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Ferring Pharmaceuticals, Inc.
100 Interpace Parkway
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November 4, 2022

Re: Docket No. FDA-2022-P-0160

Dear Dr. Nagaradona:

This letter responds to your citizen petition dated February 9, 2022 (Petition).[1] In the Petition, you request that the Food and Drug Administration (FDA or Agency) take several actions with respect to any abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and any new drug application (NDA) pursuant to section 505(b)(2) of the FD&C Act that reference Ferring Pharmaceuticals, Inc.'s (Ferring) product Firmagon (degarelix acetate) for injection (NDA 022201). In the Petition, you request FDA take the following actions:

1. Require ANDAs that reference Firmagon, and 505(b)(2) applications that rely on bioequivalence (BE) data or comparative bioavailability (BA) data, to conduct an appropriate in vivo study capable of demonstrating that a proposed drug product causes degarelix acetate to release into systemic circulation at the same rate and to the same extent as the reference listed drug (RLD) over the course of the dosing interval;

2. Require ANDA and 505(b)(2) applicants to conduct partial Area Under the Curve (pAUC) analysis as part of the in vivo BE study to ensure the generic is bioequivalent to the RLD over the required dosing interval; and

3. Re-issue the Agency's March 2021 draft product-specific guidance (PSG) entitled *Draft Guidance on Degarelix Acetate* based on the actions taken in response to the Petition.[2]

[1] On February 9, 2022, Ferring Pharmaceuticals, Inc. submitted a redacted version of the Petition that was accompanied only by publicly available references, as well as an unredacted version of the Petition that was accompanied by a full set of references. In determining what information to include in this response, we have independently evaluated whether the information in the Petition is confidential. For additional information on the Agency's disclosure policy, *see* 21 CFR Part 20.

[2] Petition at 4.

We have carefully considered the information in the Petition.[3] For the reasons described below, your Petition is denied.[4]

I. BACKGROUND

A. Firmagon (degarelix acetate)

On December 24, 2008, Ferring obtained approval for NDA 022201 for Firmagon, a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for treatment of patients with advanced prostate cancer.[5] Firmagon is supplied as a sterile lyophilized powder containing degarelix (as the acetate) and mannitol, to be reconstituted with sterile water for injection, USP.[6]

Firmagon is available in two strengths: Equivalent to (EQ) 80 milligrams (mg) base/vial and EQ 120 mg base/vial.[7] The Firmagon labeling recommends a starting dosage of 240 mg, given as two subcutaneous injections of 120 mg each at a concentration of 40 mg/milliliters (mL).[8] The Firmagon labeling recommends a maintenance dose of 80 mg, given as one injection at a concentration of 20 mg/mL and administered once every 28 days, beginning 28 days after the starting dose.[9]

According to the Petition, upon reconstitution, Firmagon forms a colloidal suspension that must be subcutaneously administered into the abdomen within one hour of mixing.[10] Firmagon forms a depot upon subcutaneous administration, from which degarelix is released to the circulation, which results in a "a very slow release of degarelix" from the depot formed at the injection site.[11] As noted in the Petition, the controlled release of degarelix "is a function of the structure adopted by the active ingredient itself after it is administered to the patient," and the structure adopted by the active ingredient (the depot) "relies on the inherent capacity of the degarelix peptide to self-assemble to form highly structured amyloid fibrils."[12]

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[3] On August 10, 2021, Ferring submitted comments to the Draft Guidance on Degarelix Acetate (Docket No. FDA-2007-D-0369-0547). The issues raised in those comments are substantially similar to the issues submitted to the Agency in this citizen petition.

[4] Although the Petition requests that we apply certain requirements to 505(b)(2) applications that rely on findings of safety and effectiveness for Firmagon based on BE or comparative BA data, we note that a drug product described in a 505(b)(2) application can differ from the listed drug in a variety of ways and also demonstrate that reliance on the listed drug is scientifically appropriate in different ways. We cannot address hypothetical requests for what demonstrations would be needed for any given 505(b)(2) application. Therefore, this response focuses solely on your request with respect to ANDAs submitted pursuant to section 505(j) of the FD&C Act. We intend to consider, as appropriate, the issues raised in your Petition to the extent they are relevant to any particular 505(b)(2) NDAs.

[5] NDA labeling for Firmagon (Feb. 2020) (Firmagon Labeling), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022201s016lbl.pdf.

[6] *Id.*

[7] *Id.*

[8] *Id.*

[9] *Id.*

[10] Petition at 5, 6; *see also* Firmagon Labeling.

