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December 4, 2022

Commissioner of Food and Drugs
Division of Dockets Management (HFA-205)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

PETITION FOR RECONSIDERATION

Docket No. FDA-2022-P-0160

Ferring Pharmaceuticals, Inc. (Ferring), respectfully submits this petition for reconsideration pursuant to 21 CFR 10.33, among other provisions of law, to request the Commissioner of Food and Drugs reconsider the November 4, 2022, decision denying Ferring's Citizen Petition[1] requesting the Food and Drug Administration (FDA) require *in vivo* studies for proposed generic versions of Firmagon® (degarelix acetate) and update accordingly its product-specific bioequivalence guidance for degarelix acetate.[2]

In denying Ferring's requests, FDA failed to adequately consider several critical issues, unnecessarily exposing patients to serious risk:

- First, FDA failed to address data and a statistical analysis presented by Ferring showing that *in vitro* dissolution tests are not adequately sensitive to detect changes in *in vivo* bioavailability of the reference product, Firmagon® (degarelix acetate). The agency's response entirely ignores the potential for reaching an erroneous conclusion when relying on *in vitro* testing in this instance, as shown by Ferring's data and analysis.

- Second, FDA does not address scientific literature presented by Ferring that shows the difficulty in characterizing the *in vitro* variables affecting Firmagon's *in vivo* bioavailability. Specifically, a study cited by Ferring, and published with support from

[1] FDA, Petition Denial from FDA CDER to Ferring Pharmaceuticals, Inc., Docket No. FDA-2022-P-0160 (Nov. 4, 2022) (Response or Petition Response).

[2] FDA, *Draft Guidance on Degarelix Acetate, Product-Specific Guidances for Generic Drug Development* (Draft, Mar. 2021), *available at*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

staff within FDA's Center for Drug Evaluation and Research, states that a valid method for such characterization is not available. The agency responded only by saying it does not agree. It does not address the underlying data or rationale.

- Third, FDA failed to adequately consider the serious risk of treatment failure for patients with advanced prostate cancer as a result of approving a generic version of Firmagon based solely on an untested *in vitro* model.

- Fourth, the agency's bioequivalence recommendations for degarelix are in conflict with its binding regulation and its prior policies for systemically-absorbed and extended-release drug products.

Because the agency's November 4, 2022, petition response fails to show that relevant data and analyses in the record were adequately considered, and because the determination in the petition is contrary to the agency's regulations on *in vivo* bioequivalence waivers, we respectfully ask for reconsideration of the decision denying the request to require an *in vivo* bioequivalence study for proposed generics to Firmagon® (degarelix acetate).

DECISION INVOLVED

Ferring submitted a Citizen Petition on February 9, 2022, that primarily requested FDA require sponsors of proposed generic degarelix acetate products to conduct *in vivo* bioequivalence studies capable of demonstrating that a proposed product releases degarelix into systemic circulation at the same rate, and to the same extent, as the reference product over the course of the dosing interval.[3] On November 4, 2022, FDA denied the request. Consequently, FDA declined to determine the appropriate elements of an adequate *in vivo* study (*e.g.*, a multi-dose *in vivo* study or a study with pAUC analysis) or to revise its draft guidance as requested by Ferring.

ACTION REQUESTED

Ferring respectfully requests that the Commissioner reconsider its November 4, 2022, decision denying the request for the following actions to be taken:

1) Require ANDAs that reference Firmagon, and 505(b)(2) applications that rely on bioequivalence data or comparative bioavailability data, to include an appropriate *in vivo* study capable of demonstrating that a proposed drug product causes degarelix acetate to release into systemic circulation at the

[3] Ferring Pharmaceuticals, Inc., Citizen Petition, Docket No. FDA-2022-P-0160-0001 (posted Feb. 17, 2022) (Petition or Citizen Petition).

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) Rescind and re-issue the *Draft Guidance* based on the actions taken in response to this petition.

