrate that the 6-month (7-cycles) cumulative pregnancy rate in Amphora™ Gel treated women is not inferior to Conception® Vaginal Gel treated women. To demonstrate non-inferiority, the upper bound of the 95% confidence interval for the treatment difference must be less than or equal to 5.5%.

The Applicant's analysis showed that the difference in pregnancy rate (Amphora™ minus Conceptrol®) was 0.5% (95% CI: -2.2%, 3.2%). Based on the upper bound of 3.2%, which was less than 5.5%, the Applicant concluded that Amphora™ Gel was not inferior to Conceptrol® Vaginal Gel.

However, this reviewer identified two major data and analysis issues: (i) inappropriate use of cycles (including cycles from the extension part of the study to replace non-evaluable cycles in the 7-cycle non-inferiority analysis and cycles that were out of the normal range)); and (ii) effect of regional (US vs Russia) differences in efficacy that have resulted in biased estimates. Cycles are considered non-evaluable if there are no diary data, no intercourse, or use of back-up or emergency contraception.

Following Division's advice, the Applicant resubmitted the analysis data and efficacy results. To address the above issues, the final efficacy analysis is based on revised cycle definition and US data only.

The final results showed that there was substantial reduction in the evaluable cycle number (less than half of the pre-specified 7,000 cycles) in the primary efficacy analysis. Further, we confirm that the treatment difference in the US population is 3.9% with the upper bound of the 95% confidence interval more than 5.5%. Therefore, the study failed to demonstrate that Amphora™ Gel is non-inferior to Conceptrol® Vaginal Gel.

From a statistical perspective, the information and data submitted by the Applicant do not provide evidence regarding the effectiveness of Amphora™ Gel, a non-hormonal vaginal contraceptive gel, indicated for use in the prevention of pregnancy in adults 18 years of age and older.

2 INTRODUCTION

2.1 Overview

The Applicant, Evofem Inc., seeks approval of Amphora™ Gel a non-hormonal vaginal contraceptive gel indicated for use in the prevention of pregnancy in adults 18 years of age and older.

According to the Applicant, Amphora™ Gel is an acid-buffering gel containing three active ingredients, 88 mg (1.76%) lactic acid, 50 mg (1.00%) citric acid, and 20 mg (0.40%) potassium bitartrate, in a 5 g dose (equivalent to 5 mL), which acidify the vaginal environment, immobilizing spermatozoa and thereby making Amphora™ gel spermicidal.

The Applicant has submitted one phase 3 clinical study (AMP001 CSR) conducted in the United States and Russia entitled "A Multicenter, Open-Label, Randomized Study of the Contraceptive Efficacy and Safety of Amphora™ Gel Compared to Conceptrol® Vaginal Gel," to evaluate the contraceptive efficacy and safety of Amphora™ Gel in preventing pregnancy in adult females 18 to 45 years of age. Table 1 presents a brief summary the study addressed in this review.

Table 1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
AMP001	Phase 3, open-label, Randomized, multicenter, active-controlled	7 cycles with a subset in Amphora™ group extend to 13 cycles	Amphora ™: 1,695 Conceptrol®: 1,694	Healthy, sexually active women at risk of pregnancy who desired contraception, aged 18 to 35 years with regular, normal, cyclic menses with a usual length of 21 to 40 days

Source: Reviewer's summary based on study reports.

2.2 Data Sources

The study data, reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\EVSPROD\NDA208352 under the submissions dated 07/06/2015, 10/30/2015, 03/10/2016, and 03/17/2016.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were several data and analysis quality issues noted by the reviewer in the original submission dated 07/06/2015, which are summarized as follows:

1) On-treatment pregnancy was not clearly defined.

   Per FDA, all pregnancies for which the estimated date of conception occurred during a cycle in which the subject considered the gel to be her primary method of contraception, or within 7 days after her last use of gel in the trial.

2) Primary endpoint is based on 6-month (183 days) cumulative pregnancy rate instead of 196 days as per Division's requirement in estimating 7-cycles cumulative pregnancy rate.

3) Use of cycles from the extension study window to replace non-evaluable cycles in the 7-cycle study that resulted in biased efficacy in favor of Amphora™ Gel.

4) The CRF did not identify the subject's cycle number at the time of entering the extension study and the extension start date was calculated post-hoc. Also the diary dataset did not flag the cycles collected in the extension part of the study. For the 7-cycle analysis, the "compressed cycle" was used by adding subsequent cycles to replace non-evaluable cycles up to cycle 17.