[11] Firmagon Labeling.

[12] Petition at 9.

B. Applicable Statutory and Regulatory Framework

1. ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the FD&C Act to, among other things, add section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs.[13] To obtain approval, an ANDA applicant is not required to provide independent evidence to establish the safety and effectiveness of the proposed drug product, as is required for an NDA. Instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.[14] To rely on this finding, an ANDA applicant must provide sufficient information to show that its drug product is bioequivalent to the RLD.[15] An ANDA applicant generally must also demonstrate, among other things, that its drug product has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[16] FDA must approve an ANDA unless it finds that, among other things, the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity.[17] The scientific premise underlying the Hatch-Waxman Amendments is that bioequivalent drug products with the same active ingredient(s), route of administration, dosage form, and strength are therapeutically equivalent and may be substituted for each other.[18]

2. The Bioequivalence Requirement

Section 505(j)(8)(B)(i) of the FD&C Act states that a drug shall be considered to be bioequivalent to a 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.....[19]

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[13] For purposes of this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

[14] A *reference listed drug* or RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (§ 314.3(b) (21 CFR 314.3(b))). RLDs are identified in FDA's list of *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the Orange Book, available at https://www.accessdata.fda.gov/scripts/cder/ob/.

[15] *See* 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"); § 314.94(a)(7) (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); and 21 CFR 314.127(a)(6)(i) (stating 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).

[16] Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; *see also* § 314.94(a).

[17] Section 505(j)(4) of the FD&C Act.

[18] *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which BE has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. § 314.3(b).

[19] *See also* §§ 320.1(e) and 320.23(b).

In § 314.3(b), FDA defines BE (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 active moiety 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. BE testing determines whether permissible differences (e.g., differences in inactive ingredients or manufacturing processes) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

As discussed further below, 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), in vitro data (data from laboratory studies), or a combination of in vivo and in vitro data.[20] This flexibility is reflected in FDA's regulations, which 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.[21]

Section 320.24(b) of FDA regulations describes acceptable BE methods in general descending order of accuracy, sensitivity, and reproducibility. The BE methods include: (1) in vivo PK studies of the active ingredient, or when appropriate its active metabolites, in whole blood, plasma, serum, or other appropriate biological fluid, or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary

[20] *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 discretion to determine whether *in vitro* or *in vivo* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process").

[21] § 320.24(a) (emphasis added). In the preamble to the final rule setting forth FDA's regulations for ANDAs, the Agency explained that, depending upon the drug, it 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, April 28, 1992) (emphasis added).

excretion of the active moiety and, when appropriate, its active metabolite(s) are measured as a function of time; (3) in vivo studies measuring acute pharmacodynamic effect; (4) comparative clinical endpoint studies; and (5) in vitro studies acceptable to FDA that ensure human in vivo bioavailability. In addition, section 320.24(b)(6) of the regulations states that FDA has the authority to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." The Agency's authority to make BE 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 BE meet the statutory and regulatory standards for approval;[22] (2) permitting the Agency to use the latest scientific advances in approving drug products;[23] (3) protecting the public by ensuring only safe and effective generic drugs are approved for marketing;[24] and (4) making more safe and effective generic drugs available.[25]

Congress intended to grant FDA wide discretion to establish BE 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 BE requirement should be met for a product or class of products, as long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion."[26]

C. FDA's Bioequivalence Recommendations and Draft Product-Specific Guidance on Degarelix Acetate

FDA's draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) describes our general recommendations for demonstrating BE for products submitted under an ANDA. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited.

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[22] *See* 21 CFR 320.25(a) (stating that a "guiding principle" for the conduct of an in vivo bioavailability study is "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 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.").

[23] *See 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.").

[24] *See Schering Corp. v. Sullivan,* 782 F. Supp. 645, 650 (D.D.C. 1992) (noting that 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").

[25] *See id*. (finding that the 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) (finding that the BE waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act," including making safe and affordable generic drugs available).

[26] *Fisons*, 860 F. Supp. at 865 (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot*, 955 F.2d 1103, 1106 (D.C. Cir. 1993)); *see also Fisons,* 860 F. Supp. at 866-67 ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion."); *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995).

In addition to our general recommendations, we often provide product-specific recommendations for demonstrating BE. These product-specific recommendations are made to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval.[27] Our process for making PSGs available to the public is explained in the guidance for industry *Bioequivalence Recommendations for Specific Products* (June 2010).