STATEMENT OF GROUNDS

I. BACKGROUND

A. Degarelix Drug Substance

Firmagon (degarelix acetate) is a long-acting injectable product approved for the treatment of patients with advanced prostate cancer. Specifically, Firmagon is an "androgen deprivation therapy" (ADT) that functions as a 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 maintain suppression for at least 12 months of treatment *via* maintenance dosing every 28 days. 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 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.

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. Importantly, Ferring determined during product development that the amyloid fibrillation process is sensitive to manufacturing conditions, as explained in the Petition.[4] Degarelix preparations that differ only in method of manufacture—and that are otherwise identically formulated—have been found to behave differently *in vivo*.[5] Given the possible clinical implications for those patients who may

[4] Grégoire Schwach, CMC Leader, *Ferring Pharmaceutical R&D, Degarelix drug substance from Liquid Phase Peptide Synthesis lyophilized with one lyophilization step (1-lyo LPPS)*, October 4, 2006 (Internal Position Paper) (Tab 3, original submission) (Schwach (2006)); NDA Module 3.2.P.2 Pharmaceutical Development (Oct. 29, 2015) at 16-17 (on file at FDA).

[5] Schwach (2006).

escape castration during the maintenance dosing interval (*e.g.*, increased morbidity, disease progression, etc.), an *in vivo* bioequivalence study is needed to assure that the rate and extent of release from the generic in clinical use is equivalent to the Reference Listed Drug (RLD).

B. Legal and Regulatory Framework

The Federal Food, Drug and Cosmetic Act (FDCA) requires proposed generic drug products to be "bioequivalent" to a drug product previously approved under section 505(b) (the RLD).[6] 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 [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .."[7] 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.

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.[8] The regulations state that applicants "*shall conduct* bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available" among those listed by FDA.[9] 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.[10]

Although degarelix acetate is a systemically absorbed, extended release product, FDA's 2021 *Draft Guidance on Degarelix Acetate* for generic drug development does not include or recommend an *in vivo* bioequivalence study. It proposes instead a series of *in vitro* comparisons in order to determine that the generic degarelix is bioequivalent to Firmagon.[11] Specifically, the Guidance recommends that the generic demonstrate qualitative (Q1) and quantitative (Q2) sameness as Firmagon as well as match 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

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[6] 21 USC 355(j)(2)(A).

[7] 21 USC 355(j)(8)(B)(i).

[8] *See* 21 CFR 320.24(b) (listing methods of proving bioavailability in descending order of accuracy, sensitivity, and reproducibility).

[9] 21 CFR 320.24(b) (emphasis added).

[10] 21 CFR 320.24(a), (b).

[11] *See generally* Draft Degarelix Guidance.

ingredient ("API") sameness based on "primary sequence, secondary sequence and aggregation states."

C. Standard for Reconsideration

The Commissioner may grant a petition for reconsideration if the Commissioner determines the petition to be in the public interest and in the interest of justice.[12] In addition, the Commissioner will grant a petition for reconsideration if the Commissioner determines that the following apply:

- The petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered.
- The petitioner's position is not frivolous and is being pursued in good faith.
- The petitioner has demonstrated sound public policy grounds supporting reconsideration.
- Reconsideration is not outweighed by public health or other public interests.[13]

II. ARGUMENT

A. FDA Failed to Adequately Consider the Statistical Analysis Presented in Ferring's Citizen Petition Showing that *In Vitro* Release Testing was Insufficient to Reliably Prove Bioequivalence.