5) Integrity of the Russian data is questionable due to the following reasons:

   a. A pregnancy rate was far less than US data and also far below what was expected with use of a spermicide gel.
   b. Discontinuation rate was far lower than the US region and also lower than what would be expected for a clinical trial.

   Although the Division communicated this concern to the Applicant at the early review phase of this NDA, the Applicant has not provided adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data are generalizable to the US population. There are extensive differences in demographic, discontinuation rate, and efficacy outcomes among US and Russian populations. Therefore, this reviewer concludes that the Russian data is not applicable to the US populations.

To address the above issues, the Division asked the Applicant to clarify and update the related datasets to reflect that the subject's study duration in the 7-cycle analysis window is Cycle 1-7 only and no more than 196 days from the enrollment date. The impact of the cycle length issue is further discussed while Applicant's efficacy results are discussed and reviewed in section 3.2.4 and 3.2.5.

3.2 Evaluation of Efficacy

The efficacy evaluation of Amphora™ Gel is based on study AMP001.

3.2.1 Study Design

APM001 was a multicenter, open-label, randomized, controlled, Phase III study of repeated use of Amphora™ Gel compared to Conceptrol® Vaginal Gel as the method of contraception over seven cycles of use. In addition, there is an opportunity for Amphora™ Gel subjects to continue with study treatment for up to 13 cycles of treatment upon completion of the first seven cycles of treatment.

Healthy, sexually active women at risk of pregnancy who desired contraception, aged 18 to 45 years, with a single male sex partner, of which both partners were at low risk for HIV and sexually transmitted

disease (STD) infection. *Subjects were required to have regular, normal, cyclic menses with a usual length of 21 to 40 days*. Subjects were willing to engage in at least two acts of heterosexual vaginal intercourse each cycle and used the study product as the only method of contraception over the course of the study with the exception of emergency contraception (EC), when indicated. Subjects were capable of using the study product properly, recording a daily diary of coital information, product use information and sign and symptom data for both the subject and her partner. In a subset group, women aged 36 to 45 were enrolled to determine the effect of age on contraceptive efficacy; these women were required to meet all other eligibility criteria.

A summary of study assessments and procedures and the time points at which they were to be made during the study is presented in Table 2.

Table 2: Schedule of Assessments

Procedures	Visit 1 Screening	Visit 2 Admission	Visit 3 After Cycle 1	Visit 4 After Cycle 3	Between Cycles 3 and 7	Visit 5 [A] After Cycle 7/ Exit Visit	Visit 6 [B] After Cycle 10	Visit 7 [B] After Cycle 13/ Extension Exit
Informed Consent	X							
Eligibility (Inclusion/Exclusion)	X	X						
Medical/Gyn History	X							
Demographics	X							
Randomization		X						
Prior 6 month History of contraceptive use	X							
Pre-Trial Medications	X	X						
Vital Signs[C]	X	X	X	X		X	X	X
CBC and Chemistry[D]	X					X		X
Gynecological Exam[E]	X		X	X		X	X	X
Colposcopy (10x)[F]		X	X	X		X	X	X
Pap Test	X[G]					X		X
Chlamydia/Gonorrhea Test[H]	X					X		X
BV Assessments[I]	X		X	X		X	X	X
Quantitative and Semi-quantitative Vaginal Culture[J]		X	X	X[K]		X	X[K]	X
Urine Culture[L]	X					X		X
Dipstick Urinalysis[M,N]			X	X			X	
Urine Pregnancy Test [O]	X	X[P]	X	X		X[P]	X	X[P]
Dispense/Review diaries	X	X	X	X		X	X	X
Dispense Study Drug		X	X	X		X	X	X
Drug Return and Accountability			X	X		X	X	X
Dispense Home Pregnancy Test Kit		X				X		X
Acceptability Questionnaire[Q]			X			X		X
Discomfort Questionnaire			X	X		X	X	X
Adverse Events	X	X	X	X		X	X	X
Concomitant Meds		X[T]	X	X		X	X	X
Between-Visit Contact		X[R]			X[S]			

A. Treatment was to end after 7 cycles for subjects who do not continue into the extension; Amphora™ subjects were given an opportunity to extend treatment to 13 cycles
B. Visit 6 and 7 procedures were only performed on subjects who continued Amphora™ treatment
C. Height, weight, and blood pressure were recorded at screening; only weight and blood pressure was recorded at subsequent visits

Source: Table 9-1 in AMP001 study report.

Eligibility determination and screening were performed at a screening visit. Participants were given weekly coital diaries at this visit and given instructions on how to complete the diary. Participants returned for an admission visit within six weeks of the screening visit.