FDA announced the availability of the Draft Guidance on Degarelix Acetate (Draft PSG) on March 25, 2021.[28] The Draft PSG recommends that a proposed generic degarelix for injection drug product should: (i) be formulated qualitatively (Q1) and quantitatively (Q2) the same as the RLD; (ii) demonstrate active pharmaceutical ingredient (API) sameness to the RLD by characterizing properties including primary sequence, secondary sequence, and aggregation states;[29] (iii) have comparable physicochemical characteristics, including reconstitution time, acetic acid content, appearance, optical density, viscosity, and pH, to the designated reference standard (RS)[30] product; (iv) compare gelling kinetics to those of the RS using the same experimental conditions; and (v) have acceptable comparative in vitro drug release to the RS.[31]

II. DISCUSSION

The Petition requests that FDA take three actions with respect to ANDAs that reference Firmagon. First, the Petition requests that FDA require all ANDA applicants to conduct an in

[27] *See* FDA's web page on Product-Specific Guidances for Generic Drug Development, available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

[28] 86 FR 15948 (Mar. 25, 2021).

[29] The Draft PSG recommends that this API characterization be conducted using the reconstituted drug product. We note, however, that this study is part of an overall demonstration of bioequivalence. As with any ANDA, this product must also demonstrate active ingredient sameness as required under section 505(j)(2)(A)(ii) and 505(j)(4)(C) of the FD&C Act. We recommend conducting the API characterization described in the Draft PSG using reconstituted drug product in order to, in conjunction with the other recommendations in the Draft PSG, detect any differences that may affect bioequivalence between the generic and RLD.

[30] A *reference standard* is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval. § 314.3(b). FDA generally selects a single reference standard that ANDA applicants must use in in vivo bioequivalence testing. Ordinarily, FDA will select the reference listed drug as the reference standard. However, in some instances, the reference listed drug and the reference standard may be different. For example, where the reference listed drug has been withdrawn from sale for reasons other than safety or effectiveness, FDA may select an ANDA that is therapeutically equivalent to this reference listed drug as the reference standard. Although the regulations do not require that an applicant use a particular product for in vitro testing, we recommend that the reference standard also be used for in vitro testing. *See* FDA guidance for industry, *Referencing Approved Drugs in ANDA Submissions* (Oct. 2020), at Part III.B.–C. For degarelix acetate, the current reference standard is the RLD (*i.e.*, Firmagon). Accordingly, in describing the recommendations in the Draft PSG, this response refers to the RS and RLD interchangeably.

[31] *Draft Guidance on Degarelix Acetate*, see: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022201.pdf. FDA reviews the acceptability criteria for the recommended comparative physicochemical characterization studies and performance testing when reviewing a specific ANDA. This is because the significance and variation of each property/measurement is product-, attribute-, and technique-specific. We have not limited the Draft PSG to preset criteria because knowledge, techniques, analysis, and statistics may evolve or improve. Moreover, by not setting specific acceptance criteria, we encourage ANDA applicants to match the physicochemical properties of the reference product as closely as possible and provide detailed scientific justification supporting their proposed product.

vivo BE study, asserting that an in vitro approach is insufficient to determine BE.[32] Second, the Petition requests that ANDA applicants conduct pAUC analysis or use a multiple-dose study design as part of the in vivo BE study to ensure the generic drug has the same rate and extent of release as the RLD over the required dosing interval. Finally, the Petition requests that FDA revise the Draft PSG accordingly based on the actions requested in the Petition. We address each of these requests below.

A. The Petition Fails To Show That In Vivo Evidence of BE Is Required

1. A Generic Degarelix for Injection Product May Demonstrate BE Without In Vivo Testing Even If It Is Not Eligible for a Waiver Under 21 CFR 320.22(b)(1)

The Petition states that Firmagon "does not have the composition or properties of a parenteral solution" and as such the criteria for a waiver of in vivo evidence of BE[33] is not applicable.[34] The Petition also states that Firmagon is not a solution in the dosage form when it is released for commercial distribution, nor when it is administered and that it should not be considered a solution for purposes of bioequivalence standards.[35] Furthermore, the Petition asserts that Firmagon does not "behave like a solution in vitro or in vivo," does not exhibit the properties of a solution, and the product is labeled as "degarelix for injection" as opposed to "degarelix for injectable solution."[36]