Firmagon's extended-release properties are a result of a complex fibrillation process in which the degarelix peptide self-assembles into amyloid-like fibers. During product development, Ferring determined that the amyloid fibrillation process is sensitive to manufacturing conditions, as described extensively in its Citizen Petition. As discussed in depth in the Petition, the method of manufacturing the drug product is an essential consideration. Degarelix self-assembly is a thermodynamically complex process resulting in a protein-like amyloid structure. The manufacturing of the final drug substance involves upstream aggregation and de-aggregation steps prior to lyophilization. The way in which upstream aggregation is controlled, the method of ion-exchange in the downstream process, holding times, and the lyophilization of the drug substance and drug product can affect the aggregation process and the properties of amyloid structure when the final lyophilized powder is resuspended for administration.[14] Degarelix preparations that differ in method of manufacture—and that are otherwise identically formulated—nonetheless may

[12] 21 CFR 10.33(d).

[13] 21 CFR 10.33(d).

[14] Petition at 14-19.

behave differently *in vivo*.[15] Thus, a proposed generic product using a different manufacturing process, starting materials, specifications, and in-process controls could form new impurities or misassemble to form structures with varying degree of aggregation and depot morphology, impacting its release profile *in vivo*. As shown in the Citizen Petition, *in vitro* methods may discern some of these differences but are insufficiently sensitive to detect a fundamental difference in bioavailability *in vivo*.[16]

In support, Ferring described *in vivo* data from a rat pharmacokinetic (PK) study specifically designed to assess whether *in vitro* dissolution testing is sufficiently sensitive to capture differences in *in vivo* bioavailability.[17] Ferring tested identically formulated products with degarelix API manufactured using two different methods. These different preparations, known *not* to be bioequivalent in the rat PK model, "passed" the *in vitro* dissolution test based on f1 and f2 statistical analysis.[18] This analysis demonstrated that *in vitro* tests are not sufficiently sensitive to accurately detect product differences that result in statistically significant differences in *in vivo* bioavailability. Proceeding with generic approvals based on an unproven *in vitro* approach—without *in vitro-in vivo* correlation—unnecessarily puts patients at risk.[19]

In its response, FDA ignores these data and their implication as to the accuracy and reliability of an *in vitro* testing approach. FDA agrees that "the manufacturing process can impact the PK for degarelix for injection because it can change key physiochemical properties of the drug product, in turn potentially affecting factors that may impact degarelix aggregation."[20] FDA also agrees that undesired aggregation may occur when manufacturing is not well-controlled.[21] Nevertheless, FDA denied the request for an *in vivo* bioequivalence study based on an assertion—in the face of contrary data—that an *in vitro* approach is capable of "detect[ing] manufacturing-induced differences that may impact PK and thus BE."[22]

FDA's response relies heavily on data from a 2006 study by Ferring (Schwach) cited in the Petition, which presents comparability data provided by the company following a manufacturing change. That study demonstrated that changes in the lyophilization step(s) during manufacturing can affect the final drug product with regard to aggregation and depot formation and therefore

[15] Schwach (2006).

[16] Citizen Petition at 14-24 (Sections II.A.3 and II.B.1-2).

[17] *Id.* at 21-24.

[18] *See id.* (analysis performed by Ferring in 2021 based on data on file at FDA).

[19] *Infra*, II.C; Petition at 28-29.

[20] Petition Response at 10.

[21] *Id.* at 10.

[22] *Id.* at 11.

affects bioavailability.[23] FDA highlights that the Schwach data show that differences in *in vivo* PK can be "tracked with faster release as observed by *in vitro* dissolution, along with changes in optical density and viscosity."[24] Thus, FDA argues that "potential difference 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."[25]

Importantly, the Schwach 2006 data demonstrate that manufacturing methods have a significant effect on product performance characteristics, including *in vivo* performance.[26] Some of these differences may be discerned by certain in process controls.[27] These data do *not* demonstrate that *in vitro* characterizations are sensitive enough to capture all significant changes in bioavailability. At the same time, FDA failed to address, and gave no indication that it had taken into account, the results of Ferring's 2021 statistical analysis showing that *in vitro* methods are not sufficiently sensitive to detect actual differences in *in vivo* PK.[28] In other words, FDA completely ignores the possibility of making a false declaration of equivalence—where products without observable differences *in vitro* demonstrate different *in vivo* bioavailability—in its proposed bioequivalence approach.

