



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
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Re: Docket No. FDA-2013-P-0664

Dear Dr. Barber:

This letter responds to your citizen petition dated June 3, 2013 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) take certain actions with respect to generic¹ versions of Crinone (progesterone gel) 4 percent and 8 percent that are submitted in an abbreviated new drug application (ANDA). Specifically, you request that FDA:

1. Refuse to approve any ANDA for a generic version of Crinone unless and until the ANDA's sponsor demonstrates bioequivalence in both a bioequivalence study with pharmacokinetic endpoints (PK study) and a bioequivalence study with a clinical endpoint (clinical endpoint study)
2. Issue a draft guidance on progesterone gel that identifies the bioequivalence studies mentioned in the first item and is consistent with the Agency's draft guidance on progesterone (reference listed drug: Endometrin), recommended in September 2012.²

As explained below, the requests in your Petition are granted in part and denied in part.

I. BACKGROUND

A. Crinone (Progesterone) and Progesterone Gel Bioequivalence

Crinone (progesterone gel) (new drug application (NDA) 020756), 8 percent was approved by FDA on May 13, 1997, for progesterone supplementation or replacement as

¹ For the purpose of this response, the term *generic* refers to a drug product for which approval is sought in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)).

² FDA's *Draft Guidance on Progesterone* (September 2012) (2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance) is available on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency. Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland.³ In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

On July 31, 1997, we approved Crinone, 4 percent, for treatment of secondary amenorrhea and also approved Crinone, 8 percent, for treatment of secondary amenorrhea in women who failed to respond to treatment with Crinone, 4 percent (NDA 020701). Crinone is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, polypropylene vaginal applicators. Each applicator delivers 1.125 grams of Crinone gel containing either 45 milligrams (mg) (4 percent gel) or 90 mg (8 percent gel) of progesterone.

B. Endometrin (Progesterone Vaginal Insert)

Endometrin (progesterone) vaginal insert (NDA 022057), 100 mg, was approved by FDA on June 21, 2007, to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an ART treatment program for infertile women. Endometrin vaginal insert contains micronized progesterone. It is supplied with polyethylene vaginal applicators. Endometrin, 100 mg, is administered vaginally two or three times daily starting the day after oocyte retrieval and continuing for up to 10 weeks total duration.

C. Statutory and Regulatory Standards

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), which established the ANDA approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant can rely on FDA's previous finding that the reference listed drug (RLD) is safe and effective.⁴ The ANDA applicant must identify the listed drug on which it seeks to rely, and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.

³ See the CLINICAL PHARMACOLOGY section of Crinone's labeling (revised August 2013), available on the internet at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020701s026lbl.pdf.

⁴ A *reference listed drug* (RLD) is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as the Orange Book).

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.⁵ Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .⁶

Section 505(j)(8)(C) of the FD&C Act provides that

[f]or a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

In 21 CFR 320.1(e), FDA defines bioequivalence (in pertinent part) as

... the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action.

The statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include *in vivo* data (data from a study on human subjects) or *in vitro* data (data from laboratory studies).⁷

⁵ See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring “information to show that the new drug is bioequivalent to the listed drug”); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the RLD); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

⁶ See also 21 CFR 320.1(e) and 320.23(b).

⁷ See section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision “vests the FDA with the discretion to determine whether *in vivo* or *in vitro* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated approval processes”).

FDA's regulations describe the types of evidence that may be used to establish bioequivalence:

FDA may require *in vivo or in vitro testing, or both*, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.⁸

Section 320.24(b) of FDA's regulations describes preferred bioequivalence methods in the generally descending order of accuracy, sensitivity, and reproducibility.⁹ They include: (1) in vivo pharmacokinetic studies in whole blood, plasma, serum, or other appropriate biological fluid, or in vitro tests that have been correlated with and are predictive of human in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety and, when appropriate, its active metabolites, are measured; (3) in vivo pharmacodynamic effect studies; (4) clinical endpoint studies; and (5) in vitro studies acceptable to FDA that ensure human in vivo availability.¹⁰ In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulation states that FDA has the authority to use “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence.”¹¹

The Agency's authority to make bioequivalence determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards for approval;¹² (2) permitting the Agency to use the latest scientific

⁸ 21 CFR 320.24(a) (emphasis added). In the preamble to the 1992 final rule, FDA explained that, depending upon the drug, the Agency would determine the appropriate bioequivalence methodology on a case-by-case basis.

Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . is determined on a case-by-case basis, depending on the drug under study (*Abbreviated New Drug Application Regulations, Final Rule*, 57 FR 17950, 17972 (Apr. 28, 1992) (emphasis added)).

⁹ This general descending order of methodologies is not applicable to many locally acting drug products due to characteristics of those products that differ from most systemically acting drug products.

¹⁰ 21 CFR 320.24(b).

¹¹ Id.; see also *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 20 (D.D.C. 2009) (quoting 21 CFR 320.24(b) in upholding FDA sameness determination of generic drug product).

¹² 21 CFR 320.25(a) (stating that a “guiding principle” for the conduct of an in vivo bioavailability study is that “that no unnecessary human research should be done”); *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR 28872, 28883 (July 10, 1989) (in discussing section 320.22, stating that “the agency does not believe that Congress intended that unnecessary human research be conducted . . . if

advances in approving drug products;¹³ (3) protecting the public by ensuring only safe effective generic drugs are approved for marketing;¹⁴ and (4) making more safe and effective generic drugs available.¹⁵

For systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biological fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers.¹⁶

By contrast, a traditional in vivo bioequivalence study comparing the rate and extent of absorption of the active ingredient into the blood stream is usually of limited utility for locally acting, non-systemically absorbed drug products. In certain instances, therefore, FDA has determined that an ANDA applicant for such a product may establish bioequivalence using in vivo studies with a clinical endpoint or endpoints. In addition, for certain locally acting, non-systemically absorbed products with formulations having the same qualitative (Q1) and quantitative (Q2) composition as the RLD, FDA has determined that an ANDA applicant may demonstrate bioequivalence using specified in vitro methods. A showing of bioequivalence, along with satisfaction of other requirements for an ANDA, will generally permit FDA to conclude that the proposed generic drug can be expected to behave in the same way as the RLD when applied to the body.

The choice of appropriate bioequivalence study design is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug, and Congress assigned this decision to FDA. Congress intended to grant FDA wide

the agency concludes that bioequivalence can be demonstrated by in vitro tests, the agency proposes to require only such tests rather than in vivo studies.”).

¹³ *Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement*, 42 FR 1624, 1629 (Jan. 7, 1977) (“As with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement.”).

¹⁴ *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992) (citing as one underlying policy of the Hatch-Waxman Amendments is to “ensure the safety of these drugs before they are substituted for their name-brand counterparts”).

¹⁵ Id. (purposes of Hatch-Waxman Amendments are “to make more inexpensive generic drugs available” and “to ensure the safety of these drugs”); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (bioequivalence waiver provision “comports with the structure and broader policy objectives of the Hatch-Waxman Act,” including making safe and affordable generic drugs available).

¹⁶ Section 505(j)(8)(B) of the FD&C Act; FDA guidance for industry, on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*, at 6 (Mar. 2003), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, at 6.

discretion to establish bioequivalence standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments, and courts have recognized FDA's discretion to determine how the bioequivalence requirement should be met for a product or class of products, so long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."¹⁷ Courts that have considered FDA's bioequivalence determinations have consistently upheld the aspects of FDA's implementation of the FD&C Act's bioequivalence requirements at issue in those cases.¹⁸

D. Progesterone Bioequivalence Recommendations

1. Endometrin (Progesterone Vaginal Insert)

In September 2012, we posted on our Web site the 2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance¹⁹ to support ANDAs for this product. We recommended two *in vivo* studies to demonstrate bioequivalence of generic progesterone vaginal inserts: (1) a fasting PK study in healthy premenopausal, nonpregnant females and (2) a clinical endpoint study in infertile women participating in an ART treatment program.

2. Crinone (Progesterone Gel)

Today we posted on our Web site a draft bioequivalence guidance on progesterone gel.²⁰ In this 2015 Progesterone Gel Draft Bioequivalence Guidance, we recommend that when the test product is found to be Q1 and Q2 the same as the reference product, applicants should conduct (1) a fasting PK study in healthy postmenopausal females and (2) a clinical endpoint study in women with secondary amenorrhea using vaginal bleeding as the primary endpoint.

II. DISCUSSION

In your Petition, you request that we issue draft guidance on progesterone gel that recommends both PK endpoints and clinical endpoint studies for demonstration of bioequivalence and is consistent with the 2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance. As described in section I.D.2 above, and in further detail, below, today FDA is issuing draft bioequivalence guidance recommending both PK endpoints and clinical endpoint studies for progesterone gel.²¹ Therefore, your Petition is granted with respect to your request that we issue draft guidance recommending PK

¹⁷ *Schering Corp.*, supra note 14, at 651; see *Fisons Corp.*, supra note 15, at 866-67 ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion.").

