FERRING
PHARMACEUTICALS

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Food and Drug Administration
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Rockville, Maryland 20852

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CITIZEN PETITION

Ferring Pharmaceuticals, Inc. (Ferring) submits this citizen petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law.[1] Ferring is the sponsor of Firmagon® (degarelix acetate) for subcutaneous injection for the treatment of patients with advanced prostate cancer. By this petition, we respectfully request that the Commissioner of Food and Drugs take the actions described below with respect to any abbreviated new drug application (ANDA) under section 505(j) of the Food, Drug and Cosmetic Act (FDCA), and any new drug application (NDA) under section 505(b)(2) of the FDCA, that references and relies on Firmagon for approval. In particular, we request a determination that any proposed generic product under section 505(j), or proposed follow-on product under section 505(b)(2) that relies on a showing of bioequivalence or comparative bioavailability to Firmagon, must be tested in human subjects. Based on Ferring's many years of experience with Firmagon, and our understanding of the variables that may influence the degarelix depot formed by the product, patient safety and patient benefit cannot be assured if generic and follow-on versions of degarelix are not subject to testing in human subjects. Ferring is not aware of any scientific evidence showing that *in vitro* testing and *in vitro* parameters correlate with *in vivo* drug release from a degarelix drug depot. Therefore, absent an adequate *in vivo* study, it would be a matter of speculation and assumption that a proposed generic or follow-on product would exhibit systemic drug release equivalent to Firmagon. For this reason, we bring this petition.

SUMMARY

Ferring markets Firmagon, a long-acting injectable product approved for the treatment of patients with advanced prostate cancer. Firmagon is an "androgen deprivation therapy" (ADT) that functions as a

[1] This citizen petition contains trade secrets and confidential commercial information, as defined by 21 CFR 20.61, that are protected from public disclosure under the Freedom of Information Act (FOIA) and the Trade Secrets Act. A redacted version of this petition has been submitted for public dissemination. The non-redacted version is for the agency's internal and confidential use. It is not for public dissemination either by posting on www.regulations.gov or through the Division of Dockets Management. Pursuant to 21 CFR 61(e), if FDA receives a request for further public disclosure and determines that disclosure may be required, Ferring requests pre-disclosure notification and the opportunity to object to any disclosure.

GnRH receptor antagonist. Firmagon forms a long-acting depot inside the body that slowly releases degarelix into systemic circulation to suppress testosterone to castrate levels and to maintain suppression for at least 12 months of treatment *via* maintenance dosing every 28 days. The extended-release properties of the depot are a result of a complex fibrillation process in which the degarelix peptide self-assembles into amyloid-like fibers. The properties of this structure control the rate of release of monomeric degarelix into systemic circulation.

Ferring determined during product development that the amyloid fibrillation process is sensitive to manufacturing conditions. [redacted]

Given the serious clinical implications for those patients who may escape castration during the maintenance interval (*e.g.*, increased morbidity, disease progression), an *in vivo* bioequivalence (BE) study is needed to assure that the rate and extent of release from a generic or 505(b)(2) product is equivalent to the RLD.

FDA experts have themselves recognized that the structure of the degarelix depot is critical to *in vivo* drug release, and that formation of the depot *in-situ* is a dynamic process involving numerous variables complex interactions between the drug in formulation and surrounding tissue. A paper by Patil *et al.* published in February 2021 with support from FDA's Center for Drug Evaluation and Research (CDER) described the depot formation process as follows:

> Upon contact with physiological fluid, degarelix undergoes quick gelation and forms a depot at the site of injection providing sustained release. The molecular gelling kinetics is a critical physiochemical quality attribute of degarelix products that may impact drug delivery. However, high-resolution and drug substance (DS)-specific analytical methods for characterizing gelling kinetics of degarelix are still lacking . . . Because the self-aggregation and gelling of degarelix can be affected by a variety of factors, such as degarelix concentration, incubation time, temperature, acetate content, and pH, **the systemic pharmacokinetic profile of degarelix is strongly influenced by the depot formation** . . .. [2]

The work presented by Patil *et al.* supports Ferring's own experience with the product and our own data.

[2] 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) (Tab 1) (Patil *et al.* (2021)) (emphasis added).

Because the manufacturing process is integral to product performance— and because the "pharmacokinetic [PK] profile of degarelix is strongly influenced by depot formation," and methods for characterizing the kinetics of depot formation are "lacking"— a conclusion that one sponsor's product will form the same depot as another sponsor's product, yielding equivalent systemic drug release *in vivo*, is a matter of speculation in the absence of *in vivo* testing.

Despite the underlying variables and inherent complexity of the degarelix depot, FDA issued a *Draft Guidance on Degarelix Acetate* that does not include or recommend an *in vivo* bioequivalence (BE) study.[3] We believe this is a mistake or is the result of unfounded, unsupported assumptions. FDA's draft BE recommendation—which allows for a determination of bioequivalence based on *in vitro* testing—fails to account for the FDA expert assessment (published one month before the *Draft Guidance*) showing that systemic PK is dependent on the characteristics of the *in vivo* depot. The *in vitro* testing described in the *Draft Guidance* involves testing of the drug formulation *prior to the formation of the rate-controlling depot.* Ferring is unaware of any evidence developed under the agency's ongoing research program, or otherwise, that would support reliance on an *in vitro* methodology to establish *in vivo* drug release of degarelix from a depot that forms *in vivo*.

Firmagon is clinically proven to provide castrate testosterone levels from Day 28 to the end of the treatment period in 97.2% of patients. A generic or follow-on product must be bioequivalent to Firmagon—including maintenance of the same level of therapeutic coverage from peak to trough through the end of the dosing interval—to be able to rely in full on the clinical studies that form the basis for the approval and labeling of Firmagon. An *in vivo* BE study is the only method that can actually prove whether the depot formed by a proposed product, manufactured by a new sponsor, exhibits the same rate and extent of drug release as Firmagon.[4]

Ferring has participated in the BE comment process with diligence and transparency in order to provide FDA with our insight regarding these issues. FDA published its *Draft Guidance* on March 25, 2021. Ferring conducted a comprehensive analysis of the *Draft Guidance* and submitted extensive comments under the guidance development process on August 10, 2021. Since that time FDA has published multiple revisions to its draft BE guidances without amending the guidance for Firmagon or otherwise responding to Ferring's comments. An ANDA referencing Firmagon was submitted in late 2019, prior to the issuance of the *Draft Guidance*, and remains under review. A second ANDA was submitted in the latter part of 2021. Given the importance of these issues to Ferring, and in light of our

[3] *See* FDA, *Draft Guidance on Degarelix Acetate*, Product-Specific Guidances for Generic Drug Development (Draft, Mar. 2021) (*Draft Guidance*) at 2, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022201.pdf.

[4] To approve a generic, FDA must find that the proposed drug product is pharmaceutically equivalent and bioequivalent to the RLD, which entails a finding that the products are therapeutically equivalent, meaning that the two products may be substituted "with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product." FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*), Preface at viii.

deep experience with the RLD and obligations to a vulnerable patient population, we are submitting this citizen petition so that FDA may address the requested actions in a timely manner in advance of any possible final action on a pending ANDA or 505(b)(2) application. To ensure patients are not exposed to any greater risk of treatment failures while using a generic or modified version of Firmagon, we request FDA revise the *Draft Guidance* to recommend a comparative *in vivo* pharmacokinetic study as a minimum step needed to establish bioequivalence to Firmagon.