Section 320.22(b) of FDA's regulations permits FDA to waive the requirement for the submission of evidence obtained in vivo demonstrating BE of certain drug products for which in vivo BE may be self-evident. Under section 320.22(b)(1), certain parenteral solutions are one such type of drug product for which in vivo BE may be self-evident. We agree with the Petition that in this case, a proposed generic degarelix for injection drug product referencing Firmagon would not qualify as a parenteral solution for which BE may be self-evident based on formulation sameness. However, although a proposed generic would not be eligible for a waiver of the requirement for the submission of in vivo BE evidence under section 320.22(b)(1), FDA has wide discretion to determine the type of evidence required to demonstrate BE, which may include in vivo or in vitro testing, or both.[37] For the reasons explained below, and consistent with our authority under section 320.24(b)(6), FDA believes that the in vitro approach recommended in the Draft PSG is adequate to establish BE for this product.[38]

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[32] Petition at 2, 3, 8-19. Although the Petition refers to the recommendations in the Draft PSG as "in vitro" testing or methods and we also use that phrase to describe the recommendations in the Draft PSG, not all of the recommendations require in vitro testing (e.g., Q1/Q2 sameness).

[33] § 320.22(b).

[34] Petition at 9-11.

[35] Petition at 10, 11.

[36] *Id.* The Petition also references interactions between Ferring and FDA "leading up to the submission of the NDA" and during review of the NDA. *Id.* at 11. FDA acknowledges that the Dosage Forms and Strengths section of the Firmagon labeling references "degarelix for injection."

[37] *See* § 320.24(a); see also section I.B.2 above (discussing FDA's discretion to determine how the BE requirement is met).

[38] § 320.24(b)(6); *see also* section I.C above (referencing the Draft PSG). We consider the multi-faceted approach recommended in the Draft PSG (which incorporates Q1/Q2 sameness, additional characterization of the active ingredient properties, comparative characterization of physicochemical characteristics, and comparative in vitro

2. Degarelix Controlled Release Is a Function of the Active Ingredient Rather Than the Inactive Ingredients

The Petition emphasizes that degarelix for injection is a complex in situ-forming depot product, where the depot formation "relies on the inherent capacity of the degarelix peptide to self-assemble to form highly structured amyloid fibrils" and is dependent on "an array of variables," including concentration of the peptide, manufacturing process and controls, pH, and acetate content.[39] According to the Petition, upon being reconstituted, Firmagon begins to self-associate and form amyloid fibers, which following subcutaneous injection form a hydrogel depot.[40] As described in the Petition, this "in-situ-forming structure" or "amyloid structure" is "essential to the product's function" because "the dissociation and release of peptide units from the depot governs the rate and extent of the peptide that is systemically available."[41] The Petition also emphasizes that, unlike other long-acting depots where controlled release is a function of a "complex copolymer formulant (such as poly(lactic-co-glycolic acid) or PLGA)," "controlled release [of degarelix] is a function of the structure adopted by the active ingredient itself."[42] The Petition acknowledges that the Firmagon formulation "is nominally simple" but asserts that "the ultimate structures and parameters responsible for controlling drug release for the depot do not form until the formulation fibrillates inside the body" and that neither the depot formation mechanism nor the drug release mechanism are completely understood.[43]

We agree that degarelix forms a depot at the site of injection and that the dissociation and release of degarelix from the *in situ*-formed depot governs the rate and extent of degarelix that is systemically available. We also agree that the precise mechanism by which the depot structure forms and by which degarelix is released is "incompletely understood." As discussed below, however, regardless of precisely how the depot forms or how degarelix is released, product performance is governed by the intrinsic properties of the drug substance, and this salient characteristic of the drug product is a basis for our recommendations in the Draft PSG.

Notably, we agree with the Petition that the Firmagon formulation is "simple" (composed of degarelix acetate and mannitol) and that the controlled release mechanism is driven by the intrinsic properties of the drug substance (i.e., "the inherent capacity of the degarelix peptide to self-assemble to form highly structured amyloid fibrils" and "the structure adopted by the active ingredient itself"), unlike other long-acting depots whereby controlled release is a function of a

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performance testing) to fall within our authority under 21 CFR 320.24(b)(6), as this approach consists of in vitro testing and more and we believe it is adequate to establish BE. Additionally, as discussed in footnote 75 below, in recommending the approach in the Draft PSG, we considered certain potential challenges with conducting an in vivo BE study for this particular product. We also note that recommending an in vitro approach to demonstrating BE, where we believe such an approach is adequate to meet the relevant statutory and regulatory requirements for approval, is consistent with FDA's broader goal of avoiding unnecessary human research. See section I.B.2 and footnote 22.

[39] Petition at 9, 12-14.