¹⁸ See, e.g., *Schering Corp.*, supra note 7, at 397-400; *Fisons Corp.*, supra note 15, at 867.

¹⁹ Supra, note 2.

²⁰ FDA's *Draft Guidance on Progesterone* (2015 Progesterone Gel Draft Bioequivalence Guidance) is available on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

²¹ Id.

endpoints and clinical endpoint studies. Your Petition is denied with respect to your request that the recommendations be consistent with the 2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance.

You also request that we refuse to approve any ANDA for a generic version of Crinone unless and until the ANDA's sponsor demonstrates bioequivalence in two studies: a PK endpoints study and a clinical endpoint study. Although we agree that sponsors should conduct both a PK endpoints study and a clinical endpoint study, as discussed in more detail below and in our 2015 Progesterone Gel Draft Bioequivalence Guidance, we disagree that these studies *must be* required before an ANDA for a generic version of Crinone can be approved. Therefore, your Petition is denied with respect to this request.

A. Progesterone Gel Bioequivalence Guidance

In the Petition, you request that we issue guidance on progesterone gel recommending a study with PK endpoints and a comparative clinical endpoint study consistent with the Agency's 2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance. You state that although Endometrin is supplied as a vaginal insert and Crinone as a vaginal gel, both products function in the same manner (Petition at 5). Thus, you argue that the Agency's bioequivalence recommendations for Endometrin are equally applicable to Crinone (Id.).

Today, as mentioned previously, we posted a draft BE guidance for progesterone gel recommending that applicants conduct both a PK endpoints study and a comparative clinical endpoint study when the test product is found to be Q1/Q2 the same as the reference product.²² Although we are recommending in the 2015 Progesterone Gel Draft Bioequivalence Guidance that ANDA applicants conduct both a PK endpoints study and a clinical endpoint study, which are the types of studies we recommended in the 2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance, we are not recommending the same PK endpoints and clinical endpoint studies in the 2015 Progesterone Gel Draft Bioequivalence Guidance as in the 2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance. As discussed above, and in further detail below, Crinone is approved for two indications: treatment of secondary amenorrhea and ART treatment. As discussed in greater detail in the next section of this response, we are recommending that applicants conduct the clinical endpoint study using an endpoint linked to the indication of treatment of secondary amenorrhea. Endometrin, however, as mentioned in section I.B, is approved only for one indication: infertile women participating in an ART treatment program. We have concluded that a clinical endpoint study for the ART treatment indication is likely to be relatively insensitive between Crinone and generics. Therefore, although we recommend that a clinical endpoint study for each product be conducted, we do not agree that the bioequivalence recommendations for Endometrin are equally applicable to Crinone.

²² Id.

Additionally, although we recommend that the study population in the PK endpoints study for generic versions of Endometrin be premenopausal women, for generic versions of Crinone we are recommending that postmenopausal women be enrolled. Progesterone levels vary considerably in normal menstrual cycles in premenopausal women,²³ thus, studies in postmenopausal women are less variable and would generally give a more efficient comparison of formulation performance.²⁴

Furthermore, based on our review of current scientific information, we do not agree with your assertion that Endometrin and Crinone function in the same manner. Endometrin is an effervescent tablet that dissolves using an adipic acid component while Crinone is a gel that is absorbed directly through the vaginal tissue. Absorption and distribution of progesterone could potentially be different between these products and could result in differences in systemic effects such as serum progesterone or tissue levels. Lastly, you have not provided any scientific evidence or references to support your statement that the two drug products function in the same manner (See Petition at 5).

As such, your request is granted in part: we are issuing a draft bioequivalence guidance recommending that applicants for a generic version of Crinone conduct both a PK endpoints study and a comparative clinical endpoint study. However, your request is denied in part because we are not recommending, in the 2015 Progesterone Gel Draft Bioequivalence Guidance, the same studies for progesterone vaginal gel that we recommended in the 2012 Progesterone Vaginal Insert Draft Bioequivalence Guidance.