ACTIONS REQUESTED

Ferring respectfully requests the Commissioner take the following actions:

1) Require ANDAs that reference Firmagon, and 505(b)(2) applications that rely on bioequivalence data or comparative bioavailability 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 RLD over the course of the dosing interval;

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

3) Re-issue the *Draft Guidance* based on the actions taken in response to this petition.

STATEMENT OF GROUNDS

I. BACKGROUND

A. Firmagon® (Degarelix Acetate)

Firmagon is a long-acting injectable, depot-forming product approved for the treatment of patients with advanced prostate cancer. Prostate cancer is the second most commonly occurring cancer in men worldwide (number one in the U.S.) and is the fourth most common cancer overall.[5] Over 1.2 million new cases and 358,000 deaths occur annually. Because the pathological growth and spread of prostate cancer is highly dependent on androgens, including testosterone (T) and dihydrotestosterone, one of the mainstays of treating patients with advanced prostate cancer is "androgen deprivation therapy" (ADT) (also known as medical castration) using gonadotropin-releasing hormone (GnRH) receptor analogues.

[5] *See* Prostate Cancer Statistics, World Cancer Research Fund International, *available at* https://www.wcrf.org/dietandcancer/prostate-cancer-statistics/.

Firmagon is an ADT that functions as a GnRH receptor antagonist. Natural GnRH is a neuropeptide hormone released from the hypothalamus that stimulates gonadotropic cells in the pituitary gland to release the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In turn, LH and FSH stimulate the gonadal production of sex steroid hormones and gametogenesis. Firmagon's active ingredient, degarelix acetate, is the acetate salt of a synthetic, 10-amino acid peptide that binds reversibly to pituitary GnRH receptors, thereby reducing the release of gonadotropins (LH and FSH) and, consequently, testosterone production.

FDA requires that all GnRH analogue products being developed demonstrate the ability to achieve and maintain "castrate T levels (<50 ng/dL) *from Day 28 through the end of the treatment period in more than 90% of patients.*" Failure to meet this efficacy endpoint is considered a clinical "treatment failure."[6] Successful treatment with ADTs relies on the ability to generate sustained, systemic drug exposure sufficient to attain *and* maintain castrate testosterone suppression through the end of treatment (the duration of which varies based on individual response and disease severity and can last up to several years).

To that end, Firmagon forms a long-acting depot inside the body that releases degarelix into systemic circulation to quickly suppress testosterone to castrate levels and to maintain suppression for at least 12 months of treatment *via* maintenance dosing every 28 days. The individual dose is distributed as a sterile lyophilized powder and must be reconstituted with Sterile Water for Injection before being administered. Upon reconstitution, Firmagon forms a colloidal suspension that must be subcutaneously injected into the abdomen within one hour of mixing. After injection, Firmagon interacts with the patient's biological environment to form a semi-solid depot at the site of injection from which degarelix is released very slowly into systemic circulation (median terminal half-life of 53 days for the first dose). The product is administered once every 28 days starting with a 240 mg loading dose (two 120 mg injections) and followed by an 80 mg maintenance dose thereafter. In its pivotal study, Firmagon achieved and maintained T levels below 50 ng/dL for 12 months, including at the end of month 12 (the primary efficacy endpoint required by FDA) in 97.2% of patients (202 of n=207; 95% CI).[7]

The extended-release properties of the depot inside the body are a result of a complex fibrillation process where the degarelix peptide self-assembles into amyloid-like fibers.[8] [redacted]

[6] *See* FDA Guidance for Industry, *Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone Analogues* (Draft, July 2019) at 7, *available at* https://www.fda.gov/media/129027/download (GnRH Guidance).

[7] *See* Firmagon Prescribing Information at 15–17 (last updated Feb. 24, 2020).

[8] Patil *et al.* (2021) ("Upon contact with physiological fluid, degarelix forms a gel depot at the injection site, from which degarelix is slowly released to the circulation. Because the self-aggregation and gelling of degarelix can be affected by a variety of factors, such as degarelix concentration, incubation time, temperature, acetate content, and pH, the systemic pharmacokinetic profile of degarelix is strongly influenced by the depot formation."). *See also* Maji *et al.*, *Amyloid as a depot for the formulation of long-acting drugs*, PLoS Biology (2008) (Tab 2) (Maji *et al.* (2008)); [redacted]

[redacted]

The properties of this structure control the rate and extent of release of monomeric degarelix into systemic circulation.[10] The bioavailability of degarelix from the depot is, among other things, dependent on the surface area of the depot and its permeability. [redacted] The administration of the defined doses of Firmagon at the defined high concentrations provides a depot which releases sufficient degarelix to sustain the required plasma concentration to have the desired therapeutic effect, but releases it sufficiently slowly that the plasma concentration is maintained at the therapeutically effective level long term. [redacted] It is not self-evident that a generic product manufactured by different processes will be bioequivalent, even if it is able to mimic Firmagon *in vitro*.

[redacted]

[redacted] NDA 022201, Clinical Pharmacology and Biopharmaceutics Review(s), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022201s000_ClinPharmR.pdf.

[9] *See* Maji *et al.* (2008).

[10] Patil *et al.* (2021); Maji *et al.* (2008); NDA Module 3.2.P.2 Pharmaceutical Development (Oct. 29, 2015) (on file at FDA); NDA 022201, Clinical Pharmacology and Biopharmaceutics Review(s), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022201s000_ClinPharmR.pdf.

[11] *See* Maji *et al.* (2008); NDA Module 3.2.P.2 Pharmaceutical Development (Oct. 29, 2015) (on file at FDA).

[12] *See infra* Section II.B; [redacted]

[13] *Id.*

[14] [redacted]

[15] *See infra* Section II.B.2; Schwach (2006).

[16] [redacted]

[redacted] Given the possible clinical implications for those patients who may escape castration during the maintenance dosing interval (*e.g.*, increased morbidity, disease progression, *etc*.), an *in vivo* BE study is needed to assure that the rate and extent of release from the generic in clinical use is equivalent to the RLD.

B. Legal and Regulatory Background

Section 505(j) of the FDCA establishes an abbreviated approval pathway for a generic drug product that is "the same as" a drug product previously approved under section 505(b) (the RLD).[17] An applicant seeking to market a generic version of the RLD submits an ANDA.[18] The ANDA approval process allows a generic applicant to rely entirely on FDA's previous finding of safety and effectiveness for the RLD rather than to independently demonstrate the safety and effectiveness of its proposed drug.[19] A generic applicant must demonstrate that the proposed generic drug product is "the same as" the RLD in all relevant respects—including active ingredient, dosage form, strength, route of administration, and (with narrowly permitted exceptions) labeling—and that it is bioequivalent to the RLD.[20]

Section 505(b)(2) of the FDCA establishes a pathway for NDAs that contain full reports of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference for use.[21] A 505(b)(2) applicant may rely on FDA's finding of safety and/or effectiveness for a listed drug only to the extent that the proposed product shares characteristics (*e.g.*, active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug.[22] Additionally, a 505(b)(2) applicant is expected to establish a scientific bridge between the proposed

[17] 21 USC 355(j).

