



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

JUN 25 2010

0330 10 JUN 28 P3:20

Frederik Defesche  
CUSTOpharm, Inc.  
14413 American Kestrel Dr.  
Austin, TX 78738

Re: Docket No. FDA-2006-P-0089

Dear Mr. Defesche:

This letter responds to your citizen petition received on March 30, 2006 (the Petition), and your supplement to the Petition dated March 19, 2007 (the Supplement).<sup>1</sup> The Petition requests that the Food and Drug Administration (FDA) determine that Delalutin (hydroxyprogesterone caproate) injection (new drug applications (NDAs) 10-347 and 16-911) was not withdrawn from sale for reasons of safety or effectiveness and therefore is suitable for submission in an abbreviated new drug application (ANDA). The Supplement requests clarification regarding the orphan drug designation of Gestiva (17 α-hydroxyprogesterone caproate) in light of the previously marketed Delalutin and the potential for ANDAs being submitted referencing Delalutin as the reference listed drug (RLD).<sup>2</sup> As described below, we grant your request for a determination that Delalutin (hydroxyprogesterone caproate) injection, 125 milligrams (mg)/milliliter (mL) and 250 mg/mL, was not withdrawn for reasons of safety or effectiveness and respond to your request for clarification on the relationship between the orphan drug status of Gestiva and the submission of any ANDAs for Delalutin.

## I. BACKGROUND

### A. Delalutin

Delalutin (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, is the subject of NDA 10-347 and NDA 16-911, which were held by Bristol-Myers Squibb Company (BMS). According to the latest version of the approved labeling for Delalutin, Delalutin (hydroxyprogesterone caproate) injection is indicated in non-pregnant women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance

<sup>1</sup> This citizen petition was originally assigned docket number 2006P-0144/CP1. The number was changed to FDA-2006-P-0089 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

<sup>2</sup> We have also received a citizen petition from Sidelines National Support Network requesting that FDA reconsider and revoke the orphan drug designation for Gestiva (FDA-2007-P-0051). (This citizen petition was originally assigned docket number 2007P-0455/CP1. The number was changed to FDA-2007-P-0051 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008). This response does not address that citizen petition.

FDA-2006-P-0089

PAV

in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a test for endogenous estrogen production (“Medical D and C”); and for the production of secretory endometrium and desquamation.

FDA originally approved NDA 10-347 for Delalutin (hydroxyprogesterone caproate) injection in 1956 based on a finding of safety. Certain Delalutin indications were reviewed under the Drug Efficacy Study Implementation (DESI) program and found effective. The regulatory history of Delalutin, its approved indications, and labeling are described in the enclosed *Federal Register* notice.

By letter dated September 13, 1999, BMS requested withdrawal of NDA 10-347 for Delalutin (hydroxyprogesterone caproate) injection and stated that the drug product had not been marketed for several years. In the *Federal Register* of September 13, 2000, FDA announced that it was withdrawing approval of NDA 10-347 and NDA 16-911, effective September 30, 2000 (65 FR 55264).

## B. Gestiva

In a *Federal Register* notice of July 20, 2006, FDA announced a public advisory committee meeting to discuss Adeza Biomedical’s NDA 21-945, proposed trade name Gestiva (17 α-hydroxyprogesterone caproate injection), 250 mg/mL, for the proposed indication for prevention of preterm delivery in women with a history of a prior preterm delivery (71 FR 41220). The advisory committee met on August 29, 2006, and discussed the adequacy of the data to support the new drug product’s safety and effectiveness. On October 23, 2006, Adeza announced that it had received an approvable letter for its Gestiva application.

According to FDA’s list of Orphan Designations available at <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>, Adeza Biomedical received orphan designation for 17 α-hydroxyprogesterone caproate with trade name Gestiva for prevention of preterm birth in singleton pregnancies with a designation date of January 25, 2007.<sup>3</sup>

## II. LEGAL FRAMEWORK

### A. Generic Drug Products

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FDCA or the Act), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA’s previous finding that the reference listed drug (RLD)<sup>4</sup> is safe and effective. Under the Hatch-Waxman Amendments, to rely on a previous

<sup>3</sup> The significance of an orphan drug designation is explained in Section II.B.

