Watson

June 3, 2013

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BY FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061 (HFA-305)
Rockville, Maryland 20852

RE: Require Certain Bioequivalence Criteria to Approve an ANDA for Generic CRINONE

Dear Sir or Madam:

CITIZEN PETITION

Watson Laboratories, Inc. ("Watson") submits this Citizen Petition under Sections 505 and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") regulations set forth at 21 C.F.R. §§ 10.25 and 10.30 to request that the Commissioner of Food and Drugs take certain actions with respect to generic versions of CRINONE® (progesterone gel) 4% and 8% submitted under FDC Act § 505(j) in an Abbreviated New Drug Application ("ANDA"). As discussed below, FDA should establish criteria for ANDA sponsors to demonstrate bioequivalence akin to those FDA has established for another progesterone drug product, namely ENDOMETRIN® (progesterone) Vaginal Insert, 100 mg. Specifically, FDA should require ANDA sponsors to demonstrate bioequivalence to CRINONE® in two studies: (1) a bioequivalence study with Pharmacokinetic ("PK") endpoints; and (2) a bioequivalence study with a clinical endpoint.

I. ACTION REQUESTED

Watson requests that FDA:

(1) Refuse to approve any ANDA for a generic version of CRINONE® unless and until such sponsor demonstrates bioequivalence in both a study with PK endpoints and in a clinical endpoint bioequivalence study; and

(2) Issue draft guidance on Progesterone Gel identifying the bioequivalence studies under item number (1) and consistent with the Agency's Draft Guidance on Progesterone (generic ENDOMETRIN®), recommended in September 2012.

FDA-2013-P-0664

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2013-4229

II. STATEMENT OF GROUNDS

A. Factual Background

Progesterone is a naturally occurring steroid secreted by the ovary, placenta and adrenal gland, which, in the presence of adequate estrogen, transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual (uterine lining/endometrium) tissue, and necessary to increase endometrial receptivity for implantation of an embryo and to maintain a pregnancy. Bound almost entirely to serum proteins (primarily to serum albumin and corticosteroid binding globulin), progesterone is metabolized principally by the liver largely to pregnanediols and pregnanolones, which are conjugated in the liver to glucuronide and sulfate metabolites.

CRINONE® is a bioadhesive gel containing micronized progesterone in an emulsion system that is administered intravaginally as either a 45 mg (4%) or 90 mg (8%) dose. The progesterone in CRINONE® is identical to endogenous progesterone. FDA first approved CRINONE® on May 13, 1997 under New Drug Application ("NDA") No. 020756 in an 8% strength for progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency. FDA approved a second NDA – NDA No. 020701 – on July 31, 1997 for CRINONE® 4% and 8% for the treatment of secondary amenorrhea (i.e., the absence of menses in women who have previously had a menstrual period).[1]

Although CRINONE®, like ENDOMETRIN® can be found in systemic circulation after vaginal administration and measured in serum, it acts locally in the vagina for purposes of the drug product's approved ART and secondary amenorrhea uses.

B. Bioequivalence Standards

Under the FDC Act and FDA's implementing regulations, in order for FDA to receive and approve an ANDA for a proposed generic version of a brand-name drug product, the application must contain, among other things, information showing that the proposed generic drug product is "bioequivalent" to the drug identified in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (i.e., the "Orange Book") as the Reference Listed Drug ("RLD"). See FDC Act §§ 505(j)(2)(A)(iv), 505(j)(4)(F); 21 C.F.R. §§ 314.94(a)(7), 314.127(a)(6)(l) (FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referenced in the ANDA).

The statute states that a generic drug is bioequivalent to the RLD 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

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[1] Although approved under separate NDAs, presumably for administrative purposes, the primary NDA is NDA No. 020701, under which both strengths and indications are approved.

> same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . . .

FDC Act § 505(j)(8)(B)(i). FDA, in the Agency's regulations, defines bioequivalence (in 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.

21 C.F.R. § 320.1(e).

The purpose of demonstrating bioequivalence is to determine whether changes in a proposed drug product's formulation or manufacturing affect the rate or extent to which the active ingredient reaches the primary site of action. A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and extent that is 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.