[18] *Id.*

[19] *Id*.

[20] 21 USC 355(j)(2)(A)(ii)-(v). A principal benefit of approval under an ANDA is to receive an A-rating as therapeutically equivalent in the Orange Book. With an A-rating in the Orange Book, the generic drug product would be eligible in most states to be automatically substituted for the approved reference product at the pharmacy level. The underlying premise is that drug products sharing the characteristics that must be demonstrated for ANDA approval are therapeutically equivalent to each other and to the RLD, meaning one can be substituted for the other "with the full expectation that the substituted product can be expected to have the same clinical effect and safety profile as the prescribed product." Orange Book, 2019, Preface viii.

[21] 21 USC 505(b)(2); *see also* 21 CFR 314.54 (defining procedures and requirements for submission of a 505(b)(2) application).

[22] As a technical matter, the FDA-approved product relied upon by a 505(b)(2) application is referred to as a "listed drug" in FDA's regulations rather than "reference listed drug" used for ANDAs. *Compare* 21 CFR 314.54 (referencing "listed drugs" for 505(b)(2) applications) *with* 21 CFR 314.3 (defining "reference listed drug" as the product relied upon by an ANDA). For ease of drafting, these terms are treated as synonyms in this petition.

product and the listed drug relied upon in order to demonstrate reliance on the listed drug is scientifically justified.[23] Often, bioavailability or bioequivalence studies form the basis of this bridge.

A drug product is considered bioequivalent to the RLD if "the rate and extent of absorption of the drug do[es] not show a significant difference from the rate and extent of absorption of the [reference] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . ."[24] For a drug product that is intended to deliver the active ingredient systemically within the body, those parameters can be measured directly in the bloodstream.[25]

By regulation, FDA has established that pharmacokinetic studies are preferred as the most accurate and dependable method of establishing bioequivalence for a systemically acting drug.[26] As FDA has observed, "the statutory definition of BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety, emphasizes the use of pharmacokinetic endpoints in an accessible biological matrix, such as blood, plasma, and/or serum, to indicate release of the drug substance from the drug product into the systemic circulation."[27] Indeed, FDA has expressly observed that it "does not recommend *in vitro* approaches for drug products that are intended to be systemically absorbed." [28]

FDA's 2021 *Draft Guidance on Degarelix Acetate* for generic drug development does not include or recommend an *in vivo* BE study.[29] It proposes a series of *in vitro* comparisons in order to determine that the generic degarelix is bioequivalent to Firmagon. It recommends that the generic match Firmagon in reconstitution time, acetic acid content, appearance, optical density, viscosity, and pH. It then proposes an *in vitro* gelling-kinetics assay and an *in vitro* release (IVR) test. There is also a recommendation for demonstrating active pharmaceutical ingredient ("API") sameness based on "primary sequence, secondary

[23] Draft Guidance for Industry, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (Oct. 2017) at 4–5, *available at* https://www.fda.gov/media/123567/download.

[24] 21 USC 355(j)(8)(B)(i).

[25] *See* 21 CFR 320.24(b)(1)(i).

[26] Under governing regulations, "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." 21 CFR 320.24(a). The regulation instructs applicants to use "the most accurate, sensitive, and reproducible approach available" among those listed by FDA. These methods include, in "descending order of accuracy, sensitivity, and reproducibility," *in vivo* pharmacokinetic studies, *in vivo* pharmacodynamic effect studies, clinical endpoint studies, and *in vitro* studies. 21 CFR 320.24(a), (b).

[27] Draft Guidance for Industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application* (Dec. 2013) at 3, *available at* https://www.fda.gov/media/87219/download (*ANDA Bioequivalence Guidance*).

[28] *Id.* at 8. *See also* 21 CFR 320.24(b)(1)(i) (stating *in vivo* studies measuring pharmacokinetic endpoints are "particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body").

[29] *See* Degarelix Guidance, *supra* note 3.

sequence and aggregation states."[30]

II. ARGUMENT

A. Evidence of *In Vivo* Bioequivalence is Required

Firmagon is a complex *in situ*-forming depot product. 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 (known and unknown), including concentration of the peptide, manufacturing process and controls, pH, and acetate content. The amyloid structure is thought to be responsible for the rate/release controlling mechanism of the depot and is therefore critical to the efficacy of the product across the month-long dosing interval, and from month-to-month with maintenance dosing.

In most cases, controlled release in a long-acting depot is a function of a complex copolymer formulant, such as poly(lactic-co-glycolic acid) (PLGA). In this case, controlled release is a function of the structure adopted by the active ingredient itself after it is administered to the patient. The active ingredient, degarelix, plays two roles. The first is conventional: Degarelix is the active moiety of the drug product that exerts pharmacological effect at the site of drug action, the pituitary GnRH receptor. The second is unconventional: The degarelix peptide can self-associate to form a fibrillated amyloid structure *in-situ* that supplies the mechanism of controlled release. The active ingredient therefore also operates inside the body as an essential and structurally complex modifier of the formulation. The fibrillation process is stochastic and can be affected by manufacturing variables lending an inherent variability and complexity to the degarelix depot.[31]

Firmagon does not have the composition or properties of a parenteral solution. For certain drug products, FDA regulations permit a biowaiver where the "*in vivo* bioavailability or bioequivalence of the drug product may be self-evident."[32] For example, if the drug product "[i]s a parenteral solution intended solely for administration by injection . . . and [c]ontains the same active and inactive ingredients in the same concentration" as an approved reference drug, FDA may waive the usual requirement for *in vivo* bioequivalence.[33] This is not the case with Firmagon. The properties that determine the rate and extent of drug released into circulation are not evident in the finished dosage form, and the *in vivo* process that determines the rate and extent of release cannot be reliably replicated outside the body. The product undergoes transformation inside the body to form the depot, which controls the rate and extent of release, and the measurable features of the drug product outside the body that may predict *in vivo* performance are

[30] Degarelix Guidance, *supra* note 3.

[31] Patil *et al.* (2021); Maji *et al.* (2008); [redacted]

[32] 21 CFR 320.22(b).

[33] *Id.*

not well understood. The drug substance undergoes aggregation, disaggregation, and lyophilization steps during the manufacturing process, all of which are carefully controlled. Data show that measured changes in these upstream aggregation, disaggregation and lyophilization steps may be carried through into the final drug product and affect the resulting depot.[34] For this reason, two degarelix products with seemingly equivalent formulations, including seemingly identical drug substances, may not behave the same way *in vivo*.