At the admission visit, participants were randomized to treatment group using a computerized randomization tool. Coital diaries were reviewed to determine eligibility for enrollment. Participants were provided with 2 home pregnancy kits, coital diaries, and test product and given instructions on how to use them. They were also reminded of their right to use Emergency Contraception during the study. Participants were instructed check a pregnancy test 2 weeks after the admission visit.

Participants returned for follow up visits after cycle 1, cycle 3 and cycle 7 where pregnancy and adverse events were assessed, discomfort and acceptability questionnaires were administered, physical (including gynecologic) examination was performed and lab assessments were collected. Following cycle 7 participants only in Amphora™ Gel group were invited to participate in a 13 cycle extension trial. If they chose not to participate an exit visit was to be performed.

Simulation methods were used to evaluate the likelihood of various sample sizes providing enough information to test the primary hypothesis (one-sided Type I error of 0.025). The simulations assumed the following:

- 31% of cycles have backup contraceptive use and are excluded from analysis
- 6.5-12% of subjects fail to provide at least one diary for evaluation
- Exponential hazard for:
  - Pregnancy rate first 6 months: 13-15%
  - Pregnancy rate last 6 months: 6%
  - Dropout rate for month 1: 10%;
  - Dropout rate for months 2-6: 38%;
  - Dropout rate for months 7-12: 16.5%

With 2,600 subjects aged 18 through 35 years (inclusive) randomized in a 1:1 ratio to use either Amphora™ or Conceptrol®, the power was 80-88% and it was estimated that 7,000 cycles of Amphora™ Gel use would be recorded. In addition, it was assumed that 40-55% of the Amphora™ Gel group who completed 7 cycles of use would continue into the 13 cycle-extension with Amphora™ Gel. When women aged 36 through 45 years old (inclusive) at entry were included, it was anticipated 209-289 subjects would complete one year (13 cycles) of use.

However, during a review of incoming data revealed that in trial planning, the Applicant found out that the number of missing diaries and the number and timing of early discontinuations was underestimated. The 500 additional subjects were enrolled from sites in the United States and Russia; thus, the total estimated sample size for the study increased to 3,300. There were 62 clinical research sites (49 from the United States and 13 from Russia) that participated in the trial.

3.2.2 Statistical Methodologies

3.2.2.1 Analysis Populations

The following analysis populations were pre-specified in the protocol:

Intent-To-Treat (ITT): Subjects randomized into the study.

All Treated (ATD): ITT subjects who used at least one application of the study drug.

Modified Intent-To-Treat (MITT): ITT subjects whose diaries indicated they had at least one episode of coitus while using the assigned study product (also referred as "Typical-Use"), between 18 to 35 years of age (inclusive) at enrollment, had at least 1 cycle without any backup contraception or EC, and for whom there was at least one report of pregnancy status. Cycles in which backup contraception or EC was used were removed and the remaining cycles were compressed to provide contiguous cycles.

Efficacy Evaluable (EE): a subset of the MITT population that includes only those subjects whose diaries indicated they used the assigned study product correctly for every intercourse for at least one menstrual cycle (also referred as "Perfect-Use" or "Per Protocol"). Cycles in which the study product was used incorrectly for one or more coital acts were removed, and the correct use cycles were compressed to provide contiguous cycles of correct use.

MITT7: In the pre-NDA meeting held on December 09, 2014, the Division reiterated that on-treatment pregnancy is defined as any conceptions that occur within 7 days after the last use of the Gel. Therefore, the Applicant defined a new analysis population (MITT7) using the corrected definition of on-treatment pregnancy. The only difference between the MITT and MITT7 population is the on-treatment pregnancy definition.

During the early review of this NDA including the SAS coding, we noted that the on-treatment pregnancy was not clearly defined. The Applicant was requested to provide a clear definition of on-treatment pregnancies as well as updated analysis results.

In order to address the FDA requests, the Applicant has created another analysis population FDA MITT7 using the following FDA recommended on-treatment pregnancy definition:

- All pregnancies for which the estimated date of conception occurred during a cycle in which the subject considered the gel to be her primary method of contraception, or within 7 days after her last use of gel in the trial.

3.2.2.2 Primary Efficacy Endpoint and Analysis

The Primary efficacy endpoint is the cumulative probability of typical-use 6-month (183 days) of Amphora™ Gel compared to Conceptrol® Vaginal Gel. MITT population is the primary efficacy population. Typical-Use referred to subjects whose diaries indicated they had at least one episode of coitus while using the assigned study product.