<sup>4</sup> A reference listed drug or 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

finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its generic drug product is bioequivalent<sup>5</sup> to the RLD.<sup>6</sup> In addition, a drug product described in an ANDA generally must contain the same active ingredient,<sup>7</sup> conditions of use,<sup>8</sup> route of administration, dosage form, strength,<sup>9</sup> and (with certain permissible differences) labeling<sup>10</sup> as the RLD, unless a petition for certain changes is approved by the Secretary<sup>11</sup> (sections 505(j)(2)(A), (j)(2)(C), and (j)(4) of the Act). Drug products that are both bioequivalent and pharmaceutically equivalent<sup>12</sup> are therapeutically equivalent, meaning that the drugs generally may be substituted for each other with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.<sup>13</sup>

The Hatch-Waxman Amendments also include what is now section 505(j)(7) of the Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is generally known as the “Orange Book.” Under FDA regulations, drugs are withdrawn from the list if the Agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from

---

FDA’s “Approved Drug Products With Therapeutic Equivalence Evaluations,” which is generally known as the “Orange Book.”

<sup>5</sup> Section 505(j)(8)(B) of the Act states that a generic drug product is bioequivalent to the RLD if:

(i) 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

(see also 21 CFR 320.1(e) and 320.23(b)).

<sup>6</sup> See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring “information to show that the new drug is bioequivalent to the listed drug referred to in clause (i) [i.e., listed drug]...”); 21 CFR 314.3 (defining *reference 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 reference listed drug upon which the applicant relies); 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 listed drug referred to in the ANDA).

<sup>7</sup> See, e.g., 21 CFR 314.94(a)(5).

<sup>8</sup> See, e.g., 21 CFR 314.94(a)(4).

<sup>9</sup> See, e.g., 21 CFR 314.94(a)(6).

<sup>10</sup> See, e.g., 21 CFR 314.94(a)(8).

<sup>11</sup> An applicant may submit an ANDA for a drug that has a different active ingredient, route of administration, dosage form, or strength from the RLD if the applicant has submitted a petition to the Agency (known as a *suitability petition*) requesting permission to file such an application and has received the Agency’s approval (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).

<sup>12</sup> Pharmaceutically equivalent drug products have identical dosage forms that contain identical amounts of the identical active drug ingredient and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. They do not necessarily contain the same inactive ingredients and may also differ in characteristics such as shape, scoring, release mechanism, and, within certain limits, labeling (see 21 CFR 320.1 and the Orange Book, 30th ed., Introduction at pp. iii-iv).

<sup>13</sup> See Orange Book, 30th ed., Introduction at p. iv.

sale for reasons of safety or effectiveness (21 CFR 314.162). Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the Agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

### **B. Orphan Drug Act**

The Orphan Drug Act (Public Law 97-414) was enacted in 1983 and amended the FDCA. Congress recognized that the market for drugs intended to treat people with rare diseases or conditions is so limited that the cost of developing the drugs makes a profit by the developer unlikely and sought to promote the development of drugs, including antibiotics and biological products, that are needed by, but not available to, people with rare diseases or conditions. Congress therefore enacted the Orphan Drug Act to create incentives for the development of these drugs. As amended, the Orphan Drug Act provides various incentives, including tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval, formal protocol assistance to sponsors of drugs for rare diseases, and a 7-year period of exclusivity during which FDA may not approve another sponsor's application "for such drug for such disease or condition," subject to certain conditions.<sup>14</sup> Orphan drug exclusivity begins on the date that the marketing application is approved and applies only to the orphan indication for which the drug has been designated and approved.<sup>15</sup>

## **III. DISCUSSION**

### **A. Whether Delalutin Was Withdrawn from Sale for Reasons of Safety or Efficacy**

In the Petition, you request that FDA determine that Delalutin (hydroxyprogesterone caproate) injection (NDA 10-347 and NDA 16-911) was not withdrawn from sale for reasons of safety or effectiveness and therefore is suitable for submission in an abbreviated new drug application. As described in the enclosed *Federal Register* notice, the FDA has reviewed its records and determined that Delalutin (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL (NDAs 10-347 and 16-911), was not withdrawn from sale for reasons of safety or effectiveness. Thus, the FDA will maintain Delalutin (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL (NDAs 10-347 and 16-911), in the "Discontinued Drug Product List" section of the Orange Book. This determination will allow FDA to approve ANDAs for hydroxyprogesterone caproate if all other legal and regulatory requirements are met.

---

<sup>14</sup> See 21 U.S.C. 360aa-ee, 42 U.S.C. 236. See also 21 CFR 316.1-316.52. FDA may approve another application during the period of marketing exclusivity if FDA finds that the holder of the approved application or license cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated or such holder provides its written consent for the approval of other applications or issuance of other licenses before the expiration of the exclusivity period (21 U.S.C. 360cc(b)).