By regulation, FDA has established that pharmacokinetic studies are the most accurate and dependable method of establishing bioequivalence for a systemically acting drug.[35] As FDA has observed, "the statutory definition of BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety, emphasizes the use of pharmacokinetic endpoints in an accessible biological matrix, such as blood, plasma, and/or serum, to indicate release of the drug substance from the drug product into the systemic circulation."[36] Indeed, FDA has stated that it "does not recommend *in vitro* approaches for drug products that are intended to be systemically absorbed."[37] Furthermore, under the regulations, FDA has stated that a biowaiver is not intended for extended release products.[38] Under FDA's regulatory framework, a biowaiver is only appropriate for immediate release products and for which bioequivalence is self-evident.[39] Firmagon is not such a product. The rate and extent of release of the drug substance *in vivo* is dependent on a structurally complex and variable depot that forms upon injection and that facilitates month-long action. Below we show (1) that Firmagon is not a parenteral solution, (2) that a complex, *in situ*-forming fibrillated matrix determines the rate and extent of release, and (3) that the resulting depot structure depends on highly controlled manufacturing conditions.

1. *Firmagon is not a Pharmaceutical Solution*

Firmagon is not a solution in the dosage form when it is released for commercial distribution, nor is it a solution when it is administered; it does not behave like a solution *in vitro* or *in vivo* and does not exhibit the properties of a solution. The word "solution" occurs only once in the product labeling, and its use in the labeling is only in the context of human factors considerations, as a safety precaution against

[34] *See infra* Section II.B.2; [redacted]

[35] Under governing regulations, "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." 21 CFR 320.24(a). The regulation instructs applicants to use "the most accurate, sensitive, and reproducible approach available" among those listed by FDA. These methods include, in "descending order of accuracy, sensitivity, and reproducibility," *in vivo* pharmacokinetic studies, *in vivo* pharmacodynamic effect studies, clinical endpoint studies, and *in vitro* studies. 21 CFR 320.24(a), (b).

[36] Draft Guidance for Industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application* (Draft, Dec. 2013) at 3, *available at* https://www.fda.gov/media/87219/download.

[37] *Id.* at 8. *See also* 21 CFR 320.24(b)(1)(i).

[38] *See* 21 CFR 320.22(d)(iv).

[39] 21 CFR 320.22(b).

administering a parenteral medical product with what could be unacceptable particulate matter. It is not a scientific description of the physicochemical form or thermodynamic properties of the product, and the term "solution" is not relevant to the clinical pharmacology of the product.

In its correspondence with Ferring leading up to the submission of the NDA, FDA agreed that Firmagon was accurately presented as an injectable *suspension*.[40] Firmagon was described as a suspension in the original NDA submission and was treated as such during its review by FDA.[41] During labeling review, FDA requested a change to the description of the dosage form to address a practical concern related to the handling of the product by end users. The precise issue that led FDA to move away from the scientifically accurate description (suspension) to a description designed to ensure safe use of the product (solution) was based on a scenario in which a healthcare provider fails to administer the product within the first hour following reconstitution. FDA stated: "It is inappropriate to label this drug product as a suspension because it may mislead the end-user to think that the expired, cloudy, self-associated gel state may be acceptable for administration."[42] Accordingly, FDA recommended that the product should be labeled as a lyophilized powder for solution, consistent with the fact that, initially, degarelix first appears as a clear liquid upon reconstitution. However, the reconstituted product is not a true solution in terms of its thermodynamic behavior, nor does it comply with the USP Monograph requirements for solutions, which require passing a clarity of solution test. The reconstituted drug product looks clear to the naked eye, but it is in fact turbid, as confirmed by optical density measurements, due to degarelix initiating the self-association process upon being mixed with water.[43]

Throughout development, Ferring maintained that the term "suspension" is more suitable than "solution," both as a matter of pharmacological and compendial classification and nomenclature, and because of concerns regarding labeling comprehension and use. FDA ultimately agreed to label the product as "degarelix for injection" as opposed to "degarelix for injectable solution." Based on this regulatory history and the product's failure to meet USP standards—and the abundant facts relating to how the product functions—Firmagon should not be considered a solution for purposes of bioequivalence standards.

[40] *See, e.g.*, IND 51222, Response to Sponsor's Specific Questions (November 2, 2004) at 3 ("the established name 'degarelix for injectable suspension' is acceptable.") (on file at FDA).

[41] *See, e.g.*, NDA 022201, Form FDA 356 (February 29, 2008) (on file at FDA); NDA 22201, Clinical Statistical Review at 18, *available at* (describing the product's pharmacokinetics following depot formation as being "strongly influenced by its concentration in the injection suspension."), *available at* *https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022201s000_MedR.pdf*.

[42] *See* FDA Email to Ferring (November 12, 2008) (on file at FDA).

[43] [redacted]

2. *Drug Release from Firmagon is Determined by a Complex*, In Situ-*forming Fibrillated Structure*

Drug release from Firmagon is governed by an *in situ*-forming depot structure. The *in situ*-forming structure is essential to the product's function. The product is designed to form a depot inside a patient's body, and to release degarelix slowly from the depot over multi-week intervals. Upon being reconstituted, Firmagon begins to self-associate and form amyloid fibers, which following subcutaneous injection form a hydrogel depot. As with most drug products that deposit the formulation to a local site inside the body, and that remain in place and release drug over a prolonged interval, bioavailability is a function of complex nano-structural features of the depot and its interaction with the endogenous environment, the outcome of which is not self-evident.

The complex mechanism of release of degarelix monomers from the *in-situ* depot is dependent on the self-association and fibrillation mechanism, discussed above. Upon formation, the kinetics of monomer binding and unbinding to the amyloid fibrils, fibril shape/size/number, and stability of the fibrils are considered important to the controlled release profile of the depot, where sufficient levels of active monomer can be released for the intended duration of action.[44] This complex process is incompletely understood. While Ferring studied these phenomena in depth during development and has advanced the understanding of degarelix depot formation, the mechanism of formation of the *in-situ* depot, and the precise mechanism of release from the depot, remains subject to hypothesis. Release of monomers from the fibril termini has been hypothesized to be one possible mechanism.[45] Release of free monomers from the fibril network is another.[46] These two processes may be interrelated and dynamic, with release from the fibril termini leading to progressive degradation of the amyloid depot, allowing further diffusion of free monomer from the fibril network.

[redacted]

[44] Patil *et al.* (2021); Maji *et al.* (2008); [redacted]

[45] Maji *et al.* (2008); [redacted]; G. Schwach, *Degarelix, a potent peptidic self-depoting GnRH receptor blocker*, AAPS Annual Meeting, New Orleans, Nov. 14–18, 2010 (Tab 4) (Schwach (2010)).

[46] *Id.*

[redacted]

[redacted]

[redacted] It is hypothesized that ions and other components of the interstitial fluid infiltrate the depot, contributing to its maturation and consolidation.[48] Degarelix is then able to slowly diffuse through the depot surface at a rate sufficient to achieve its biological and clinical effect.[49] The surface area and permeability of this complex, evolving structure may be relevant to bioavailability and are difficult to predict.

[47] [redacted]

[48] *Id.* In the context of PLGA-based depots, FDA has recognized that "[o]ne of the major reasons the *in vivo* release mechanisms of PLGA microspheres are not well understood is due to the difficulty of retrieving the particles following administration;" furthermore, "[f]actors present in the subcutaneous administration environment . . . are not accurately represented by current [IVR] environments [and] little work to date has been done in attempt to validate . . . hypotheses regarding how these factors influence drug release." Doty, A.C. *et al*., *Mechanisms of* in vivo *release of triamcinolone acetonide from PLGA microspheres*, J Controlled Release (2017) 256: 19–25 ("Biological factors that may influence the way drugs are released from PLGA matrices include the inflammatory response and the presence of enzymes, lipids, organic amines, and other endogenous compounds present in the administration environment.") (citations omitted) (Tab 5).

