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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Organon USA, LLC (Organon)¹ submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations to request that the Commissioner of Food and Drugs take the actions set forth below in Section A with respect to any abbreviated new drug application (ANDA) for an etonogestrel implant that cites NEXPLANON® (etonogestrel implant) as the reference listed drug (RLD).²

Organon is a global health care company dedicated to making a world of difference for women, their families, and the communities they care for. At Organon, we believe in a better and healthier every day for every woman. We build upon our strong foundation of more than 60 medicines and other products across a range of areas including reproductive health, heart disease, dermatology, allergies, and asthma.

A. Action Requested

Organon requests that the U.S. Food and Drug Administration (FDA) take the following actions with respect to ANDAs citing NEXPLANON.

1. Require that an ANDA applicant establish bioequivalence (BE) of the generic drug to NEXPLANON through (a) an in vivo BE study with pharmacokinetic (PK) endpoints evaluating the full duration of the approved, labeled in-use period of NEXPLANON, which is the duration of use for which the generic contraceptive implant also would be labeled; or (b) a validated in vivo-in vitro correlation (IVIVC) model covering the labeled duration of use; and require that the ANDA applicant conduct comparative dissolution testing profiles (f2 test) in

¹ For convenience, “Organon” as used in this petition also refers to Organon’s predecessors in interest with respect to IMPLANON and NEXPLANON.

² The actions requested in this petition are equally applicable if an ANDA references the discontinued product IMPLANON. We note, however, that FDA’s Approved Drug Products With Therapeutic Evaluations (Orange Book) designates NEXPLANON, and not IMPLANON, as an RLD. See FDA, [Approved Drug Products with Therapeutic Equivalence Evaluations](#) (44th ed. 2024).

- three different media (including at least six-month data) and data on dissolution profile comparison in water (three-year data).
2. To the extent that FDA determines that a proposed ANDA product does not need to demonstrate BE as described above in item 1, require a demonstration of physicochemical and structural (Q3) sameness between the proposed ANDA product and the RLD; require biocompatibility risk assessment including characterization of extractables and leachables as per current FDA guidance ‘Use of International Standard ISO10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process", specifically Section VII. Chemical Assessment, conducting chemical characterization in relevant polar, semi-polar and non-polar solvents as part of the Q3 characterization; and require safety and biocompatibility testing for the generic drug product.
 3. Require generic etonogestrel implants to have equivalent device constituents—i.e., the applicator device and the implant—to NEXPLANON in performance, operating principles, and critical design attributes.
 4. To ensure the safe and effective use of the proposed generic product, require an ANDA applicant to implement measures to ensure appropriate training on the use of the generic product. Specifically, require the ANDA applicant’s proposed labeling to include the same language as the reference product label on proper training and instructions for implant insertion, removal, and localization. Further require the ANDA applicant to implement a training program that covers the proper techniques for use of the generic implant and limits access to the generic product only to those healthcare professionals who complete such training.
 5. Revise FDA’s product specific guidance for etonogestrel implants to reflect the above requirements.

B. Statement of Grounds

II. Summary of Grounds

Organon is committed to supporting women’s health. Our product NEXPLANON is a radiopaque birth control implant that provides long-acting (up to 3 years), reversible contraception. Organon supports access to safe and effective generic contraceptive products, including generic etonogestrel implants and has concerns that FDA’s draft product-specific guidance on etonogestrel (Draft Guidance), issued in August 2022, will not ensure the approval of safe and effective generic etonogestrel implants.³ Organon recommends that FDA require ANDA applicants referencing NEXPLANON to meet the requirements described below and revise the Draft Guidance accordingly to ensure safe and effective contraceptive etonogestrel implants.

³ See FDA, *Draft Guidance on Etonogestrel*, Docket No. FDA-2007-D-0369-0653 (Aug. 5, 2022).