<sup>15</sup> See 21 U.S.C. 360cc(a).

## B. Gestiva and Delalutin

In the Supplement, you assert that granting orphan drug status to Gestiva will provide Adeza with a 7-year exclusivity period during which time no generic products can be approved for the indication for which Adeza receives approval, deterring generic competition and possibly benefiting Adeza at the expense of public health and consumers (Supplement at 2). You assert that “Delalutin was available on the market as a treatment to prevent preterm births, the same indication as Gestiva” (Supplement at 2). You further assert that if Delalutin was not discontinued because of safety or efficacy reasons, it would be suitable for an ANDA, and “[d]esignating a product as an Orphan Drug when an ANDA (for the same formulation and indication) could be filed seems to contradict the purpose behind designating products as Orphan Drugs and disregarding the intent of the Hatch-Waxman Act” (Supplement at 2). You request that FDA clarify its position with regard to granting orphan drug designations on products with the same formulation and indications as discontinued RLDs (Supplement at 2).

We disagree with your assertion that FDA has granted an orphan drug designation on a product with the same formulation and indication as a discontinued RLD because your assumption that Delalutin and Gestiva would have the same indication is incorrect.<sup>16</sup> In the *Federal Register* notice of October 10, 1973, FDA determined that the labeling for Delalutin should be revised to delete the indication for use in threatened and habitual abortion. As reflected in the latest version of its labeling, Delalutin (hydroxyprogesterone caproate) injection is not approved for the indication for use in threatened or habitual abortion or Gestiva’s proposed indication for the prevention of preterm birth in singleton pregnancies.<sup>17</sup> Because Delalutin is not approved for such an indication, a generic version of Delalutin could not be approved for that indication. An ANDA may be approved only for indications that were previously approved for the RLD.<sup>18</sup>

You state that “Delalutin was available on the market as a treatment to prevent preterm births, the same indication as Gestiva” (Supplement at 2). To the extent that Delalutin was used in that manner after 1973, such a use would have been an “off-label” use of the drug product. Off-label use of a drug product occurs when a physician, in his or her practice of medicine, prescribes a drug product for a use not granted an FDA-approved indication in the labeling of the drug product. Prescribing a drug product for an off-label use in the course of the practice of medicine is not a violation of the law. FDA does not restrict such usage when the use is within the

---

<sup>16</sup> To respond to the Petition and the Supplement, we need not address your assertion that Gestiva’s formulation is the same as Delalutin.

<sup>17</sup> As noted in section I.A of this response, Delalutin (hydroxyprogesterone caproate) injection is indicated in non-pregnant women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a test for endogenous estrogen production (“Medical D and C”); and for the production of secretory endometrium and desquamation.

<sup>18</sup> See 21 CFR 314.54(a)(“The act does not permit approval of an abbreviated new drug application for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change. Any person seeking approval of a drug product that represents a modification of a listed drug (e.g., a new indication or new dosage form) and for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the changes may, except as provided in paragraph (b) of this section, submit a 505(b)(2) application.”). See also 21 CFR 314.94(a)(4).

practice of medicine. FDA does, however, prohibit the promotion of a drug product for an off-label use. Therefore, because (as described in the previous paragraph) a generic version of Delalutin would be ineligible to receive approval for the indication of prevention of preterm births, such a use of that drug product would be an off-label use, and an applicant for a generic version of Delalutin would be prohibited from promoting the drug product for that off-label use.

Because any ANDA referencing Delalutin may receive approval only for indications for which Delalutin was approved, the scenario you envision — granting orphan designations on products with the same formulation and indications as discontinued RLDs — is not presented here by Gestiva and Delalutin. Therefore, we need not address that hypothetical scenario. As described, with respect to Delalutin, FDA may approve any future ANDAs for generic versions of Delalutin for the same indications as Delalutin if all other legal and regulatory requirements are met. With respect to Gestiva, if it is approved for the designated orphan indication, FDA will not approve any drug applications proposing the same drug and the same use as Gestiva during the period of orphan drug exclusivity, subject to certain statutory conditions. Orphan drug exclusivity for Gestiva would not bar approval of ANDAs for Delalutin because orphan drug exclusivity applies only to the indication for which the orphan drug has been designated and approved. We believe that this approach is consistent with the purposes underlying the Hatch-Waxman Amendments and the Orphan Drug Act as well as the applicable statutory and regulatory requirements.