[49] Schwach (2010).

Based on the available science, the dissociation and release of peptide units from the depot governs the rate and extent of the peptide that is systemically available. This is distinct from parenteral solutions where bioavailability is self-evident based on the complete solubilization and immediate systemic availability of the drug substance. While like-like (Q1/Q2) degarelix preparations will all form amyloid-like structures in the right environment, the structure of these fibrillar networks and the way they interact with the *in-situ* environment may differ based on (among other things) the manufacturing process used to produce the lyophilized product. The extent to which these manufacturing variables may be discerned in the *in vitro* environment by testing the finished drug product is uncertain. Ferring's data suggests that an *in vivo* model is more sensitive to manufacturing changes than an IVR test (*see* II.B.2 *infra*).[50]

While the formulation is nominally simple, the process of aggregation is dynamic and complex and, as shown below, is significantly affected by variables in the manufacturing process. In all the proposed models, the structure of the final depot, fibril-monomer thermodynamic driven exchange, and the stability of the fibrils, are considered important to ensure a long duration of action and sufficient release of active monomer to generate effective drug concentration. These structures are initiated *in vitro* and thereafter evolve *in-situ*, and as described below, the manufacturing process is known to affect the traits of the final drug substance and the final drug product. These traits can be impacted by the conditions of manufacture of both the drug substance and final drug product. While some of these traits are measurable *in vitro*, the form of the product that governs the rate and extent of release is not manifest until the depot is formed *in-situ* in humans. In the case of degarelix, the ultimate structures and parameters responsible for controlling drug release for the depot do not form until the formulation fibrillates inside the body.

3. *The Manufacturing Process Plays a Key Role in the Aggregation Properties of the Drug and Can Affect PK*

Degarelix self-assembly is a thermodynamically complex process resulting in a protein-like amyloid structure. Amyloid protein structures or fibers are common in nature and can play an important role in cellular systems. They are complex, multimeric, and highly variable structures. The mechanism of formation of amyloid fibrils, as well as the morphology and properties of the amyloid, are imperfectly understood and can vary in ways that are difficult or impossible to accurately predict. [redacted] it is possible for the same nominal substance to self-assemble to form, on the one hand, a safe and effective depot aggregate (*e.g.*, Firmagon), and on the other, structures with varying degree of aggregation

[50] 21 CFR 320.24(a) ("Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available….").

[51] Patil *et al.* (2021); Maji *et al.* (2008); Schwach (2010); [redacted]

that may resemble Firmagon *in vitro* but whose behavior *in vivo* is not known.[52]

The manufacturing of the final drug substance [redacted] can affect the [redacted] properties of amyloid substance [redacted]

[redacted]

[redacted]

5[redacted]); Patil *et al.* (2021); Maji *et al.* (2008); [redacted]

53 [redacted]

54 *Id.*

55 *Id.*

56 *Id.*

57 [redacted]

[redacted]

[redacted]

Ferring's extensive experience with degarelix confirms that manufacturing changes can impact the characteristics of degarelix depot formation *in vitro* and *in vivo*. [redacted]

[redacted]

[redacted]

[59] [redacted]

[60] *Id.*

[61] *Id.*

[62] *Id.*

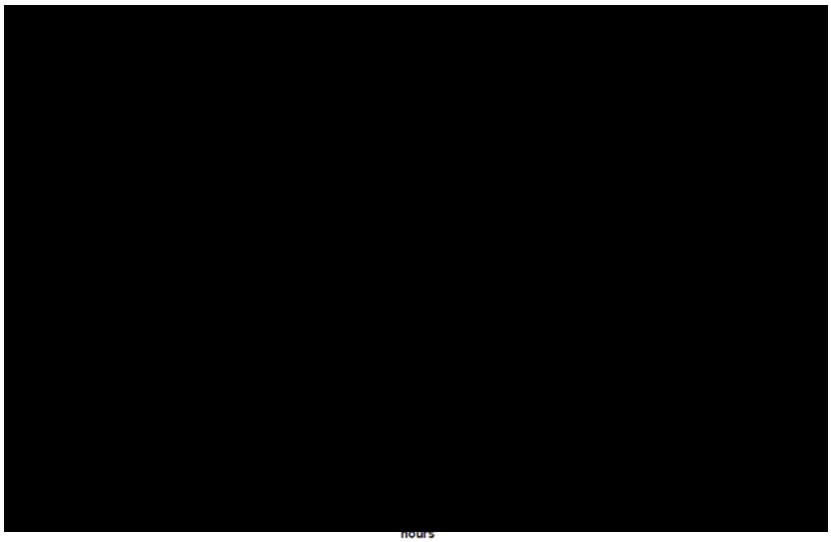
[63] [redacted]

[64] *Id.*

[65] [redacted]

[66] [redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

In summary, Ferring's extensive experience with degarelix confirms that manufacturing processes can impact the characteristics of degarelix depot formation *in vitro* and *in vivo.* [redacted]

As described further below, [redacted]

[redacted] *In vitro* testing on the finished drug product is not sufficient on its own in the context of a proposed generic of Firmagon. Thus, while Firmagon is able to self-assemble to form a safe and effective amyloid depot based on a process that has been controlled within narrow limits, and calibrated against what was tested clinically, a proposed generic using a different manufacturing process, [redacted] could form new impurities or misassemble to form structures with varying degree of aggregation and depot morphology, impacting its release profile *in vivo*.

B. *In Vitro* Testing that Adequately Predicts *In Vivo* Drug Release from the Depot is Lacking

FDA officials, writing for publication, have acknowledged that the "pharmacokinetic profile of degarelix is strongly influenced by depot formation" methods for characterizing the kinetics of depot formation are "lacking." 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. As stated above, the structural properties of the depot that control the rate of release are not evident until after the product is administered. The product undergoes transformation inside the body to form an amyloid-like depot. While a fibrillated structural form of the product can be evolved *in vitro* by reconstituting and developing the amyloid, the resulting structure is subject to the experimental conditions and varies based on those conditions. The structure is unfixed, and the relevant point of comparison between test and reference product is subjective. Even if the point of comparison could be fixed, the dynamics and kinetics of self-assembly *in vitro* are not the same as those observed *in vivo*. [redacted] Thus, in the absence of equivalent processes and controls to ensure that the manufacturing method is equivalent, the *in vitro* model is not a reasonable surrogate for *in vivo* BE.

The extent to which the molecular structure and physical characteristics observed *in vitro* can accurately predict the rate and extent of drug release from the depot, has not been determined. [redacted]

[redacted]

[redacted]

Below we describe (1) the attempts made by Ferring during development to [redacted], (2) Ferring data showing [redacted], and (3) the general and specific "lack" of *in vitro* methodology with proven capacity to serve as surrogate for *in vivo* BE.

1. In Vitro *Methodologies and Testing by Ferring*

[redacted]

[redacted]

[68] [redacted]

[69] *Id.* at 24–25.

