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APPLICATION NUMBER:

210326Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

IND 122336

**MEETING REQUEST-
WRITTEN RESPONSES**

Fresenius Kabi USA, LLC.
Attention: Andrea Redd
Director, Regulatory Affairs
Three Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Redd:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Fulvestrant Injection.

We also refer to your submission dated March 31, 2014, containing a pre-IND meeting request.

The purpose of the requested meeting was to obtain feedback and guidance from the Division on the proposed 505(b)(2) NDA submission.

Further reference is made to our Meeting Granted letter dated May 19, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 30, 2014, background package.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Amy McKee, M.D.
Clinical Team Leader
Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-IND
Application Number: IND (b) (4)
Product Name: Fulvestrant Injection
Indication: Hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
Sponsor/Applicant Name: Fresenius Kabi USA, LLC
Regulatory Pathway: 505(b)(2)

BACKGROUND

Fresenius Kabi USA, LLC (FK USA) is proposing a new formulation of Fulvestrant for Injection for the proposed indication: Indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The difference between the approved product, Faslodex and Fulvestrant for injection is the change in co-solvent benzyl benzoate in the RLD to polysorbate 80 and α -tocopherol as shown in the following table:

Table 1 Comparison of Excipients in FK USA's Formulation with Those in Faslodex

Ingredient	FK USA's Formulation		Faslodex		IID Level
	(%)	Single Dose (mg)	(%)	Single Dose (mg)	
(b) (4) alcohol	10	1000 ¹	10	1000 ¹	Intramuscular – 12%
Benzyl alcohol	10	1000 ¹	10	1000 ¹	Intramuscular – 10.962%
Benzyl benzoate	NA	NA	15	1500 ¹	NA
α -tocopherol	0.06	6	NA	NA	Intravenous – 0.064%
Polysorbate 80	0.12	12	NA	NA	Intramuscular – 12%
(b) (4) castor oil	QS	(b) (4)	QS	(b) (4)	Intramuscular – 27.78%

¹ Assumes a density of (b) (4)

IID = FDA Inactive Ingredients Database; NA = not applicable; QS = quantum satis (the amount needed to complete the formulation)

With the new formulation with amount of castor oil in the formulation will also be increased. The purpose of this pre-meeting is to gain agreement on the following:

- the suitability of the 505(b)(2) pathway for approval of the proposed Fulvestrant
- To discuss with the Agency FK USA's proposed clinical Bioequivalence (BE) study design and primary outcome(s).
- To confirm with the agency that no further non-clinical or clinical studies are required to support the approval of FK USA's Fulvestrant for Injection for the currently approved Listed Drug label indications.

FK USA believes that the non-clinical and proposed *in-vivo* BE study, in addition to the reference literature in the public domain, will provide sufficient evidence to support the use of its Fulvestrant for Injection for the same label indications as the Listed Drug.

QUESTIONS AND RESPONSES

Regulatory

Question 1

Is the Agency in agreement that the 505(b)(2) regulatory pathway is appropriate for the proposed Fulvestrant for Injection drug products?

FDA Response:

Based upon the information you have provided in your briefing document, the 505(b)(2) pathway is appropriate. See our additional comments regarding a 505(b)(2) development program below.

Question 2

Can the Agency confirm if an IND submission package will be required prior to submission of our 505(b)(2) application?

FDA Response:

Yes, the *in vivo* BE study should be conducted under an IND and should be included in the initial IND submission.

Clinical/Non-clinical

Question 3

Does the Agency concur with FK USA's proposed *in-vivo* BE study design?

FDA Response:

See responses to questions 4-8.

Question 4

Does the Agency agree that the bioequivalence conclusion can be based on the two primary endpoints C_{max} and AUC_{t-last} ?

FDA Response:

Yes

Question 5

Will a BE study using a single dose administration of 250 mg support the approved administration of 500 mg dose (administered as two single intra-muscular injections of 250 mg)?

FDA Response:

Yes.

Question 6

Can the patient population be expanded to include healthy, non-smoking male subjects?

FDA Response:

The study population in the BE study should reflect the target population in terms of gender. However, if a limited number of males are to be included in the study, the Sponsor should ensure that the male/female ratio is the same for both arms of the BE study. The consent form should adequately describe the potential adverse reactions in the study population, with particular regard to male volunteers.

Question 7

Does the Agency agree to [REDACTED] (b) (4) for the proposed bioequivalence study?

FDA Response:

No, we do not agree.

You propose [REDACTED] (b) (4)

We have the following comments on your proposed approach.

First [REDACTED] (b) (4)

Please justify whether the type I error can be controlled when other values of the ratio of GM are applied, such as 0.90. In addition, please justify whether or not the type I error rate will be inflated due to the futility decision at stage II and the possible impact from sample size imbalance between the two treatment groups.

Second, [REDACTED] (b) (4)

Please provide possible impacts of using t-statistics on the overall type I error rate when [REDACTED] (b) (4) function is used.

Third, it is not clear if there is a targeted overall power. If so, please specify what the value is.

Question 8

FK is proposing 126-day sampling with a sampling schedule of : 0(pre-dose), 2, 8, and 12 hours then 2, 4, 5, 6, 7, 8, 10, 14, 21, 28, 35, 42, 56, 70, 84, and 126 days after dosing. Does the Agency agree that this is sufficient to demonstrate bioequivalence?

FDA Response:

Your sampling schedule appears reasonable.

Question 9

Does the Agency confirm that based on the published literature findings demonstrating the safety and efficacy of the RLD Faslodex as well as the in-vivo BE study outlined above, no further non-clinical or clinical studies are required to support the approval of FK USA's Fulvestrant for Injection for the LD label indications?

FDA Response:

There is insufficient information at this time to answer this question; for example, the results of the BE study are unknown at this time.

We have not identified any additional nonclinical studies that would be required to support an NDA submission at this time; however, we cannot determine whether additional nonclinical studies will be needed to support approval of an NDA until we review your complete submission.

Be advised that levels and specifications of any impurities or degradation products above the qualification levels specified in the ICH Q3A(R2) and Q3B(R2) Guidances should either be qualified by GLP-compliant nonclinical toxicology studies or sufficiently justified at the time of your NDA submission.

Additional Comments:

We have concerns about the potential for increased injection site pain given the increased castor oil in your formulation.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#)

(<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your

proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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

/s/

MODUPE O FAGBAMI
06/30/2014