The primary hypothesis to be tested is whether subjects administered Amphora™ Gel has a six-month cumulative pregnancy probability that is not inferior to that of subjects using Conceptrol® Vaginal Gel. Using Blackwelder's approach for non-inferiority testing, the null and alternative hypotheses are expressed as:

$$\text{Ho: } \pi_A > \pi_C + 0.055$$

$$\text{VS} \quad H_A: \ \pi_A \leq \pi_C + 0.055$$

Where π_A and π_C represent the six-month cumulative pregnancy probabilities for Amphora™ Gel and Conceptrol® Vaginal Gel, respectively.

Kaplan-Meier methods were used to estimate the six-month cumulative pregnancy probability of women in the MITT population by treatment group. Any pregnancies that occurred prior to

randomization or post-discontinuation from the study were excluded. Greenwood's method for calculating variance was used to construct 95% confidence intervals.

The non-inferiority hypothesis was tested by calculating a 95% confidence interval for the treatment differences. If the upper bound for the confidence interval of the difference was < 5.5, then the null hypothesis would be rejected.

Reviewer's Comment

During the pre-NDA meeting held on December 09, 2014, the Division pointed out that the Statistical Analysis Plan (SAP) for study AMP0001 had not been submitted for review, but the Applicant did not follow through in submitting the final SAP prior to NDA submission.

Although this was a seven cycle study, the primary endpoint which the Applicant pre-specified was the cumulative probability of typical-use 6-month (183 days). In the 74-Day Filling Review Issues letter dated September 11, 2015, the Division advised the Applicant the pregnancy rates for contraceptive products are typically based on 7-cycle (196 day) trial period, 28 day per cycle.

In the early review phase of this NDA, we also identified the cumulative pregnancy rates of the US and Russian population is dramatically different. In addition to pregnancy rates, these populations were also differed with regards to discontinuation rate, weight, and BMI. The concerns were communicated to the sponsor in the 74-Day Filling Review Issues letter. Although the Applicant provided response to these review issues, however, we believed that the Applicant did not provide adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data is generalizable to the US population.

Therefore from this point on, all the analyses are presented separately by region, US versus Russia. The primary analyses are based on FDA MITT7 population. The primary endpoint would be 7-cycles (196 days) cumulative pregnancy rate.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Details of subject disposition in study AMP001 are summarized in Table 3. Discrepancies in subject disposition were similar by arm but, were significantly different by country. US participants in each arm discontinued the trial at a rate of approximately 47% for reasons other than pregnancy or adverse event, while over 96% of Russian participants completed the study and much less likely to experience pregnancy compared to US participants. According to the clinical reviewer, the pregnancy rates in Russian sites were also much lower than in previously published spermicide trials evaluating efficacy of spermicide gels and not comparable to the US population.

The low completion rate in the trial and the number of premature discontinuations in the US population is problematic as it yields poor quality trial data.

Table 3: Subject Disposition

	US				Russia			
	Amphora Gel™ n (%)		Conceptrol® n (%)		Amphora Gel™ n (%)		Conceptrol® n (%)	
Enroll	1,371		1,376		324		318	
Age 18 - 35	1,256		1,289		324		318	
ITT	1,341		1,342		324		317	
ATD	1,135		1,160		324		316	
FDA MITT7	971	100%	999	100%	323	100%	316	100%
Completed Treatment	355	37%	401	40%	310	96%	307	97%
Pregnancy	136	14%	119	12%	9	3%	4	1%
Discontinued Prematurely	480	49%	479	48%	4	1%	5	2%
Reasons for Discontinuation								
Lost to Follow-up	180	19%	165	17%	0	0%	0	0%
Withdrew Consent	101	10%	114	11%	1	0%	0	0%
Protocol Deviation	103	11%	112	11%	1	0%	3	1%
Not sexually active	22	2%	15	2%	2	1%	0	0%
Adverse Event	18	2%	19	2%	0	0%	0	0%
Investigator/Sponsor Decision	17	2%	19	2%	0	0%	0	0%
no longer primary method	10	1%	7	1%	0	0%	0	0%
Other	29	3%	28	2%	0	0%	2	0%

Source: Reviewer's analysis.

Because the large discrepancy between the number of subjects in the Intent to Treat (ITT) population and FDA-MITT7, the demographics and baseline characteristics of the treatment groups are summarized in Table 4 by region using FDA-MITT7 population. Overall, the demographic and baseline characteristics appear to be balanced across treatment groups but differed significantly across regions for race, ethnicity, body weight and BMI.

The majorities of subjects in U.S. were white (54%), followed by black (35%) and other races, among which 30% were Hispanic or Latino. In Russia region 100% of subjects were white and only one subject was Hispanic or Latino.