[40] Petition at 12.

[41] Petitioner at 9, 14. The Petition also references potential monomeric release models for degarelix depots. *Id.* at 12, 13.

[42] Petition at 9, 14.

[43] Petition at 12-14

"complex copolymer formulant."[44] The only excipient, mannitol, is known to be inert to the gelling and aggregation of degarelix.

It is recognized that the physicochemical characteristics of the product are closely related to the depot formation process. For example, as the self-aggregation fibril formation increases, the optical density and viscosity increase. Similarly, pH and acetate content have been shown to affect aggregation: at basic pH (>9), for example, aggregation is promoted; conversely, the presence of acetic acid has been shown to reduce aggregation. For these reasons, for two products with the same active ingredient and formulation, similarity in physicochemical characteristics is important to assure similar in vivo performance. Additionally, comparing in vitro gelling kinetics under the same conditions enables an assessment of whether two products can form gel in the same way and in the same timeline, and comparing in vitro drug release is important because bioavailability depends on the rate and extent of drug dissolution.

Accordingly, the Draft PSG recommends that a proposed generic product: be Q1/Q2 the same as the RLD; demonstrate active ingredient sameness as compared to the RLD (including characterizing the following properties: primary sequence, secondary sequence, and aggregation states);[45] have comparable physicochemical characteristics (including reconstitution time, acetic acid content, appearance, optical density, viscosity, and pH) to the RLD; be compared to the RLD with respect to gelling kinetics, under the same experimental conditions; and have acceptable comparative in vitro drug release to the RLD. Taken together, we believe that these recommendations are appropriate and adequate to demonstrate BE of a proposed generic product to Firmagon.

3. *Although Different Manufacturing Processes and Controls Can Affect PK, Manufacturing-Induced Differences in the Rate and Extent of Release Can Be Detected Using the In Vitro Approach Recommended in the Draft PSG*

The Petition asserts that the manufacturing process plays a key role in the aggregation properties of the drug and can affect its PK.[46] Several "critical" steps during the manufacturing of the drug substance are identified that must be "carefully controlled;" otherwise, according to the Petition, changes in manufacturing steps could affect the properties of the drug in the lyophilized state and "affect the evolution and behavior of identically formulated drug products."[47] The Petition further states that Ferring's "experience with degarelix confirms that manufacturing changes can impact the characteristics of degarelix depot formation in vitro and in vivo," wherein "the evidence shows that the drug substance manufacturing process can change the properties of the amyloid structures that evolve from otherwise identically formulated products."[48] The Petition concludes that "a proposed generic using a different manufacturing process, starting materials, specifications, and in process controls could form new impurities or misassemble to form

[44] *See* Petition at 9.
[45] The Draft PSG recommends such characterization to include physical properties of the active ingredient in the reconstituted drug product because, in this case, differences between a proposed generic drug product and the RLD in secondary structure and/or aggregation states may impact bioavailability.
[46] Petition at 14-19.
[47] Petition at 15.
[48] Petition at 16, 18.

structures with varying degree of aggregation and depot morphology, impacting its release profile in vivo."[49]

We generally agree that the manufacturing process can impact the PK for degarelix for injection because it can change key physicochemical properties of the drug product, in turn, potentially affecting factors that may impact degarelix aggregation. For example, certain manufacturing process changes could result in a drug substance with a higher propensity to aggregate compared to Firmagon, and this higher propensity to aggregate may be carried into the drug product. We also generally agree that undesired aggregation of degarelix may occur when manufacturing is not well controlled. This, however, does not preclude development of a bioequivalent and therapeutically equivalent product to the RLD using a different manufacturing process or different controls;[50] nor does it compel FDA to require in vivo BE evidence to demonstrate BE.

We believe that the in vitro approach recommended in the Draft PSG is adequate to detect differences in manufacturing processes and controls that may result in differences in degarelix depot formation and PK and, consequently, affect BE. As explained above, the Draft PSG recommends not only formulation sameness (including additional characterization of the active ingredient properties), but also comparison of critical physicochemical characteristics and comparative in vitro performance testing. Given that product performance is governed by intrinsic properties of the active ingredient, as well as the ways in which the tests recommended in the Draft PSG work together to assess BE (as explained in section II.A.2), we are confident that following the recommendations in the Draft PSG would ensure no significant difference—including differences that may result from differences in manufacturing processes or controls—between the extent and rate of absorption between a generic degarelix for injection drug product and Firmagon. As discussed below, that such manufacturing-induced differences can be captured with comparative in vitro testing is further supported by the data provided in the Petition.