#### IV. CONCLUSION

For the reasons discussed in this response, we grant your request for a determination that Delalutin (hydroxyprogesterone caproate) injection was not withdrawn for reasons of safety or effectiveness and respond to your request for clarification on the relationship between the orphan drug status of Gestiva and the submission of any ANDAs for Delalutin.

Sincerely,



Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research

Enclosure

must be submitted within 90 days after the budget period ends. Final FSRs are due within 90 days of expiration of the project period. Standard Form 269 (long form for those reporting on program income; short form for all others) will be used for financial reporting.

Federal Cash Transaction Reports are due every calendar quarter to the Division of Payment Management, Payment Management Branch, Department of Health and Human Services at: <http://www.dpm.gov>. Failure to submit timely reports may cause a disruption in timely payments to your organization.

Grantees are responsible and accountable for accurate reporting of the Progress Reports and Financial Status Reports which are generally due annually. Financial Status Reports (SF-269) are due 90 days after each budget period and the final SF-269 must be verified from the grantee records on how the value was derived. Annual financial status reports must be submitted within 90 days after the end of the budget period. Final financial status reports are due within 90 days of expiration of the budget/project period. Standard Form 269 (long form) will be used for financial reporting.

5. Telecommunication for the hearing impaired is available at: TTY 301-443-6394

## VII. Agency Contacts

For program information, contact Mr. Michael Berryhill, Office of Public Health Support, Division of Health Professions Support, 801 Thompson Avenue, TMP Suite 450A, Rockville, Maryland, 20852 (301) 443-2443.

For grant application and business management information, contact Ms. Denise Clark, Division of Grants Operations, Indian Health Service, 801 Thompson Avenue, TMP Suite 360, Rockville, Maryland 20852 (301) 443-5204.

**Yvette Roubideaux,**  
*Director, Indian Health Service.*

[FR Doc. 2010-15423 Filed 6-24-10; 8:45 am]

BILLING CODE 4165-16-P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2006-P-0089 (formerly Docket No. 2006P-0144)]

#### Determination That DELALUTIN (hydroxyprogesterone caproate) Injection, 125 Milligrams/Milliliter and 250 Milligrams/Milliliter, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) has determined that DELALUTIN (hydroxyprogesterone caproate) injection, 125 milligrams (mg)/milliliter (mL) and 250 mg/mL, was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for hydroxyprogesterone caproate injection, 125 mg/mL and 250 mg/mL, if all other legal and regulatory requirements are met. However, in considering whether to file an ANDA for hydroxyprogesterone caproate, future applicants are advised that they may not be able to obtain DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, for bioequivalence testing because the product has not been commercially available for a number of years. An ANDA applicant who is unable to obtain DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, for bioequivalence testing should contact the Office of Generic Drugs for a determination of what is necessary to show bioavailability and same therapeutic effect.

**FOR FURTHER INFORMATION CONTACT:** Nam Kim, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6320, Silver Spring, MD 20993-0002, 301-796-3601.

**SUPPLEMENTARY INFORMATION:** In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as

the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)) (the act), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is generally known as the "Orange Book." Under FDA regulations, drugs are withdrawn from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162). Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, is the subject of NDA 10-347 and NDA 16-911 held by Bristol-Myers Squibb Company (BMS). According to the latest version of the approved labeling for DELALUTIN (hydroxyprogesterone caproate) injection, DELALUTIN is indicated in non-pregnant women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a test for endogenous estrogen production ("Medical D and C"); and for the production of secretory endometrium and desquamation.

FDA originally approved NDA 10-347 for DELALUTIN (hydroxyprogesterone caproate) injection based on a finding of safety in 1956. The indications section of the original labeling approved in 1956 states that DELALUTIN appears to be useful in conditions generally responding to progestogens and provided suggested dosing and administration for the following indications: primary and secondary amenorrhea; metropathia hemorrhagica

(functional uterine bleeding) not associated with genital malignancy; infertility with inadequate corpus luteum function; production of secretory endometrium and desquamation during estrogen therapy; premenstrual tension; dysmenorrhea; cyclomastopathy, mastodynia, adenosis, chronic cystic mastitis; habitual and threatened abortion; postpartum afterpains; test for endogenous estrogen production; and test for continuous endogenous progesterone production. In 1970, a supplement to NDA 10-347 was submitted for the additional indication of treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV). FDA reviewed this supplement as an original NDA (NDA 16-911) because it proposed a new indication, and approved it as both safe and effective in 1972. Both NDA 10-347 and NDA 16-911 reference the same drug product and utilize the same labeling.