The mean BMI in U.S. subjects was greater than 29 kg/m^2, while the mean BMI in Russia subjects was 22 kg/m^2. Almost all of the subjects with BMI 30 kg/m^2 or greater were from U.S. region (40% US region, 3% Russia). Also over 40% of the U.S. subjects weighted greater than 175 kg and only less than 6% of the Russian subjects weighted greater than 175kg.

Table 4: Demographics and Baseline Characteristics (FDA-MITT7 Population)

Demographic and Baseline	US		Russia	
	Amphora™ N=971 n (%)	**Conceptrol® N=999 n (%)**	**Amphora™ N=324 n (%)**	**Conceptrol® N=316 n (%)**
Age (years)				
Mean years (SD)	26.9 (4.6)	26.9 (4.7)	26.8 (4.7)	26.6 (4.4)
Median years	27	27	26	26
Race				
White	507 (52)	548 (55)	323 (100)	326 (100)
Black or African American	345 (36)	338 (34)	0 (0)	0 (0)
Asian	28 (3)	33 (3)	0 (0)	0 (0)
Other	78 (9)	73 (8)	0 (0)	0 (0)
Ethnicity				
Hispanic or Latino	291 (30)	289 (29)	322 (100)	316 (100)
Not Hispanic or Latino	679 (70)	710 (71)	1 (0)	0 (0)
Weight (kg)				
Mean weight (SD)	175 (52)	171 (49)	133 (23)	132 (24)
Median weight	163	161	130	128
Weight < 175	565 (58)	595 (60)	305 (94)	300 (95)
Weight $\geq$ 175	406 (42)	401 (40)	18 (6)	16 (5)
BMI (kg/m^2)				
Mean BMI (SD)	30 (8)	29 (8)	22 (3)	22 (4)
Median BMI	28	28	21	21
BMI < 30	570 (59)	605 (61)	313 (97)	308 (97)
BMI $\geq$ 30	399 (41)	391 (39)	10 (3)	8 (3)

Source: Reviewer's analysis.

3.2.4 Applicant's Original Efficacy Results and Conclusions

The primary efficacy endpoint was the cumulative percentage of typical-use 6-month (183 days) pregnancy. The Applicant's primary analysis was conducted using Kaplan-Meier methods to estimate the six-month cumulative pregnancy probability of women in the MITT population by treatment group. The non-inferiority hypothesis was tested by calculating a 95% confidence interval for the difference. If the upper bound for the confidence interval of the difference was < 5.5, then the null hypothesis would be rejected.

The results based on the pre-specified analysis are summarized in Table 5. The results showed that the difference in pregnancy percentages (Amphora™ minus Conceptrol®) was 0.5% (95% CI: -2.2%, 3.2%). The Applicant thus concluded that since the upper bound of the 95% CI for the difference in pregnancy percentages was less than the non-inferiority margin of 5.5%, Amphora™ Gel was not inferior to Conceptrol® Vaginal Gel.

Table 5: Six-Month (183 Day) Cumulative Pregnancy Percentages (MITT Population)

Six-Month Pregnancy Percentage	Amphora™ (N=1,292)	Conceptrol® (N=1,314)	Difference [2]
Number of Subjects at Risk of Pregnancy at the Time of Randomization [1]	1,259	1,281	
Number of Pregnancies on or before Day 183	111	100	
Six-Month (183 days) Cumulative Pregnancy Percentage	10.5%	10.0%	0.5%
95% CI for Pregnancy Percentage	(8.6%, 12.3%)	(8.1%, 11.9%)	(-2.2%, 3.2%)

[1]Excludes MITT subjects who had a pregnancy detected after being randomized but the pregnancy was determined to have started before the randomization date. Subjects with no cycles without backup or EC are excluded unless they became pregnant while on study.
[2]Difference = Amphora™ – Conceptrol®. If the upper bound of the confidence interval at 6 months is ≤ 5.5%, we conclude non-inferiority
Source: Table 11-4 in AMP001 study report.

During the review of this NDA, we found two major review issues which would significantly impact the efficacy results besides the region differences. First, because the Applicant did not collect information in the CRF to identify the subject's cycle number at the time of entering the extension study as pointed out in section 3.1, cycles from the extension study window were used to replace non-evaluable cycles in the 7-cycle analysis. Second, lengths of many cycles included in the original primary efficacy analysis fall outside normal range of 21 to 42 days.

In a teleconference on February 10, 2016, the Applicant acknowledged that cycles observed in the Amphora™ arm in the extension part of the study (beyond Cycle 7) were used to supplement the 7 cycle non-inferiority analysis. As showed in Table 6, most of the cycles beyond cycle 7 were only collected in Amphora™ Gel treatment arm and not in active comparator Conceptrol® treatment arm. Therefore, using cycles occurring in the extension study did bias the non-inferiority test in favor of Amphora™ Gel.