[70] *Id.* at 25–28.

[redacted]

2. In Vitro *Testing, Including IVD/IVR, Fails to Pick Up Significant Biological Differences*

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

At the very least, these data suggest that an *in vivo* PK study may be more sensitive to potential differences and therefore should be required.[74]

3. *Adequate Methods of Characterizing Degarelix are "Lacking"*

For long-acting parenteral products, including *in situ*-forming implants, FDA has emphasized that there are no standard or applicable compendial IVR assays and that the release mechanism (especially *in vivo*) is not fully understood. Firmagon is an *in situ*-forming depot for which a detailed mechanistic understanding of its *in vitro* and *in vivo* behavior is lacking. After injection, Firmagon undergoes a complex transformation between different structures [redacted] (*see* II.A.2 *supra*). Accordingly, identifying adequate characterization methods is challenging or even impossible. To understand the behavior of Firmagon both inside and outside the body, we must differentiate between (1) the early degarelix interactions leading to formation of small, soluble aggregates (nucleation), (2) concomitant nucleation of β-sheet ordered fibrils and (3) the later formation of amyloid fibril structures and gelled networks. Initial aggregation-nucleation kinetics (the early processes) and elongation-gelling kinetics (later process) can be studied with different techniques. In studying one of these processes it is not scientifically reasonable to draw conclusions or inferences across all other parts of the aggregation process. At the same time, it is difficult to study one process in isolation without interference from other processes. For example, when studying the early onset of aggregation, interference of soluble and insoluble aggregates can be expected. It is therefore critical to be clear on which part of the complex and dynamic system is being targeted by a particular experimental inquiry and what information will and can be obtained with that specific technique.

With regard to Firmagon, an article published in February 2021 by Patil *et al.*, funded in part by FDA's CDER, recognized that the "pharmacokinetic profile of degarelix is strongly influenced by depot formation," which in turn is a highly variable-dependent process, and that methods for characterizing

[74] 21 CFR 320.24(a) ("Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available….").

degarelix are "lacking."[75] Patil *et al.* acknowledged that Firmagon is "challenging to study" because of fast aggregation under physiological conditions, and that "no validated method is available."[76] The paper goes on to describe what it claims to be an *in vitro* method of obtaining 1D ^{1}H NMR spectra for reconstituted degarelix to derive aggregation kinetics.[77] However, it is clearly stated that the aim is NMR method development "*to measure the gelling kinetics of degarelix drug product*" and, hence, not to study the kinetics of the initial part of the aggregation process which includes the nucleation phase.[78] Accordingly, the paper tends to conflate the early and late parts of the aggregation process. The use of the term aggregation when discussing both the early and later parts of the processes unfortunately renders the terminology ambiguous, and understanding the results and conclusions, difficult.

Notably, the published NMR method used degarelix resuspended in pure D_2O as negative control.[79] Patil *et al.* claim to observe no spectral changes over the fixed time course (44 hours) for degarelix in pure D_2O and therefore concluded that there is no further aggregation (by which the author's appear to mean gelation) in the pure D_2O experimental preparation.[80] In contrast, it is claimed that degarelix could be observed to self-aggregate virtually instantaneously in a simple sodium phosphate buffer, with further NMR spectral shift from 0-44 hours indicating ongoing aggregation (by which the author's again may mean gelation). However, in the Supplementary Information to the article, data and statements suggest that not only are aggregates present in neat D_2O already at T=0, but that the aggregates are also changing with time as given by cryo-TEM images at T=5 h (Figure S5).[81] Additionally, dynamic light scattering data show that degarelix aggregates in D_2O are not constant over time; they change, and elongation/ fibrillation cannot be excluded to occur although the NMR data do not seem to capture this. In fact, it is known that large aggregates and aggregates that phase separate are either partially or not at all captured by ^{1}H NMR.[82] Accordingly, it is questionable if degarelix in D_2O is a true "negative control." This illustrates the difficulties of defining a relevant control for a possible *in vitro* method. Furthermore, the study illustrates the problem of drawing inferences relating to the overall aggregation process—early and late—based on just part of the process, let alone extrapolate those observations to an inference of what may happen *in vivo*.

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[75] Patil *et al.* (2021) at 1.

[76] *Id.* at 3.

[77] *Id.* at 1–2, 6–7.

[78] *Id.* (emphasis added).

[79] *Id.*

[80] *Id.* at 2-5.

[81] *Id.*, Supplementary Information.

[82] *See, e.g.*, Hjalte, J. *et al.*, *Aggregation Behavior of Structurally Similar Therapeutic Peptides Investigated by ^{1}H NMR and All-Atom Molecular Dynamics Simulations*, Molecular Pharmaceutics at F, J–K (Feb. 2022) DOI: 10.1021/acs.molpharmaceut.1c00883. PMID: 35104408 (Tab 7) (Hjalte *et al.* (2022)) ("Molecules residing in large aggregates become practically undetectable in liquid-state NMR . . . In some instances, the fact that large aggregates may not give rise to a detectable NMR signal can be an obvious drawback.").

In addition, while the article by Patil *et al*. reports that degarelix could be observed to aggregate (or gel) at the first timepoint of NMR measurement in a simple sodium phosphate buffer[83]—with further NMR spectral shift up to 44 hours, indicating ongoing changes in the structures formed—it is likely that the early aggregation/nucleation had already started prior to the NMR measurement in both this and the neat D_2O case. The broadening of parts of the NMR signals, observed for the negative control, and interpreted as containing no gelled degarelix, in fact strongly indicate that soluble degarelix aggregates were present at the start of the measurement. [redacted] This leads Ferring to conclude that the method published by Patil *et al*. accounts largely for the latter part of the aggregation process, the gelation process. Again, as NMR measurements capture only fibrillation and gelation, which constitute only a part of the aggregation process, this method provides insufficient information for *in vitro* predictability of *in vivo* behavior.

Finally, batch-to-batch variation, as investigated here, should not be evaluated using fractions of single dosage units. This is insufficient for demonstrating content uniformity and/or average content within a batch. Instead, the complete content of a vial must be reconstituted. In the work presented in the article by Patil *et al*., only a small fraction of the lyophilized powder in a vial is weighed for each sample (<3% of the content for the 80 mg product and <5% for the 120 mg product) and thus no conclusion on within-batch and batch-to-batch variability can be drawn based on the study design presented in the article.

Although the NMR method reported by Patil *et al.* adds to the understanding of degarelix aggregation, the method is experimental in nature and is not sufficiently developed to differentiate between different preparation of degarelix in a meaningful way. While the kinetics of the latter part of degarelix aggregation *in vitro* is an interesting and potentially informative parameter, it provides only one dimension of quantitative information relating to what may be of relevance for the rate of degarelix gel formation. Moreover, no data on actual gel formation by, *e.g.*, rheology measurements, were given. Nor does such data supply qualitative or quantitative insight on the structure or kinds of aggregates that are formed. Finally, while the behavior of degarelix in a simple salt buffer is relevant and informative of self-aggregation, it is not predictive of the process that occurs *in vivo*. The rate of formation of the depot *in vitro* may be an interesting manufacturing quality attribute worth investigating, it reveals limited information on the central question, *i.e.*, the predictability of the rate and extent of release of degarelix from the *in situ*-forming depot, inside the body.