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 biologic fluid, such as blood or urine, after administration of a single or multiple doses of each drug product to healthy volunteers. When this methodology is not appropriate – e.g., when a drug product is locally acting – FDA may rely on other in vivo and in vitro methods to assess bioequivalence. FDA regulations describe these methods in descending order of accuracy, sensitivity, and reproducibility. They include: (1) in vivo PK studies; (2) in vivo pharmacodynamic effect studies; (3) clinical endpoint studies; and (4) in vitro studies. See 21 C.F.R. § 320.24. In addition, FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence," id. § 320.24(b)(6); see also FDC Act § 505(j)(8)(C), so long as the Agency's determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion." Schering Corp. v. Sullivan, 782 F.Supp. 645, 651 (D.D.C. 1992). For a drug product with multiple indications, it is FDA's policy to require only those studies necessary to assess bioequivalence in just one indication.

C. Argument: FDA Should Require Bioequivalence Data From Both a PK Study and Clinical Endpoint Study Before Approving an ANDA for Generic CRINONE®

The typical methods of assessing bioequivalence are usually inadequate for topical products, such as CRINONE®, because such drug products act locally, not systemically. Even though some topical drug products produce measurable concentrations of drug or metabolite in an accessible biologic fluid, there is often a dearth of evidence of any correlation between these

systemic concentrations and concentrations at the site of drug action. For some of these products, FDA can review data from pharmacodynamic effect studies to assess bioequivalence. For other drug products, however, no pharmacodynamic endpoints can be readily and adequately measured. As such, data from PK studies and "appropriately designed comparative clinical trials" are necessary to assess bioequivalence. 21 C.F.R. § 320.24(b)(4). The purpose of such a 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, therefore, can be assumed to be as safe and effective as the RLD for the approved uses.

FDA's Draft Guidance on Progesterone (generic ENDOMETRIN®), identifies two studies ANDA sponsors should conduct to demonstrate bioequivalence to the RLD:

> 1. Type of study: Bioequivalence (BE) study with Pharmacokinetic (PK) endpoints
> Design: Single-dose, two-treatment, two-period, crossover, fasting in vivo
> Strength: 100 mg (dose: 1x100 mg)
> Subjects: Healthy premenopausal, nonpregnant females, general population.
>
> 2. Type of study: BE study with clinical endpoint
> Design: Multiple-dose, 2-treatment, parallel, randomized in vivo
> Strength: 100 mg
> Subjects: Infertile women participating in an Assisted Reproductive Technology (ART) treatment program

Draft Guidance on Progesterone at 1. The draft guidance provides further, specific comment on the recommended bioequivalence study with PK endpoints, and, for both studies, notes that a determination of bioequivalence will be based on:

> Progesterone (for PK endpoints) and clinical pregnancy, defined as the presence of a gestational sac and fetal heart activity beginning at six weeks and maintained to ten weeks post embryo transfer (for clinical endpoint)

Id.

Watson believes the bioequivalence recommendations FDA has proposed for ENDOMETRIN® are equally applicable to CRINONE®. Although ENDOMETRIN® is supplied as a vaginal insert and CRINONE® as a gel, the drug product functions in the same manner in both drug products. As such, the requirements for an ANDA sponsor to demonstrate bioequivalence of its proposed drug product to CRINONE® for ART should be the same as those for ENDOMETRIN® for ART.

D. Conclusion

For the reasons set forth above, FDA should not approve an ANDA for a generic version of CRINONE® unless and until the ANDA applicant demonstrates bioequivalence in both a

study with PK endpoints and a clinical endpoint study consistent with FDA's Draft Guidance on Progesterone (generic ENDOMETRIN®).

III. ENVIRONMENTAL IMPACT

Watson claims a categorical exclusion under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT STATEMENT

Watson will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. CERTIFICATIONS

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to Watson which are unfavorable to the Petition.