B. Bioequivalence

You also request in your Petition that we require bioequivalence data from both a PK endpoints study and a clinical endpoint study before approving an ANDA for a generic version of Crinone (Petition at 1, 3, and 4-5). You state that the typical methods of assessing bioequivalence are inadequate for topical products such as Crinone because such drug products act locally, not systemically (Petition at 3). You also state that even though some topical drug products produce measurable concentrations of drug or metabolite in an accessible biological fluid, there is often a dearth of evidence of any correlation between these systemic concentrations and concentrations at the site of drug action (Petition at 3-4). You further state that for some of these topical drug products, we can review data from pharmacodynamic effect studies to assess bioequivalence, but for others, no pharmacodynamic endpoints can be readily and adequately measured (Petition at 4). You conclude that data from PK studies and “appropriately designed comparative clinical trials,” as described in 21 CFR 320.24(b)(4), are necessary to assess bioequivalence (Petition at 4). You assert that the purpose of the clinical endpoint study is not to directly establish the safety and efficacy of the generic drug, but rather to demonstrate that the proposed generic drug product is bioequivalent to the RLD (and,

²³ Abrams LS and Berger BM. Progesterone pharmacokinetic study (Letter to the Editor). Fertil Steril. 2010 March 1; 93(4): 317.

²⁴ For generic versions of Endometrin, FDA recommended that the PK population for this product should be premenopausal women, who are more representative of the clinical population.

therefore, that the proposed generic drug can be assumed to be as safe and effective as the RLD for the approved uses) (Petition at 4).

We agree that for generic versions of Crinone, bioequivalence should be demonstrated through PK endpoints and clinical endpoint studies.

For most drug products, bioequivalence is assessed by conducting one or more in vivo tests in humans, under fasting conditions or under both fasting and fed conditions, respectively, with PK endpoints, i.e., an in vivo test in humans in which the concentration of the active ingredient or active moiety, and when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time.²⁵ However, for topical drug products that are applied directly to the area of the body where the disease is located, bioequivalence is usually demonstrated by conducting an appropriately designed comparative clinical endpoint study.²⁶ Although a clinical endpoint study may be considered less accurate, sensitive, and reproducible than a PK study for demonstrating bioequivalence in some products, it may be considered a sufficiently accurate, sensitive, and reproducible method for demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., certain topical preparations for the skin.

Crinone is a topical drug product that is applied to the vagina instead of to the diseased part of the body, i.e., the uterine endometrium, and various plausible mechanisms could explain the vaginal-to-uterus transport. These mechanisms could include direct diffusion through tissue, intraluminal (transcervical) passage, transport through the venous or lymphatic circulation systems, or facilitated diffusion with countercurrent artery-to-vein exchanges in which progesterone diffuses from the uterovaginal lymph vessels or veins to the uterine arterial system. It is also possible that the progesterone in these drug products reaches the uterus through absorption into vaginal blood vessels with a potential first uterine pass effect in addition to systemic absorption.²⁷

As mentioned previously, Crinone is approved for two indications: ART treatment and secondary amenorrhea. When a drug product is approved for more than one indication we determine whether demonstrating bioequivalence for one indication is sufficient to demonstrate bioequivalence for the additional indication(s). Based upon the results provided in the Crinone labeling approved in August 2013 for the ART study COL1620-007US, a clinical endpoint study conducted in a population linked to the ART treatment indication is likely to be relatively insensitive to differences between the RLD and the

²⁵ See 21 CFR 320.23(b) and 320.24(b)(1)(i).

²⁶ 21 CFR 320.23(b)(4).

²⁷ See Bulletti, C, et al., 1997, Targeted Drug Delivery in Gynaecology: The First Uterine Pass Effect, Hum Reprod, 12(5):1073-79; Cicinelli, E, et al., March 1998, Plasma Concentrations of Progesterone Are Higher in the Uterine Artery Than in the Radial Artery After Vaginal Administration of Micronized Progesterone in an Oil-Based Solution to Postmenopausal Women, Fertil Steril, 69(3):471-3; Cicinelli, E, et al., 2000, Mechanisms of Uterine Specificity of Vaginal Progesterone, Hum Reprod, 15(Suppl. 1):159-165; Cicinelli, E, et al., March 2000, Direct Transport of Progesterone From Vagina to Uterus, Obstet Gynecol, 95(3):403-6.

generic product because the endometrial biopsy results provided for this study appear to be on the upper plateau of the dose-response curve, i.e., 100% of the evaluable endometrial biopsies in the Crinone group performed on Days 25-27 were histologically “in-phase,” consistent with luteal phase biopsy specimens of menstruating women at comparable time intervals. Because there are no reliable methods for diagnosis of progesterone deficiency during the luteal phase or early pregnancy, not all women undergoing ART may have needed progesterone supplementation, as progesterone supplementation necessarily is empiric.²⁸ The overall percentage of women who delivered a newborn in the ART study COL1620-007US was rather low. If the endpoint of a clinical endpoint study linked to the ART treatment indication was “clinical pregnancy” or “delivery of a newborn,” it could make it difficult to differentiate between the effects of the RLD versus the generic drug products because many other factors, such as the age of the subject, other concomitant medications, or the success rate of the in vitro facility, could affect the outcome and therefore mask any difference between the RLD and the generic drug product.