B. FDA Failed to Adequately Consider a Study Published by FDA's Own Scientists Illustrating the Problems of Using an *In Vitro* Approach.

Firmagon is an *in situ*-forming depot, and the properties of the depot structure control the rate of release of monomeric degarelix into systemic circulation.[29] The variables controlling these properties are not fully understood. As such, and as Ferring's data confirms, it is unreliable to predict the release profile of the depot *in vivo* without some kind of clinical or *in vivo* validation.[30]

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[23] Schwach (2006).

[24] Petition Response at 10.

[25] *Id.* at 11.

[26] Petition at 14-19.

[27] *Id.* at 18-19.

[28] *Id.* at 21-24; Petition Response at 12 n.60.

[29] 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 (Tab 1, original) (Patil et al. (2021)); Maji, S.K. *et al., Amyloid as a depot for the formulation of long-acting drugs*, PLoS Biology (2008) (Tab 2, original); 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.

[30] *See* Schwach (2006); NDA Module 3.2.P.2 Pharmaceutical Development (Oct. 29, 2015) (on file at FDA).

The difficulty linking Firmagon's *in vitro* characteristics to the product's *in vivo* performance was covered extensively in an article published in February 2021 by Patil *et al.* That article, funded in part by FDA's CDER, stated: "Because the self-aggregation and gelling of degarelix can be affected by a variety of factors . . . the systematic pharmacokinetic profile of degarelix is strongly influenced by depot formation."[31] Patil *et al.* underscored that Firmagon is "challenging to study" and that "analytical methods for characterizing gelling kinetics of degarelix are still lacking."[32] The analysis in Patil *et al.*, along with the data submitted by Ferring in support of its Citizen Petition, demonstrate the unreliability of using *in vitro* characteristics to predict *in vivo* bioavailability of degarelix. Despite these findings, FDA's *Draft Guidance* for degarelix allows for a determination of bioequivalence based on *in vitro* testing.

FDA states that it does "not find the Petition's analysis of the Patil *et al.* article to be persuasive" and that it does "not agree that identifying adequate characterization methods" for degarelix self-aggregation *in vitro* is difficult.[33] However, the agency does not address any of the underlying rationale or data to the contrary. Without any counterpoint or argument based on the data, FDA simply dismisses its own scientists' analysis with a blanket declaration that "its recommendations are not dependent on the findings reported in Patil *et al*."[34] Yet the agency does not supplant Patil *et al.* with any countervailing findings. Ferring's Petition acknowledged the important work of Patil *et al.* in contributing to a data-backed understanding and characterization of the aggregation states of degarelix. The Petition sought to shed light on several analytic shortcomings in this analysis.[35] Without pointing to any other findings, the agency simply sets Patil *et al.* aside; no attempt was made to address the issues it raised. Regardless of whether the *Draft Guidance* is premised on Patil *et al.*, the study highlights foundational concerns, corroborated by Ferring's own data and experience, about whether an *in vitro* approach is sufficiently sensitive to ensure that a generic product is bioequivalent to Firmagon, and thus safe and effective as required by law. Indeed, the study was motivated by the lack of validated *in vitro* methods for characterizing the gelling kinetics of degarelix that control the product's bioavailability.

Although the Petition exhaustively describes the limitations of *in vitro* testing, FDA posits by an inadequately supported assertion that its recommended approach, based on several different *in vitro* tests, amounts to a reasonable foundation for demonstrating bioequivalence. FDA fails to

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[31] Patil et al. (2021) at 1.

[32] *Id.* at 3. The paper goes on to describe what it claims to be an *in vitro* method of obtaining 1D 1H NMR spectra for reconstituted degarelix to derive aggregation kinetics.

[33] Petition Response at 12.

[34] *Id.* at 13.