The Petition describes degarelix preparations "that differ only in method of manufacture" that were "otherwise identically formulated."[51] In particular, the Petition references different changes in the method of manufacture of the active ingredient that, according to the Petition, affected the final drug product with regard to aggregation and depot formation, specifically higher bioavailability as observed in a PK rat model.[52] Notably, the Petition also concedes that the higher bioavailability observed in the in vivo PK rat data (and in a population PK model based on human clinical study data) "*also tracked with faster release as observed by in vitro dissolution, along with changes in optical density and viscosity*."[53]

[49] Petition at 19.
[50] An ANDA applicant is not required to use the same manufacturing process and controls as the RLD. See section 505(j)(2)(A) of the FD&C Act; § 314.94(a). If FDA finds, however, that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to ensure and preserve its identity, strength, quality, and purity, FDA will refuse to approve the ANDA. § 314.127(a)(1); *see also* section 505(j)(4)(A) of the FD&C Act.
[51] Petition at 2, 16-18.
[52] *Id.*
[53] *Id.* at 16 (emphasis added).

FDA agrees with the Petition's acknowledgement that the in vitro dissolution data "tracks with" the in vivo PK rat data. Moreover, in addition to differences in in vitro dissolution, the data show that other in vitro characteristics (e.g., optical density and viscosity) can be assessed to reveal bioavailability differences between "identically formulated" drug products made using different manufacturing processes.[54] These in vitro characteristics are among the physicochemical characteristics that are identified as part of the in vitro BE approach recommended in the Draft PSG.

The Petition acknowledges that these manufacturing changes "are distinguished in a number of quality parameters" but claims there is no "predictable pattern or ability to predict in vivo PK."[55] Although we agree that some parameters may be more or less sensitive to a particular type of manufacturing process change, the in vitro approach recommended in the Draft PSG does not rely on one or two in vitro tests; rather the recommended approach relies on a comparative assessment of *multiple* characteristics, and we believe that taken together, these tests will detect manufacturing-induced differences that may impact PK and thus BE. In summary, the data provided in the Petition illustrate how potential differences in performance resulting from manufacturing differences can be captured by comparative in vitro characterization, including through assessing such characteristics as optical density and viscosity, as well as comparative in vitro release tests.[56] We believe that these in vitro tests, along with following the other recommendations identified in the Draft PSG, would ensure a proposed generic drug and Firmagon would not have any significant difference in the rate and extent of absorption of degarelix.

B. The Absence of an In Vitro Test With an In Vitro-In Vivo Correlation Does Not Warrant Requiring In Vivo BE Studies

The Petition states that "the structural properties of the depot that control the rate of release are not evident until after the product is administered," and that "[a] conclusion that one sponsor's product will form the same depot as another sponsor's product, yielding an equivalent PK profile in vivo (and therefore not expose patients to greater risk of treatment failure), is a matter of speculation in the absence of in vivo testing."[57] The Petition also states that "Ferring is not aware of any acceptable comparative in vitro drug release-rate tests of the finished product that are biorelevant, in terms of modeling the in-situ depot or that would correlate with rate and extent of in vivo drug release," referencing its own in vitro methodologies and testing.[58] The Petition concludes that "in the absence of equivalent processes and controls to ensure that the

[54] The data submitted with the Petition show that manufacturing differences that impacted PK were captured through in vitro testing, including optical density, viscosity, and in vitro dissolution. Moreover, the in vitro dissolution data provided in the Petition are consistent with the bioavailability data from the PK rat model, in that drug product batches derived from a particular drug substance showed faster release in vitro, and also had higher bioavailability in the PK study, than their counterparts derived from a differently manufactured (though identically formulated) drug substance.
[55] Petition at 18.
[56] Petition at 15-19.
[57] Petition at 19.
[58] Petition at 19, 20.

manufacturing method is equivalent, the in vitro model is not a reasonable surrogate for in vivo BE."[59]

As noted above, we generally agree with the Petition's characterization that once reconstituted, Firmagon begins to self-associate and form amyloid fibers, which following subcutaneous injection form a hydrogel depot, and that the structural properties of the depot control the rate of drug release. However, we disagree that without in vivo BE evidence it is "a matter of speculation" whether two different depots will "yield an equivalent PK profile in vivo." As an initial matter, the Petition's description of Ferring's own in vitro dissolution testing method is not dispositive as to whether a discriminating in vitro release testing method can be developed.[60] Moreover, although a single in vitro test that has been correlated with and is predictive of human in vivo bioavailability data (in vitro-in vivo correlation, IVIVC) is one acceptable approach for demonstrating BE, it is not a prerequisite for every in vitro approach used to demonstrate BE.[61] Section 320.24(b) additionally lists, among other things, "[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" as an acceptable approach for demonstrating BE.[62] Here, the in vitro release test recommended in the Draft PSG is only one of many comparative in vitro studies that the Agency recommends, if an applicant chooses to use an in vitro approach to establish BE.