First, given that generic etonogestrel implants will be labeled for three-year use, FDA should require that an ANDA applicant establish BE to NEXPLANON through a three-year in vivo BE study with PK endpoints (or a BE study that otherwise aligns with the labeled duration of use) or a validated IVIVC covering this time frame. The Draft Guidance instead recommends a six-month BE study, which would not be sufficient, given that the concentrations of etonogestrel go beyond the in-use period of 3-years. The NEXPLANON labeling notes that etonogestrel concentrations continue to be measurable at year three after implantation.⁴ The 6-month BE recommendation does not align with FDA's general recommendation to assess drug concentrations in single-dose BE studies until "the last time point with a measurable concentration."⁵ Further, we have seen no scientific justification for the notion that in vivo BE at six months would predict in vivo BE at three years. Scientific literature concerning contraceptive implants with similar compositions indicates that drug levels observed at an earlier time point are not necessarily predictive of future drug levels or clinical efficacy and that the full duration of intended use should be evaluated.⁶

Without three-year in vivo BE or a validated IVIVC for this time frame, there is a significant risk that the drug concentration from a generic etonogestrel implant could deviate from the PK profile of the RLD over time, resulting in *bioinequivalence*. A bioinequivalent product could be less effective than NEXPLANON and poses an unacceptable risk of pregnancy.

In addition, ANDA applicants should be required to conduct comparative dissolution testing that includes (f2 test) in three different media and different pH levels (including at least six-month data) and data on dissolution profile comparison in water (three-year data) consistent with FDA's expectations for Organon for post-approval changes to NEXPLANON, and FDA should take public comment on the proposed dissolution methodology, which was not incorporated into the Draft Guidance due to a cross-reference that does not actually provide the dissolution methodology.

Second, if FDA does not adopt the requirement for a three-year BE study or an IVIVC covering this time period, FDA should require the proposed generic drug to have Q3 similarity to NEXPLANON (i.e., same components in same concentration with the same arrangement of matter (microstructure)). NEXPLANON has an ethylene vinyl acetate (EVA) copolymer core containing the active ingredient etonogestrel, as well as an EVA copolymer skin.⁷

Differences between NEXPLANON and the proposed generic in the product design or polymer degree of substitution, distribution, or the

⁴ [NEXPLANON Labeling](#) § 12.3 (September 2023).

⁵ FDA, [Draft Guidance for Industry, Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA](#), at 6 (Aug. 2021).

⁶ See M.J. Steiner et al., *Randomized trial to evaluate contraceptive efficacy, safety and acceptability of a two-rod contraceptive implant over 4 years in the Dominican Republic*, CONTRACEPTION: X 1, 1, 2 (2019).

⁷ [NEXPLANON Labeling](#) § 11.

length of polymer chains may provide a differing rate of release. Particularly where an ANDA applicant does not show BE over the labeled duration of use, FDA should require the ANDA applicant to show Q3 sameness to the RLD. This requirement will help assure that the generic product is BE to the RLD despite the lack of in vivo testing covering the full duration of use. Additionally, to meet the manufacturing requirements for a generic application and ensure that the composition of the generic drug product does not raise serious questions of safety or efficacy, generic applicants should conduct comparative biocompatibility testing and extractable and leachable testing between the reference product and a proposed generic product.⁸

Third, consistent with precedent, FDA should require that ANDA applicants show that the generic implant and applicator are equivalent to those of NEXPLANON in performance, operating principles, and critical design attributes.⁹ The Draft Guidance does not articulate these principles and instead merely advises that the generic applicant “examine” device properties of the RLD. Equivalence in these device features is critical from a public health perspective. Differences in the applicator or implant’s critical design attributes, operating principles, or performance could lead to errors in implantation or removal with both efficacy implications (unintended pregnancy) and safety implications (adverse events). This conclusion aligns with FDA’s past guidance to Organon, in which FDA recommended conducting a post approval observational safety study (the NEXPLANON Observational Risk Assessment Study, “NORA”) to sufficiently understand the safety, effective and successful insertion, palpation and removal of the implant.¹⁰ Ensuring implant and applicator equivalence to those of NEXPLANON in performance, operating principles, and critical design attributes will be important for patient safety.