The indications for DELALUTIN (hydroxyprogesterone caproate) injection, other than the indication for treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV), were reviewed for efficacy under the Drug Efficacy Study Implementation (DESI) program. In the **Federal Register** of September 9, 1971 (36 FR 18115), FDA announced that preparations containing hydroxyprogesterone caproate are effective for use in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a presumptive test for pregnancy; as a test for continuous endogenous progesterone production; and for production of secretory endometrium and desquamation—as a test for endogenous estrogen production (medical D and C). FDA also announced that preparations containing hydroxyprogesterone caproate are *probably* effective for habitual and threatened abortion and cyclomastopathies (mastodynia, adenosis, chronic cystic mastitis) and *possibly* effective for use in premenstrual tension and dysmenorrhea and disturbances of the menstrual cycle (hypomenorrhea, oligomenorrhea, irregular cycles). In addition, FDA announced that hydroxyprogesterone caproate lacks substantial evidence of effectiveness for use in postpartum afterpains and, when used alone, in deficiency syndromes (castration, primary ovarian failure, menopause, senile vaginitis, and pruritis vulvae). The notice announced that FDA was prepared to approve NDAs and

supplements to previously approved NDAs under the conditions described in the notice, including the condition that the revised labeling include only the indications for which the drug was classified as effective or probably effective.

In the **Federal Register** of October 10, 1973 (38 FR 27947), FDA announced that it was modifying its prior conclusions with respect to the indications for DELALUTIN (hydroxyprogesterone caproate) injection that were determined to be probably effective and possibly effective. FDA stated that the additional information submitted by BMS to support use of DELALUTIN in threatened and habitual abortion does not constitute substantial evidence of effectiveness. In addition, the notice stated that data had become available which suggested a possible association of prenatal hormonal treatment of mothers with congenital heart defects in the offspring. The notice stated that the potential risk of teratogenic effects is considered high enough to warrant removal of pregnancy-related indications from the labeling of progestins currently marketed for systemic use, which are as follows: (1) Presumptive test for pregnancy, (2) treatment of threatened and habitual abortion, and (3) treatment of any abnormalities of pregnancy, including pregnancy complicating diabetes. The notice concluded that the labeling section given in the September 9, 1971, announcement for hydroxyprogesterone caproate should be amended to read as follows: "This drug is indicated in amenorrhea; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; for production of secretory endometrium and desquamation; and as a test for endogenous estrogen production (Medical D & C)."

In the **Federal Register** of July 22, 1977 (42 FR 37646), FDA stated that reports during the past several years had indicated that the use of sex hormones during early pregnancy may seriously damage the offspring. FDA stated that in view of the adverse effects on the fetus that may be associated with its exposure to pregestational hormones, the labeling for all pregestational drug products except those for use as contraceptives should be revised to include an additional contraindication and warning regarding the use of pregestational agents during pregnancy. In the **Federal Register** of October 13, 1978 (43 FR 47178), FDA published a final rule requiring the labeling of pregestational drug products to include warnings

informing patients of an increased risk of birth defects associated with the use of these drugs during the first 4 months of pregnancy. In the **Federal Register** of January 12, 1989 (54 FR 1243), FDA published revised guideline texts for professional and patient labeling for prescription pregestational drug products not including progestogen-containing oral contraceptive drug products. The notice revised the guideline texts by: (1) Deleting the warning about possible congenital heart defects and limb reduction defects, and (2) adding a warning stating that the use of pregestational drugs in pregnancy may cause certain genital abnormalities.

In the **Federal Register** of November 16, 1999 (64 FR 62110), FDA revoked its regulation requiring such patient labeling for pregestational drug products because it concluded, based on a review of the scientific data, that such labeling for all progestogens was not warranted. In the notice, FDA stated that the diversity of drugs that can be described as pregestational and the diversity of conditions these drugs may be used to treat make it inappropriate to consider these drugs a single class for labeling purposes.

By letter dated September 13, 1999, BMS requested withdrawal of NDA 10-347 for DELALUTIN (hydroxyprogesterone caproate) injection and stated that the drug product had not been marketed for several years. In the **Federal Register** of September 13, 2000 (65 FR 55264), FDA announced that it was withdrawing approval of NDA 10-347 and NDA 16-911, effective September 30, 2000.