Thus, in the case of Crinone, we are recommending that a clinical endpoint study be conducted with an endpoint of secondary amenorrhea, e.g., a study of premenopausal women with secondary amenorrhea using vaginal bleeding as the primary endpoint. The clinical endpoint study should be conducted in the population linked to the secondary amenorrhea indication because there are no similar concerns of relative insensitivity for comparative clinical endpoint studies in this indication. The efficacy results in the recommended subject population, i.e., females aged 18-44 years with hypothalamic amenorrhea or premature ovarian failure, are anticipated to be similar to the efficacy results demonstrated in the subjects treated in the three parallel, open label studies conducted to support Crinone’s approval for this indication.²⁹ It is important to note that although we are recommending that bioequivalence be demonstrated using the secondary amenorrhea indication, the progesterone gel produces the same action for both indications, i.e., conversion of uterine proliferative endometrium to uterine secretory endometrium. We expect that if a generic applicant demonstrates bioequivalence of its proposed product to the RLD in a bioequivalence study with a clinical endpoint for Crinone’s secondary amenorrhea indication, the study (along with satisfying the other criteria of the draft guidance) would be sufficient to demonstrate the bioequivalence of the proposed product for Crinone’s ART indication.

Because of the uncertainty of whether Crinone’s activity depends upon local actions, systemic absorption, or a combination of both of these mechanisms, we recommend that both clinical endpoints (which are related to the total exposure, both local and systemic,

²⁸ Practice Committee of the American Society of Reproductive Medicine, April 2008, Progesterone Supplementation in the Luteal Phase and in Early Pregnancy in the Treatment of Infertility: An Education Bulletin, Fert Steril, 89(4):789-92.

²⁹ Crinone, 4 percent and 8 percent, labeling (revised August 2013), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020701s026lbl.pdf. The primary endpoint in these studies was induced bleeding in cycle 2, which occurred in 79% of women treated with Crinone 4 percent and in 77% of women treated with Crinone 8%.

at the site of action) and PK studies (which are related only to the systemic exposure) as part of the bioequivalence demonstration.

A proposed generic product that is Q1/Q2 to Crinone reduces uncertainty by eliminating the possibility that a different inactive ingredient either enhanced or decreased the bioavailability of the progesterone active ingredient or altered its possible local effects. This reduced uncertainty supports that a Crinone generic that meets these recommendations will be bioequivalent to its RLD for all of the indications of the RLD.

We recommend that, when the test product is found to be Q1/Q2³⁰ the same as the reference product, ANDA applicants conduct (1) a fasting PK study in healthy postmenopausal females to ensure that the presumed systemic effects (or lack thereof) are assessed, and (2) a clinical endpoint study in women with secondary amenorrhea using vaginal bleeding as the primary endpoint to ensure that the presumed topical effects are assessed.

Although we agree that ANDA applicants should conduct both a clinical endpoint and a PK endpoints study, we disagree that these studies must be required before an ANDA for a generic version of Crinone can be approved. As is the case for the majority of other FDA guidance documents, the recommendations in the 2015 Progesterone Gel Draft Bioequivalence Guidance are nonbinding,³¹ and persons “can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.”³² Therefore, your petition is denied with respect to your request that we *require* ANDA applicants for generic Crinone to demonstrate bioequivalence in both a PK endpoints and a clinical endpoint study. However, when the test product is found to be Q1 and Q2 the same as the reference product, we recommend that applicants conduct those two studies to demonstrate bioequivalence of the test product.

³⁰ The draft guidance indicates that potential applicants may propose an alternative approach for a specific non-Q1/Q2 product, but they are encouraged to discuss the approach with OGD via a pre-ANDA meeting request.

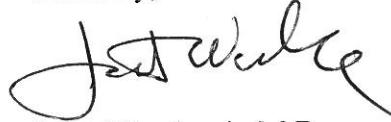
³¹ See 21 CFR 10.115(d) (“Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or the FDA.”).

³² See *supra*, note 20.

III. CONCLUSION

For the reasons discussed in this response, your Petition is granted in part and denied in part.

Sincerely,



Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research