Finally, in the interest of patient safety and public health, FDA should require that an ANDA applicant implement measures that support proper insertion, localization and removal of the generic implant as such measures are key to safe and effective use of etonogestrel implants. FDA should require that the labeling of generic etonogestrel implants include the same language regarding training and instructions on implant insertion, localization, and removal as found in the NEXPLANON labeling, except for differences necessary to refer to different product names, manufacturer names, or manufacturer contact information. As discussed extensively throughout the NEXPLANON labeling, improper insertion, localization, or removal can lead to safety issues, such as implant migration and the need for surgery, as well as ineffectiveness. Omitting or substantially changing the related labeling information would “render the proposed [generic] drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.”¹¹ In alignment with the labeling, FDA should also require that a generic manufacturer develop and implement a training program to cover the same information contained in the

⁸ NDA 021528/ S-025 comparative studies conducted to support major change.

⁹ FDA Response to King Pharmaceuticals, Docket Nos. FDA-2007-P-0128, FDA-2009-P-0040, at 10 (Jul. 29, 2009) (King Response) (“[W]e agree that the auto-injector constituent in an ANDA for a combination product should be equivalent to that of the RLD product in terms of performance, operating principles, and critical design attributes”).

¹⁰ See [Clinical Review/Cross Discipline Team Leader Review](#), NDA 21-529/SES-007, at 158 (May 12, 2011); Reed S, Minh TD, Lange JA et al. Real world data on Nexplanon® procedure-related events: final results from the Nexplanon Observational Risk Assessment study (NORA). Contraception 2019;100:31-6.

¹¹ 21 C.F.R. § 314.127(a)(7).

NEXPLANON labeling regarding the proper insertion, removal and localization of the implant, and limit access to the product to only those healthcare professionals who have undergone such training. Without these steps, a proposed generic product would have a higher risk of errors in insertion, localization, or removal that could lead to safety or effectiveness concerns.

III. Factual Background

A. NEXPLANON and IMPLANON

NEXPLANON is a radiopaque birth control implant that is placed under the skin of the inner, non-dominant arm.¹² NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method indicated for use by women to prevent pregnancy.¹³ Each implant consists of an EVA copolymer (28% vinyl acetate, 43 mg) core containing 68 mg of the synthetic progestin etonogestrel, barium sulfate (15 mg) (radiopaque ingredient), and magnesium stearate (0.1 mg), surrounded by an EVA copolymer skin.¹⁴ As provided in the current labeling for NEXPLANON, the implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal if continued contraceptive protection is desired.¹⁵

FDA approved NEXPLANON on May 13, 2011, via a supplement to the NDA for Organon’s prior product IMPLANON, which has since been discontinued.¹⁶ NEXPLANON differs from IMPLANON in that it is radiopaque and has a new insertion device. Specifically, the addition of barium sulfate to the rod core “facilitates localization of the implant when the implant is not palpable after insertion” and allows use of widely available diagnostic modalities for localization, such as two-dimensional x-ray imaging.¹⁷ As FDA explained in its review documents for NEXPLANON, among the “improvements” reflected in the new insertion device are: “(1) one hand operation, (2) a locking mechanism to prevent the implant from falling out of the device, (3) less likelihood of the implant not being completely inserted in the proper subdermal location, and (4) the possibility that there will be fewer inadvertent ‘deep’ insertions of the implant.”¹⁸

Because proper placement of the implant is critical to its safety and effectiveness, the NEXPLANON labeling contains extensive directions on insertion, localization, and removal of the implant.¹⁹ It specifically directs that “[a]ll healthcare professionals performing insertions and/or removals of NEXPLANON should receive instructions and training prior to inserting or removing the implant.”²⁰ The labeling contains warnings and precautions

¹² [NEXPLANON Labeling](#) § 2 (September 2023).

¹³ *Id.* §§ 1, 2.

¹⁴ *Id.* § 11.

¹⁵ *Id.* § 2.

¹⁶ [Approval Letter](#) for NEXPLANON (May, 13, 2011).

¹⁷ [Clinical Review/Cross Discipline Team Leader Review](#), NDA 21-529/SES-007, at 11 (May 12, 2011).