Table 6: Cycle Distribution (FDA-MITT7 Population)

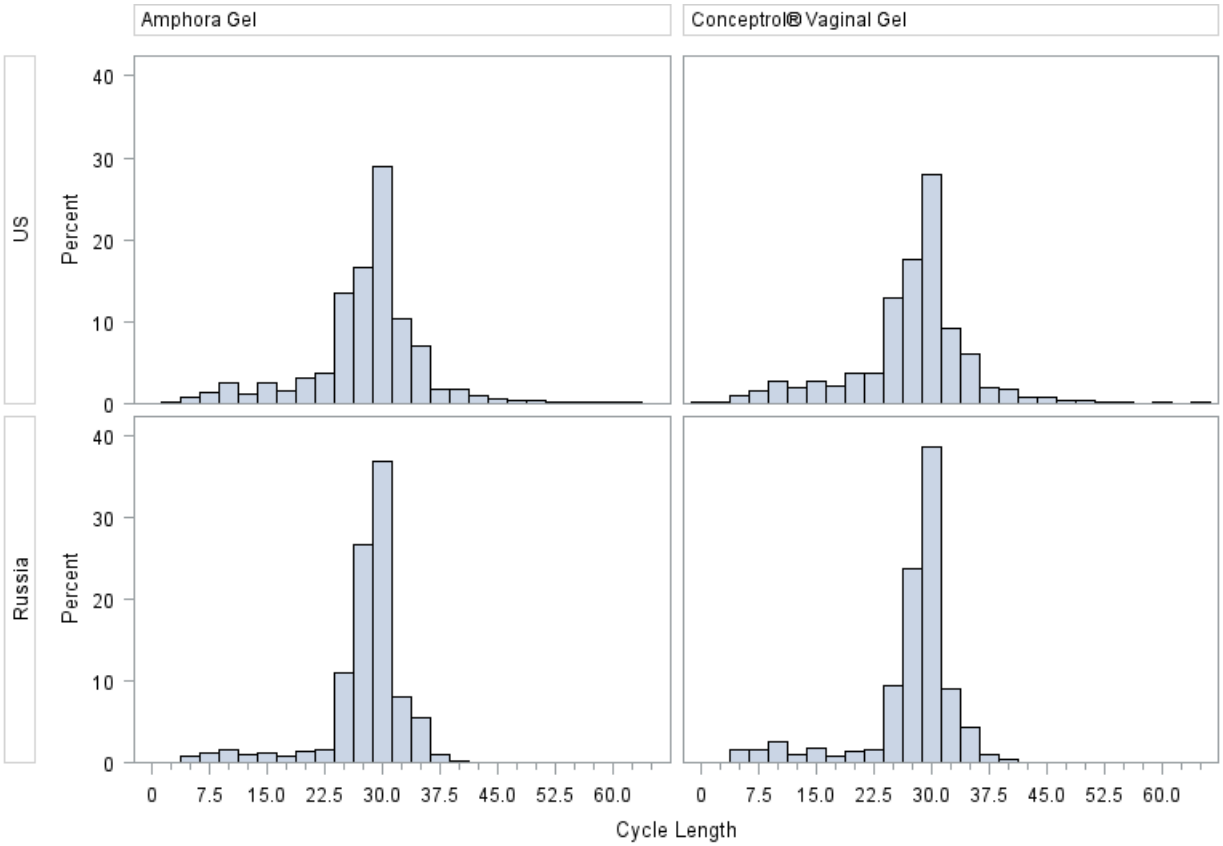
Diary Cycle	US		Russia	
	Amphora™	Conceptrol®	Amphora™	Conceptrol®
Cycle 0	936	965	297	288
Cycle 1	945	979	322	313
Cycle 2	887	912	319	311
Cycle 3	788	808	318	311
Cycle 4	711	718	316	309
Cycle 5	619	612	315	309
Cycle 6	566	576	314	307
Cycle 7	536	543	313	307
Cycle 8	430	421	311	303
Cycle 9	248	105	135	31
Cycle 10	194	22	111	9
Cycle 11	180	9	105	1
Cycle 12	168	4	103	
Cycle 13	160	2	103	
Cycle 14	143	1	100	
Cycle 15	28		19	
Cycle 16	10		1	
Cycle 17	4			

Source: Reviewer's analysis.