Watson makes the following certification pursuant to FDC Act § 505(q)(1)(H):[2] I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 14, 2012. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Watson. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Kevin Barber, Ph.D., R.A.C., P.M.P.
Vice President, Regulatory Affairs
U.S. Proprietary Products

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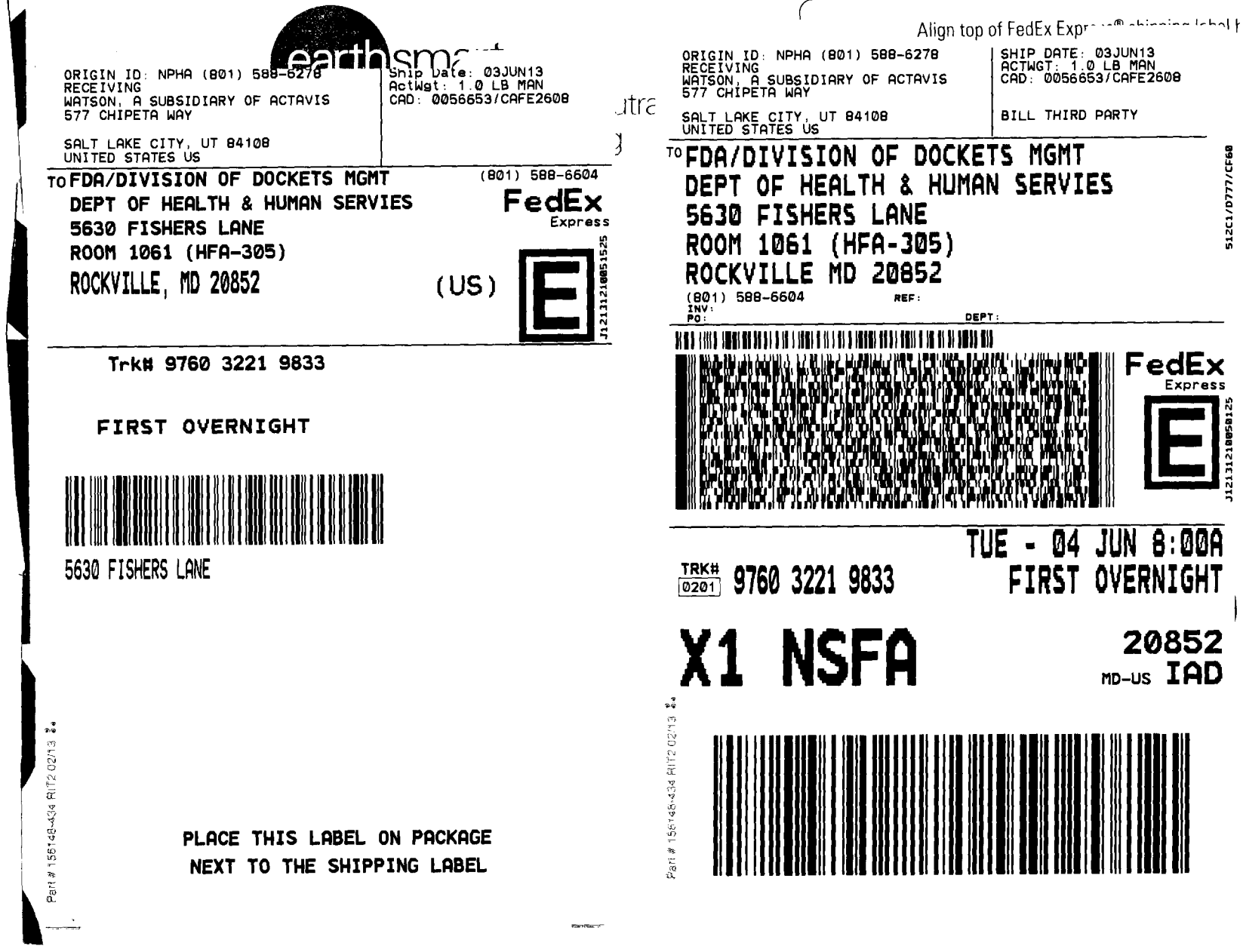
2 CRINONE® is listed in FDA's Orange Book with a single patent – U.S. Patent No. 5,543,150 ("the '150 patent") – that expires on September 15, 2013. Watson has not received notice of FDA's receipt of an ANDA with a Paragraph IV certification to the '150 patent. Out of an abundance of caution, Watson is including a certification pursuant to FDC Act § 505(q)(1)(H) in the instance an ANDA is pending at FDA for a generic version of CRINONE® containing a Paragraph III certification to the '150 patent.



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