The Petition also states that adequate methods of characterizing degarelix are "lacking," reiterating the absence of a "detailed mechanistic understanding" of the in-situ forming depot, citing extensively an article published in February 2021 by Patil et al.,[63] and concluding that "[a] demonstrated IVIVC, or validation of a biorelevant in vitro test, is an essential step before it would be appropriate to recommend a waiver of in vivo BE."[64]

First, we do not agree that identifying adequate characterization methods is "challenging or even impossible," as there are a number of methods that can be used to support a characterization of degarelix self-aggregation in vitro. These methods include, for example, nuclear magnetic resonance (NMR), spectroscopy, and microscopy. An ANDA applicant may use a combination of these and other methods to conduct in vitro testing in accordance with the recommendations in the Draft PSG, and a single test need not have demonstrated IVIVC to be used as part of a demonstration of BE.[65]

Second, we do not find the Petition's analysis of the Patil et al. article to be persuasive. Patil et al. describes a preliminary study conducted to explore how a real-time NMR analytical method

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[59] *Id.*

[60] The Petition also includes difference factor (f1) and similarity factor (f2) statistical analyses (Petition at 21-24), but we were not able to conduct an independent assessment and do not have sufficient information on the in vitro release test method used to verify the claims in the Petition; nevertheless, this specific dataset is not determinative of all in vitro release testing methods. Moreover, as noted above, the in vitro dissolution data did, in fact, distinguish between "identically formulated" drug products made using different manufacturing methods. *See* footnote 54.

[61] Compare § 320.24(b)(1)(ii), with *id.* at (b)(5)-(6).

[62] *See* § 320.24(b)(6).

[63] Petition at 24-23. *See* Patil, S.M. *et al.*, A real-time NMR method for measurement of *in vitro* aggregation kinetics of degarelix drug products, AAPS PharmSciTech (2021) 22:73 at 1 (internal citation omitted) (Patil et al).

[64] Petition at 24-28.

[65] Any methods used must be validated by the applicant, and the appropriateness and validation of those methods would then be evaluated during our review of the ANDA.

can be used to characterize degarelix aggregation and examined the impact of a few factors (such as pH, degarelix concentration, and salt concentration) that are known to affect degarelix aggregation kinetics.[66] The Draft PSG neither states nor suggests that the real-time NMR method described in Patil et al. can be used as a "biorelevant surrogate for bioequivalence." It should also be noted that the recommendations in the Draft PSG are not dependent upon the findings reported in Patil et al.

Finally, we reiterate that an in vitro approach may be acceptable for demonstrating BE under section 320.24 even in the absence of a waiver of in vivo BE evidence under section 320.22(b).[67] And as discussed above, an in vitro test with IVIVC is not the only type of acceptable approach for demonstrating BE under section 320.24(b).

In sum, based on our current scientific thinking, if an ANDA applicant relying on Firmagon as the RLD were to pursue an in vitro approach to demonstrate BE, FDA recommends not only a Q1/Q2 same formulation (including additional characterization of the active ingredient properties) and comparative in vitro release testing, but also additional comparative in vitro testing, including reconstitution time, acetic acid content, appearance, optical density, viscosity, pH, and gelling kinetics.

C. Use of the Recommended In Vitro BE Approach Would Not Put Patients at Risk of Breakthrough Testosterone Levels

The Petition emphasizes that advanced prostate cancer is a serious and life-threatening condition that can result in significant morbidity and mortality if left untreated, and that successful treatment using androgen deprivation therapy depends, in part, on maintaining testosterone suppression through the end of the treatment period.[68] The Petition states that "based on [Ferring's] many years of experience with [Firmagon] and [Ferring's] understanding of the variables that may impact *in vivo* drug release, [Ferring] do[es] not believe patient safety and patient benefit can be assured if a generic version of Firmagon were approved without testing in humans."[69] The Petition further states that "[t]his is not a product for which BE can be taken lightly," and that "reliance on *in vitro* methods to reach a conclusion of BE in this instance would be based on an untested hypothesis and will put patients at unnecessary risk of treatment failure."[70]