Although the subjects entered the study were required to have regular, normal, cyclic menses with a usual length of 21 to 40 days, as depicted in Figures 1, lengths of many of the cycles included in the original efficacy analysis fall outside of 21 to 42 days which is also physiologically expected length for ovulatory cycles. The Division believed that these cycles should not be counted as evaluable cycles.

Furthermore, regional heterogeneity (unexpectedly favorable efficacy in Russia) has impacted the overall point estimate in favor Amphora™ Gel.

Figure 1: Distribution of Cycle Length (FDA-MITT7 Population)



Note: Means of cycle length around 28 days and median 29 days with STD of 13 and 6 in the US and Russia, respectively; Range of the cycle length was 1 – 468 days and 1 to 69 days in US and Russia region, respectively.

Source: Reviewer's analysis.

3.2.5 Final Efficacy Results and Conclusions

After the discussion on February 10, 2016, a finalized Information Request (IR) was sent to the Applicant on February 26, 2016. In the IR, the Division clearly defined that the cycles to be included in the 7 cycle analysis are Cycles 1-7, through a maximum of 196 days. Efficacy analysis should begin on Day 1 of menses of Cycle 1. Also the diary cycle should be considered non-evaluable if:

- The subject did not enter any diary data during a given cycle
- The subject did not have any intercourse during a given cycle
- The subject used back-up or emergency contraception at any time during a given cycle
- In addition, in accord with your entry criteria, the typical cycle length should be ≥21 days and ≤42 days. Cycles outside these limits should be excluded from analysis.

Per Division's request, the Applicant addressed all the data issues and provided revised datasets and final efficacy results in the submission dated 03/01/2016, 03/10/2016 and 03/17/2016. This reviewer confirmed these results. The summary of primary efficacy results using evaluable cycles (exclude cycles that are ≤ 21 days or ≥ 42 days in length) is summarized in Table 7. As showed in Table 7, the upper bounds of the

95% confidence intervals for the difference in 7-cycles cumulative pregnancy rates were 8.9% in the US population (exceeding the non-inferiority margin of 5.5%), demonstrating that Amphora Gel™ was not as effective as Conceptrol® Vaginal Gel. As previously mentioned in this review, Russian data was not included in the final primary efficacy analysis due to large discrepancies in regards to demographics, discontinuation rates and cumulative pregnancy percentages.

Further note that there were only 3,232 evaluable cycles in Amphora™ Gel treatment arm in the FDA-MITT7 population which is less than half of the pre-specified 7,000 cycles in the primary efficacy analysis, thus no valid conclusion can be draw from these limited available data. This was also considerably less than the 5,000 that was recommended for the evaluation of efficacy and safety by the Division.

Table 7: Cumulative Pregnancy Rate by Region, FDA MITT7 Population

	US		Russia	
	Amphora™	**Conceptrol®**	**Amphora™**	**Conceptrol®**
FDA-MITT7	971	999	323	316
# of Subjects at Risk of Pregnancy at the Time of Enrollment	823	859	320	310
Number of On-treatment Pregnancies	98	87	6	4
7-Cycles Cumulative Pregnancy Rate (196 days)	18.0%	14.1%	2.1%	1.3%
7-Cycles 95% CI	(14.0%, 22.1%)	(11.2%, 17.1%)	(0.4%, 3.7%)	(0.0%, 2.6%)
Treatment Differences	3.9% (-1.1%, 8.9%)		0.8% (-1.3%, 2.9%)	
Number of Evaluable Cycles*	3,232	3,229	2,082	1,992

*Exclude cycles that are ≤ 21 days or ≥ 42 days in length
Source: Table 14.2.41 in study report and Reviewer's analysis.

Results of sensitivity analysis using all cycles (including cycles that are ≤ 21 days or ≥ 42 days in length) (Table 8) and Applicant's pre-specified primary endpoint of 6-month (183 days) cumulative pregnancy rate for evaluable cycles and all cycles (Table 9 and Table 10;APPENDIX) showed that the upper bounds of the 95% confidence intervals exceeding the non-inferiority margin of 5.5% in the U.S. population.

Table 8: Cumulative Pregnancy Rate by Region (All Cycles), FDA-MITT7 population

	US		Russia	
	Amphora™	**Conceptrol®**	**Amphora™**	**Conceptrol®**
FDA-MITT7	971	999	323	316
# Subjects at Risk of Pregnancy at the Time of Enrollment	849	895	320	310
Number of On-treatment Pregnancies	98	87	6	4
7-Cycles Cumulative Pregnancy Rate (196 days)	16.8%	13.8%	2.1%	1.3%
7-Cycles 95% CI	(13.3%, 20.2%)	(10.9%, 16.7%)	(0.4%, 3.7%)	(0.0%, 2.6%)
Treatment Differences	3.0% (-1.5%, 7.5%)		0.2% (-1.6%, 2.1%)	
Number of All Cycles*	4,572	4,722	2,186	2,129

* Include cycles that are ≤ 21 days or ≥ 42 days in length
Source: Table 14.2.43 in study report and Reviewer's analysis.