[35] Petition at 25-26.

justify how these tests, despite being insufficient on their own, adequately assure bioequivalence when taken together. Without a proven correlation between *in vitro* characteristics and *in vivo* bioavailability, a conclusion that one sponsor's product will form the same depot as Firmagon, yielding an equivalent PK profile *in vivo*, is a matter of speculation in the absence of *in vivo* testing. Relying on such an untested hypothesis puts patients at unnecessary risk of treatment failure.

C. FDA Failed to Adequately Consider the Serious Risk of Treatment Failure for Patients with Advanced Prostate Cancer.

Advanced prostate cancer is a serious and life-threatening condition that results in significant morbidity and mortality if left untreated. Patients with advanced or metastatic prostate cancer are not only at risk of death (with a 5-year survival average of up to 30%)[36] but are also at risk for significant morbidity, including complications such as skeletal-related events (*e.g.*, spinal cord compression, vertebral collapse, and pathological fractures). 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 demonstrated above, and at length in the Petition, 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.

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 identify clinically meaningful differences in the rate and extent of release *in vivo*, in humans. Reliance on *in vitro* methods to reach a conclusion of bioequivalence in this instance would be based on an untested hypothesis and will put patients at unnecessary risk of treatment failure. The fundamental question is without an *in vitro-in vivo correlation* how can the agency sufficiently *quantify* the efficacy impact for the prostate cancer patient of an *in vitro* difference (for example, a 5% change in drug release *in vitro*) between the RLD and a generic product?

As stated in the agency's own guidance for new product development in this field it is critical that a high percentage of patients (more than 90% with 95% confidence interval) achieve and maintain a T-level less than 50 ng/dL throughout the treatment period for this year-long treatment. As shown by Ferring, *in vitro* testing alone is not sensitive enough to detect a biologically significant difference. Firmagon demonstrated very high efficacy (castration) rates

[36] *Id.* at 28; 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, original).

97.2% (93.5; 98.8) and 96.4% (92.5; 98.2) after one year of treatment. Without a rigorous *in vitro-in vivo* correlation, only an *in vivo* PK comparison between the RLD and the generic can ensure the generic product has the same rate and extent of release to ensure the same efficacy as Firmagon and other products in this class, for this life-threatening disease.

FDA states that it "believe[s] that the recommended *in vitro* tests" are sufficient.[37] This is not an adequate response to bioequivalence concerns for a product intended to treat advanced prostate cancer. Either there is scientific evidence for establishing bioequivalence, or there is not. Currently there is no *in vitro* method alone, or in combination, that has been proven to be predictive of PK or PD. To establish such a correlation, if at all possible, substantial *in vitro* method development where the results are correlated to *in vivo* outcomes is needed.

D. FDA's Bioequivalence Recommendations for Degarelix are in Conflict with its Binding Regulation and Prior Policies.

The FDCA requires proposed generics to be "bioequivalent" to the RLD.[38] By statute, bioequivalence must occur "*when administered* . . . under similar experimental conditions in either a single dose or multiple doses."[39] In implementing this provision, the agency has recognized that "the statutory definition of [bioequivalence], 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."[40] The reliance on *in vitro* tests for demonstrating bioequivalence between two different manufacturers' degarelix depot products violates this statutory command because the relationship between the *in vitro* physical and chemical properties of degarelix acetate that determine *in vivo* drug release is not yet determined.

The agency's bioequivalence recommendations for degarelix are in conflict with its binding regulation and its prior policies for systemically-absorbed drugs and extended-release drug products, of which long acting depots are a particular case. We recognize that FDA may permit a waiver of *in vivo* bioequivalence data for products for which bioavailability is "self-evident."[41] However, the regulations define these products as parenteral solutions; solutions applied via the skin, orally, nasally, or as other solubilized forms; and products administered by inhalation.

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[37] Petition Response at 13.

[38] 21 USC 355(j)(2)(A).