FDA acknowledges advanced prostate cancer as a serious and life-threatening condition, but we do not agree that the in vitro BE approach recommended in the Draft PSG is inadequate for establishing BE or that it would place patients at risk. As noted above, we believe that the recommended in vitro tests, along with following the other recommendations identified in the Draft PSG, would ensure a proposed generic drug and Firmagon would not have any significant difference in the rate and extent of absorption of degarelix, thereby supporting a conclusion that

[66] Moreover, the Patil et al. article notes that "[t]he high-precision real-time NMR method was demonstrated to quickly differentiate lot to lot differences in degarelix aggregation kinetics, and to reveal the effects of degarelix concentration, pH, salt, and temperature on the kinetics."
[67] *See* section II.A.1.
[68] Petition at 28-29.
[69] *Id.*
[70] *Id.*

the generic product is bioequivalent to Firmagon. Such a showing of BE, along with other information required for approval, would then support a conclusion that the generic product can be expected to perform the same way in the body, and thus have the same clinical effect and safety profile, as Firmagon when administered to patients under the conditions specified in the labeling.[71]

D. Because We Conclude That an In Vivo Study Is Not Required, at This Time We Need Not Determine the Appropriate Elements of an Adequate In Vivo Study

In addition to requesting that FDA require in vivo BE evidence generally, the Petition asserts that either a multi-dose in vivo study or an in vivo study with pAUC analysis must be required to ensure that a proposed generic has the same rate and extent of release as Firmagon over the course of the dosing interval.[72] As discussed above, we believe that an in vivo study is not required to demonstrate BE and that an ANDA applicant can demonstrate BE by following the in vitro approach recommended in the Draft PSG.[73] Accordingly, it is not necessary to determine whether a specific type of in vivo BE study—i.e., a multiple-dose in vivo study or an in vivo study with pAUC analysis—would be required if an ANDA applicant chose to conduct an in vivo study.[74,75]

E. Revisions to the Draft PSG

The Petition requests that FDA revise the Draft PSG in accordance with the other requests in the Petition and re-issue the Draft PSG. For the reasons described, we deny the requests to require in vivo BE evidence and to specifically require pAUC analysis or a multiple-dose design as part of an in vivo BE study. Therefore, we also deny the request to revise the Draft PSG at this time. We note that the Draft PSG is not binding and thus an ANDA applicant may use an approach different from what the current Draft PSG recommends, as long as it satisfies the requirements of the applicable statutory provisions and regulations.[76] The Draft PSG is a science-based

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[71] We also note that, for all approved ANDAs, as well as NDAs, FDA monitors for adverse events through postmarketing surveillance and would take appropriate steps if warranted.

[72] Petition at 29-31.

[73] If an ANDA applicant demonstrates that its proposed generic is bioequivalent to Firmagon and the other requirements for approval are met, then we are confident that there will be no significant difference in the rate and extent of absorption—and specifically, that the trough levels for the generic drug will be adequate (*see* Petition at 29-31)—throughout the dosing interval.

[74] In asserting that either a multiple-dose steady state in vivo study or a single-dose in vivo study with analysis of pAUC metrics should be required, the Petition points to draft PSGs for two long-acting depot products, leuprolide acetate and triptorelin pamoate. Petition at 31. However, Firmagon is unlike these products, for which the in vivo drug release is a function of PLGA polymers. As discussed, because the controlled release for Firmagon does not rely on any carrier and rather is a function of the structure adopted by the active ingredient itself, we believe that an in vitro approach can be used to demonstrate BE and therefore need not determine the appropriate elements of an adequate in vivo study.

[75] We note that there are potential challenges with conducting an in vivo study with either a single-dose or a multiple-dose design. For example, it is unclear whether a single-dose study at the doses for Firmagon would be appropriate in healthy subjects, and using patients in a single-dose study is less sensitive because of confounding factors due to illness. Also, a multiple-dose steady state study would not be appropriate for the 120 mg/vial strength that is used only as a starting dose.

[76] *See* 21 CFR 10.115(d)(2). The acceptability of a given alternative approach will be evaluated during the review of a specific ANDA.

document that is subject to change as new data and information on degarelix for injection become available. We will continue to evaluate the Draft PSG to determine whether it should be revised if new information becomes available that changes our scientific thinking. If you have any additional comments about the recommendations in the Draft PSG, such comments should be submitted to the Draft PSG docket (Docket No. FDA-2007-D-0369-0547).

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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