[83] Patil *et al.* (2021) at 3.

[84] Hjalte *et al.* (2022).

[redacted]

Indeed, Patil *et al.* recognized that its experimental conditions were an important limitation on the utility of its findings:

> Per Firmagon® label, the actual administration concentration of degarelix is 40 or 20 mg/mL. The current experimental design of measuring degarelix at 2 mg/mL allowed the *in vitro* kinetics to be obtained under slower aggregation kinetics, not necessarily the time scale of the *in vivo* gelling kinetics. Another *in vitro* study of degarelix at 1 mg/mL revealed much longer $t_{1/2}$ of 15 days for amyloid fibril formation…. The composition of the solution used for reconstitution and concentration of degarelix played important roles in aggregation kinetics of degarelix. The presence of higher salt concentrations, higher pH, and higher concentrations of degarelix in solution increased the observed aggregation kinetics and should be considered when setting up a protocol for aggregation studies.[86]

The authors also recognized the limitations of using D_2O:

> Though the current experiments were performed in D_2O buffer using high-field NMR instrument equipped with cryogenic probe, the possibility of transferring the method to H_2O based solvent with a lower field NMR using room temperature probes is possible although longer NMR measurement time would be needed to overcome the lower sensitivity.[87]

Ultimately, Patil *et al.* concluded that the published method is suitable only for product quality.[88] It does not serve as a biorelevant surrogate for bioequivalence. The experimental conditions may reveal or distort biorelevant differences. Experimental variables may accentuate differences that are not relevant or mask those that are. At its core, the experimental framework described by FDA provides too much room for an observer to engineer the "right" conditions and choice of instrument and equipment details to establish a match. This is similar to Ferring's observations with IVD, which can mask differences that are revealed *in vivo*.

We remain unaware of any evidence developed under the agency's ongoing research program or elsewhere that would support reliance solely on *in vitro* methods in order to demonstrate BE for a proposed generic version of Firmagon. A demonstrated IVIVC, or validation of a biorelevant *in vitro* test, is an

[86] Patil *et al.* (2021) at 7.

[87] *Id.*

[88] *Id.* ("Overall, the observed differences in aggregation $t_{1/2}$ may be suitable as an analytical metric for batch to batch comparisons of drug product quality with respect to gel formation.").

essential step before it would be appropriate to recommend a waiver of *in vivo* BE.[89] *In vivo* studies are presently the only scientifically reasonable method of determining BE.

C. Failure to Require an *In Vivo* BE Study Places Patients at Risk of Breakthrough T Levels and Thus Serious Clinical Consequences for Patients Undergoing Treatment for Advanced Prostate Cancer

Advanced prostate cancer is a serious and life-threatening condition that can result in significant morbidity and mortality if left untreated.[90] While prostate cancer is a relatively slow-growing malignancy, patients with advanced or metastatic prostate cancer are not only at risk of death (with a 5-year survival average of up to 30%)[91] [redacted]

Castration, through surgical means or ADT, has been used to treat prostate cancer for decades and remains the foundational therapy in this disease state. Successful treatment with ADTs relies on the ability of the drug to maintain sustained systemic drug exposure sufficient to attain *and* maintain testosterone suppression through the end of the treatment period. Based on Ferring's many years of experience with the product and our understanding of the variables that may impact *in vivo* drug release, we do not believe patient safety and patient benefit can be assured if a generic version of Firmagon were to be approved without testing in humans. As indicated above (II.A.3) the manufacturing process can impact the PK profile of otherwise Q1/Q2 products, including in propensity to exhaust drug from the depot and deplete degarelix to below 9-10 ng/mL at the end of the dosing interval, risking testosterone escape. As a result, Ferring urges FDA to require that a generic sponsor of degarelix acetate conduct an *in vivo* BE study showing that the generic has the same rate and extent of release as the RLD. The BE study should be designed to assure the generic is able to maintain adequate trough levels (C_{min}) through month 12 to ensure an equivalent number of patients have treatment success and will not escape castration during treatment.

While a generic need not reprove the efficacy of degarelix, it must establish that it is bioequivalent by a method that is sufficiently sensitive to clinically meaningful differences in the rate and extent of release *in vivo*, in humans. This is not a product for which BE can be taken lightly. Reliance on *in vitro* methods to reach a conclusion of BE in this instance would be based on an untested hypothesis and will

[89] *See, e.g.*, Guidance for Industry, *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (Sept. 1997), *available at* https://www.fda.gov/media/70939/download; *see also* Kaur, P. *et al., Applications of* in vitro-in vivo *correlations in generic drug development: case studies*, AAPS J (July 2015) 17(4):1035-39 (Tab 8).

[90] The 5-year survival rate for men with advanced or metastatic prostate cancer ranges from 26% to 30%. *See* Survival Rates for Prostate Cancer, *available at* https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.html.

[91] Steele *et al.*, *Prostate Cancer Survival in the United States by Race and Stage* (2001–2009): Findings From the CONCORD-2 Study, Cancer. 2017 Dec 15; 123 (Suppl 24): 5160–5177 (Tab 9).

put patients at unnecessary risk of treatment failure. As emphasized above, Ferring is unaware of any evidence that would support reliance on *in vitro* measures to confirm that a generic version of Firmagon made using a different manufacturing process would have the same rate and extent of release *in vivo* as the RLD (*i.e.*, the ability to maintain target trough levels during the 12 month treatment period). A generic version of Firmagon must be bioequivalent to the RLD. A regulatory and scientific finding that the generic and the RLD are bioequivalent requires confidence that the generic will provide sustained systemic drug exposure through month 12 to ensure patients who start treatment on generic degarelix or who switch over to the generic version of Firmagon for maintenance dosing do not experience treatment failures.

D. FDA Must Require either a Multi-Dose *In Vivo* Study or an In *Vivo* Study with Partial AUC Analysis to Ensure That a Proposed Generic has the Same Rate and Extent of Release Over the Course of the Dosing Interval

FDA must ensure that a proposed generic has the same rate and extent of release over the course of the dosing interval. To that end, a single-dose study with the usual PK parameters for *in vivo* BE (C_{max}, AUC_{0-t}, and $AUC_{0-\infty)}$ is insufficient to demonstrate BE and to assure that patients are equivalently served by both the RLD and the generic, including patients who may be at risk of escaping castration during treatment and at the end of month 12 (which depends on steady state trough concentrations). Thus, a single-dose *in vivo* BE study with additional PK parameters, or a multiple-dose study design, is needed.