CUSTOpharm, Inc., submitted a citizen petition dated March 27, 2006 (Docket No. FDA-2006-P-0089), under 21 CFR 10.30, requesting that the agency determine whether DELALUTIN (hydroxyprogesterone caproate) injection was withdrawn from sale for reasons of safety or effectiveness and therefore is suitable for submission in an ANDA. After considering the citizen petition (including comments submitted) and reviewing agency records, FDA has determined that DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, was not withdrawn from sale for reasons of safety or effectiveness. The petitioner identified several publications discussing the potential teratogenic properties of DELALUTIN (hydroxyprogesterone caproate) injection over the years but asserts that recent studies indicate that with proper administration (beginning in the second trimester) in high risk patients these risks are minimal or not evident. In view of these studies, the petitioner

seeks a determination that DELALUTIN (hydroxyprogesterone caproate) injection was not withdrawn for reasons of safety or efficacy. FDA has reviewed the information submitted by petitioner and has independently evaluated relevant literature and data for adverse event reports for DELALUTIN (hydroxyprogesterone caproate) injection. Based on its evaluation, FDA does not consider this information to indicate that DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, was withdrawn for reasons of safety or effectiveness.

For the reasons outlined in this document, FDA determines that DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, may be approved by the agency as long as they meet all relevant legal and regulatory requirements for approval of ANDAs. If FDA determines that labeling for these drug products should be revised to meet current standards, the agency will advise ANDA applicants to submit such labeling.

In considering whether to file an ANDA for this drug product, future applicants should be advised that they may not be able to obtain DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, for bioequivalence testing because the product has not been commercially available for a number of years. An ANDA applicant who is unable to obtain DELALUTIN (hydroxyprogesterone caproate) injection, 125 mg/mL and 250 mg/mL, for bioequivalence testing should contact the Office of Generic Drugs for a determination of what showing is necessary to satisfy the requirements of section 505(j)(2)(A)(iv) of the act. If an ANDA is approved without a showing of bioequivalence, the approved product will not be considered therapeutically equivalent (i.e., granted an AB rating) in the Orange Book.

Dated: June 21, 2010.  
**Leslie Kux,**  
*Acting Assistant Commissioner for Policy.*  
[FR Doc. 2010-15416 Filed 6-24-10; 8:45 am]  
**BILLING CODE 4160-01-S**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration [Docket No. FDA-2010-D-0283]

#### Draft Guidance for Industry on Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes Reportable in Annual Reports; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "CMC Postapproval Manufacturing Changes Reportable in Annual Reports." This draft guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of changes that may be reported in annual reports. Specifically, the draft guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that FDA has determined will likely present minimal potential to have adverse effects on product quality and, therefore, may be reported by applicants in an annual report. (The draft guidance excludes positron emission tomography (PET) drug products.)

**DATES:** Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by September 23, 2010.

**ADDRESSES:** Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to <http://>

[www.regulations.gov](http://www.regulations.gov). Submit written comments, including comments regarding the proposed collection of information, to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Jon Clark, Center for Drug Evaluation and Research, Food and Drug Administration, Bldg. 51, rm. 4178, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-2400.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

FDA is announcing the availability of a draft guidance for industry entitled "CMC Postapproval Manufacturing Changes Reportable in Annual Reports." This draft guidance provides recommendations to holders of NDAs and ANDAs regarding the types of CMC postapproval manufacturing changes that FDA has determined will likely present minimal potential to have adverse effects on product quality, and therefore, may be reported by applicants in an annual report under § 314.70 (21 CFR 314.70).

In its September 2004 final report, "Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century—A Risk-Based Approach" (Pharmaceutical Product Quality Initiative, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticesCGMPforDrugs/ucm137175.htm>), FDA stated that to keep pace with the many advances in quality management practices in manufacturing and to enable the agency to more effectively allocate its limited regulatory resources, FDA would implement a cooperative, risk-based approach for regulating pharmaceutical manufacturing. As part of this approach, FDA determined that to provide the most effective public health protection, its CMC regulatory review should be based on an understanding of product risk and how best to manage this risk.

The number of CMC manufacturing supplements for NDAs and ANDAs has continued to increase over the last several years. In connection with FDA's Pharmaceutical Product Quality Initiative and its risk-based approach to CMC review, FDA has evaluated the types of changes that have been submitted in CMC postapproval manufacturing supplements and determined that many of the changes being reported present very low risk to the quality of the product and do not need to be submitted in supplements.