[39] 21 USC 355(j)(8)(B)(i) (emphasis added).

[40] 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.

[41] 21 CFR 320.22.

Firmagon is none of these. Additionally, 21 CFR 320.22(d) provides: "For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained *in vitro* in lieu of *in vivo* data." However, 320.22(d)(4) expressly states that this "does not apply to delayed release or extended release products."

FDA, by regulation, has previously taken the position that *in vivo* studies are preferred as the most accurate and dependable method of establishing bioequivalence for a systemically acting drug.[42] FDA's regulations specifically require that applicants "*shall conduct* bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available."[43] Further, FDA's preamble to the final rules promulgated in 21 CFR Part 320, in discussing FDA's ability to require *in vitro* or *in vivo* bioequivalence data, notes that the FDCA "permits and FDA's longstanding regulations provide for both indirect and direct measurements of bioequivalence *applicable to nonsystemically absorbed drug products.*"[44] Similarly, FDA also has observed that it "does not recommend *in vitro* approaches for drug products that are intended to be systematically absorbed."[45] And, FDA has emphasized that for long-acting parenteral products, including *in situ* forming implants such as Firmagon, there are no standards or applicable tests for determining *in vitro* release. Rather, as the agency itself acknowledges, the release mechanism (especially *in vivo*) in this instance is not fully understood.[46] Given this array of factors, there is no basis for a departure from the established rules and practices governing bioequivalence testing for a systemically acting drug product such as Firmagon and, in fact, FDA provided none in the petition response.

III. CONCLUSION

For the reasons described above, FDA's action in denying the Petition unnecessarily exposes patients who are undergoing treatment for advanced prostate cancer to serious risk. Accordingly, Ferring respectfully requests that FDA grant the action requested in this petition for reconsideration. Specifically, in accordance with 21 CFR 10.33(d), we have demonstrated that important aspects of the administrative record have not been adequately considered, nor has the law been faithfully applied in this case. We have pursued our request for a determination that any 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

[42] 21 CFR 320.24(a), (b).

[43] 21 CFR 320.24(a).

[44] 57 FR 17950, 17972 (April 28, 1992).

[45] FDA, Draft Guidance for Industry, *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application* (Dec. 2013) at 3.

[46] *See* Wang, Y., "Bioequivalence Approaches for Long-Acting Drug Products: Regulatory and Scientific Considerations," at 3-4, Complex Generic Drug Product Development Workshop (Sep. 25-26, 2019).

in human subjects, based on sound scientific and statutory grounds. Public policy is advanced by ensuring that only safe and effective generic drugs are approved for marketing.[47] Given the importance of controlling the rate and extent of degarelix release in a long-acting injectable, it is critical that generic products form the same *in situ* depot and demonstrate the same *in vivo* PK profile in order to prevent treatment failure for patients with advanced prostate cancer.

While the Hatch-Waxman Amendments are designed in part "to make more inexpensive generic drugs available," the law is also intended to ensure the safety and effectiveness of generics.[48] Ignoring bioequivalence concerns associated with different manufacturing and thereby exposing patients to an unjustified risk of treatment failure is contrary to the public policy cited by the agency in its Response.[49] Similarly, as detailed in FDA's mission statement, it is in the interest of public health for FDA to protect the public from unsafe and ineffective drugs, and also to promote confidence in the rigorous regulatory standards applied to approved drug products. For the agency to proceed with a legally, factually, and analytically flawed basis for declining to require *in vivo* bioequivalence studies would be counter to the public interest. This petition therefore meets the standard for reconsideration under 21 CFR 10.33 and should be granted.

[47] *See Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (DDC 1992) (noting that the one underlying policy of the Hatch-Waxman Amendments is to "ensure *the safety* of drugs before they are substituted for their brand-name counterparts") (emphasis added).

[48] *See id.*

[49] Petition Response at 5.

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: November 4, 2022. 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: 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,

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