As described, Firmagon is an extended release product with a prolonged dosing interval of 28 days that continues to release drug from a single dose for up to 290 days and reaches steady state over several doses. A single intramuscular injection of Firmagon resides at the site of deposition for weeks, releasing degarelix in a controlled manner over the entire course and beyond. For a single injection dose (240 mg), the mean C_{max} was 26.2 ng/mL (typically reached within 2 days after administration), and the mean AUC was 1054 ng·day/mL.[92] The robustness of the depot was also demonstrated with a median terminal half-life of 53 days, supporting that the 240 mg depot releases beyond the initial 28 days.[93] Multiple-dose PK analysis showed that after receiving the 240 mg loading dose and multiple cycles of 28-day maintenance therapy, steady state levels were achieved on average after 8–10 maintenance doses and were sufficient to maintain testosterone suppression at month 12.[94] Thus, adequate suppression and maintenance over the course of successive doses relies on the cumulative sustained release of degarelix from the loading dose and subsequent maintenance doses to keep C_{min} and trough levels elevated to therapeutic levels across the maintenance dosing regimen. A generic drug that exhibits different *in vivo* rate and extent of release not only impacts whether the initial dose selected would reach sufficient degarelix levels after the first

[92] Firmagon Prescribing Information (last updated Feb. 24, 2020) at 14.

[93] *Id.* at 15.

[94] *Id.* at 15–16. PK samples were taken "intensively" following the loading dose (Day 0 (dose administered), 1, 3, 7, 14) and pre-dose "troughs" before each 28-day maintenance injection (up to day 364).

injection, but also, more importantly, could impact patients who would be switched from Firmagon to a generic or modified version after achieving an optimal maintenance dose.

FDA has acknowledged the criticality of testosterone suppression in treating advanced prostate cancer and recommends that all GnRH analogue products being developed demonstrate the ability to achieve and maintain castrate T levels (< 50 ng/dL) from Day 28 *through the end of the treatment period* in more than 90% of patients (*i.e.*, less than 10% "treatment failures").[95] FDA considers treatment failure to mean not only those patients who fail to achieve castrate T level at Day 28, *but also patients who successfully achieve a castrate T level on Day 28 but fail to maintain it throughout the treatment period.* For this reason, FDA requires T level assessments at the end of a dosing interval for GnRH analogues, with the study period extending for at least two dosing intervals for long-acting (3- to 6-month) formulations and three to four dosing intervals for short-acting (1-month) formulations. Importantly, FDA has recognized that assessing mean T levels *would not* provide an adequate measure of drug efficacy "because averaging T levels will not reveal the patients who did not benefit (*i.e.*, achieve castrate levels); therefore, it is critical to show that a high percentage of patients achieved and maintained a T level < 50 ng/dL."[96]

Ferring's experience with the product showed testosterone escape [redacted] resulting in treatment failures.[97] As a result, the correlation between degarelix plasma concentration and clinical response was extensively studied.[98] During the End of Phase 2a meeting, FDA advised that a maintenance of a target degarelix trough level of > 9-10 ng/mL through the end of the 12 month treatment period was critical to achieve treatment success in over > 90% of patients. These trough levels were used to select 240 mg as the loading dose and 80 mg as the maintenance dose, resulting in sustained levels of drug release through month 12 with degarelix levels over 10 ng/mL and sustained castrate T suppression.

[95] *See* GnRH Guidance, *supra* note 8, at 7.

[96] *Id.*

[97] [redacted]

[98] NDA 22201, Clinical Pharmacology and Biopharmaceutics Review at 44.

These data establish that to reproduce the same effect as Firmagon over the course of the dosing interval, a test product must maintain adequate trough levels (C_{min}) through month 12 to ensure an equivalent number of patients have treatment success and will not escape castration during treatment. The data presented above and on file at FDA show that the manufacturing process can impact the PK of otherwise identically formulated products, risking potential depletion of degarelix at the end of the dosing interval and potential testosterone escape. The C_{min} parameter can be affected by a different terminal half-life of the generic product, which is limited by the release from the depot ("flip-flop" phenomenon). Thus, the rate of release from a generic product can be expected to have an impact on the minimum concentration at Day 28 and on hormonal control of GH and IGF1.

For other long-acting depot products, including GnRH agonists, FDA has developed bioequivalence recommendations that require either a multiple-dose steady-state study, or a single-dose study with analysis of additional partial AUC metrics.[99] In the present case, because the clinical endpoint for efficacy is tied to maintenance of therapeutic drug trough concentration through month 12 (after loading and repeat dosing to steady state), a multiple-dose BE study is likely required to demonstrate bioequivalence at steady state by measuring trough concentrations up to month 12. Alternatively, FDA could require a single-dose *in vivo* PK study assessing the 240 mg loading dose with partial AUC analysis designed to provide adequate PK profile match as a surrogate for equivalence at steady state. Regardless of the BE study design selected, the study must be capable of ascertaining potential therapeutic deficits at month 12. Failure to do so will unnecessarily increase the risk of castration escape and treatment failure, with a potential for serious public health implications.

III. CONCLUSION

For the reasons described above, Ferring respectfully requests that FDA grant the actions requested in this citizen petition. Firmagon is an *in situ*-forming, slow releasing depot. A reasonable foundation for an *in vitro*-only testing regime for purposes of demonstrating bioequivalence for Firmagon is lacking. Firmagon, substantively, is not a solution for injection. Bioequivalence is not self-evident. The aggregation and fibrillation process that is responsible for the product's long-acting drug release, is variable, dynamic, and influenced by the manufacturing process.

Ferring ensures consistent performance of Firmagon by carefully calibrated in-process manufacturing controls in addition to quality control release-testing on the final product developed and validated through *in vivo* data. Our experience with the product has shown that *in vitro* testing on the final product alone is not sufficient to ensure that the release quality of the RLD is the same when using different manufacturing processes. Q1/Q2 degarelix preparations will all form amyloid-like structures in the right

[99] *See, e.g., Draft Guidance on Leuprolide Acetate* (May 2010; Revised Draft, February 2014), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/Leuprolide_acetate_inj_19732_20011_20263_RV02-14.pdf; *Draft Guidance on Triptorelin Pamoate* (July 2008; Revised Draft, February 2014), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/Triptorelin%20pamoate_IMinj_20715_21288_22437_RV02-14.pdf.

environment, but the structure of these fibrillar networks and the way they interact with the *in-situ* environment may differ. The extent to which the molecular structure and physical characteristics observed *in vitro* accurately predict formation of the depot, and the rate and extent of drug release from the depot, has not been determined. Nor has an IVIVC been established.

In the absence of an *in vivo* BE study, a generic or modified version of Firmagon produced using different methods and in-process controls will be unable to definitively show that it performs the same way as the RLD inside the body. This could impact patient outcomes among those battling advanced prostate cancer and undergoing ADT treatment. As emphasized by FDA, adequate treatment for prostate cancer depends on the ability of the product to ensure castrate T levels (<50 ng/dL) from Day 28 through the end of the treatment period in more than 90% of patients. In the case of Firmagon, this requires adequate trough level maintenance through month 12. A generic product must be able to provide the same castrate coverage in order to avoid unnecessary treatment failures for those starting ADT treatment or switching to a generic for continuation of maintenance therapy. As we have explained above, this can only be accomplished through an *in vivo* BE study, with the need for either a multi-dose study design or the assessment of partial AUC.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: March 25, 2021. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None, other than my compensation as an employee of Ferring. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Harindranath Nagaradona

Digitally signed by Harindranath Nagaradona
Date: 2022.02.09 21:43:44 -05'00'

Hari Nagaradona, Ph.D.
Vice President Regulatory Affairs
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