Failure to demonstrate non-inferiority of Amphora Gel™ to Conceptrol® Vaginal Gel in the U.S. population did not warrant further subgroup analyses.

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

During the review of the original NDA submission, we have noted the following data definition and statistical issues with regards to efficacy analysis.

1. On-treatment pregnancy was not clearly defined.
   Per FDA, all pregnancies for which the estimated date of conception occurred during a cycle in which the subject considered the gel to be her primary method of contraception, or within 7 days after her last use of gel in the trial.
2. Primary endpoint is based on 6-month (183 days) cumulative pregnancy rate instead of 7-cycles (196 days) cumulative pregnancy rate as per Division's requirement in estimating 7-cycles cumulative pregnancy rate.
3. Regional heterogeneity in efficacy.

   Although the Division communicated this concern to the Applicant at the early review phase of this NDA, the Applicant has not provided adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data are generalizable to the US population. There are extensive differences in demographic, discontinuation rate, and efficacy outcomes among US and Russian populations. Therefore, this reviewer concludes that the Russian data is not applicable to the US populations.
4. Use of cycles from the extension study window to replace non-evaluable cycles in the 7-cycle study that resulted in biased efficacy in favor of Amphora™ Gel.

   The CRF did not identify the subject's cycle number at the time of entering the extension study and the extension start date was a calculated post-hoc. Also the diary dataset did not flag the cycles collected in the extension part of the study. For the 7-cycle analysis, the "compressed cycle" was used by adding subsequent cycles to replace non-evaluable cycles up to cycle 17.
5. Lengths of many cycles included in the original efficacy analysis fall outside of 21 to 40 days.

4.2 Conclusions and Recommendations

Based on the corrected datasets, the results did not demonstrate that Amphora™ Gel was non-inferior to Conceptrol® Vaginal Gel in the US. From a statistical perspective, the information and data submitted by the Applicant with one controlled study do not provide evidence regarding the effectiveness of Amphora™ Gel, a non-hormonal vaginal contraceptive gel, indicated for use in the prevention of pregnancy in adults 18 years of age and older.

APPENDIX

Sensitivity Analyses

Table 9: Six-Month (183 days) Cumulative Pregnancy Rate by Region, FDA-MITT7 Population

	US		Russia	
	Amphora™	**Conceptrol®**	**Amphora™**	**Conceptrol®**
FDA-MITT7	971	999	323	316
# Subjects at Risk of Pregnancy at the Time of Enrollment	823	859	320	310
Number of On-treatment Pregnancies	96	87	4	4
Six-Month Cumulative Pregnancy Rate (183 days)	16.6%	14.1%	1.3%	1.3%
Six-Month 95% CI	(13.0%, 20.1%)	(11.2%, 17.1%)	(0.0%, 2.5%)	(0.0%, 2.6%)
Treatment Differences	2.4% (-2.2%, 7.1%)		-0.1% (-1.8%, 1.7%)	
Number of Evaluable Cycles*	3,232	3,229	2,082	1,992

*Exclude cycles that are ≤ 21 days or ≥ 42 days in length
Source: Table 14.2.41 in study report and Reviewer's analysis.

Table 10: Six-Month (183 days) Cumulative Pregnancy Rate by Region, FDA-MITT7 Population

	US		Russia	
	Amphora™	**Conceptrol®**	**Amphora™**	**Conceptrol®**
FDA-MITT7	971	999	323	316
# Subjects at Risk of Pregnancy at the Time of Enrollment	849	895	320	310
Number of On-treatment Pregnancies	96	87	4	4
Six-Month Cumulative Pregnancy Rate (183 days)	15.7%	13.8%	1.3%	1.3%
Six-Month 95% CI	(12.5%, 18.9%)	(10.9%, 16.7%)	(0.0%, 2.5%)	(0.0%, 2.6%)
Treatment Differences	1.9% (-2.4%, 6.2%)		-0.1% (-1.8%, 1.7%)	
Number of All Cycles*	4,572	4,722	2,186	2,129

* Include cycles that are ≤ 21 days or ≥ 42 days in length
Source: Table 14.2.43 in study report and Reviewer's analysis.

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/s/

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04/15/2016

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