¹⁸ FDA, [Summary Review for Regulatory Action](#), NEXPLANON (Mar 13, 2011).

¹⁹ [NEXPLANON Labeling](#) § 2 (September 2023).

²⁰ *Id.* (emphasis in original).

regarding complications of insertion and removal. For example, the labeling notes that “[u]ndetected failure to insert the implant may lead to an unintended pregnancy.”²¹ It also warns that “[c]omplications related to insertion and removal procedures may occur, e.g., pain, paresthesia, bleeding, hematoma, scarring, or infection,” and “[i]f NEXPLANON is inserted deeply (intramuscular or intrafascia), neural or vascular injury may occur.”²² The labeling further notes that insertion in the directed location “is intended to avoid the large nerves and blood vessels lying within and surrounding the sulcus” and that “[i]mplant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated.”²³ Per the labeling, “[f]ailure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.”²⁴ Finally, the NEXPLANON labeling notes reports of migrated implants to the pulmonary artery, some of which were associated with “chest pain and/or respiratory disorders (such as dyspnea, cough, or hemoptysis),” and it advises that, “where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.”²⁵

In light of the importance of proper insertion and removal to both safety and effectiveness of the implant, Organon’s training program on proper insertion and removal technique was the subject of extensive discussion with FDA in the approval of both IMPLANON and NEXPLANON.

B. IMPLANON and NEXPLANON Training and Controlled Distribution

On July 17, 2006, FDA approved new drug application (NDA) 21-529 for IMPLANON (etonogestrel subdermal implant) for the prevention of pregnancy.²⁶ Like NEXPLANON, IMPLANON was a long-acting, reversible contraceptive method inserted in the upper arm that could be used for up to three years before removal and potential replacement by a new IMPLANON device.²⁷

In evaluating Organon’s application, FDA noted that “[t]he primary risk management concern of Implanon is the insertion and removal related events (IRRE) that were noted from foreign postmarketing experience.”²⁸ FDA explained that “[f]ailure to appropriately insert or remove the implant can result in inadequate contraception and was considered the major factor that contributed to unintended pregnancies.”²⁹ Indeed, “[o]f the 1814 medically confirmed

²¹ *Id.* § 5.1.

²² *Id.*

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ [Approval Letter](#), NDA 21-529 (July 17, 2006); [IMPLANON Labeling](#) (July 2006).

²⁷ See [IMPLANON Labeling](#) (July 2006).

²⁸ [Risk Assessment and Risk Mitigation Review\(s\)](#), NDA 21-529, at 1-2 (July 20, 2005).

²⁹ *Id.* at 2.

reports of IRREs to Organon, 561 reported an unintended pregnancy.³⁰ Such adverse events were not reported in the clinical trials, so “[the Division of Reproductive and Urologic Drug Products (DRUDP)] felt that it was possible that these complications were related to inadequate training of healthcare providers regarding proper insertion/removal of the implant.”³¹

To address the concerns raised in connection with the insertion and removal of the implant, Organon proposed—and FDA agreed with—development and deployment of a clinical training program for health care professionals (HCPs) to properly insert and remove the implant as well as a monitoring program for insertion and removal related events. Organon’s 2.5-3-hour training program addresses (1) implant clinical information and data; (2) insertion, removal, and localization procedures; (3) hands-on training of insertion and removal techniques using specially designed model arms; and (4) patient counseling information.³²

In connection with the NEXPLANON approval, Organon committed to updating the training for HCPs, and FDA concurred with this strategy.³³ Per agreement with FDA, HCPs who had already been trained on IMPLANON were re-trained with NEXPLANON and its new applicator, and untrained HCPs were trained with the new training materials for NEXPLANON in line with the training program outlined above.³⁴

In addition to the development and implementation of the clinical training program, Organon also committed – and FDA concurred – to a process of controlled distribution through which only those HCPs who completed the training program would be permitted to order and purchase the implant.³⁵ This controlled distribution process is yet another way of ensuring the safe and effective use of the product.

Recently, FDA has continued to emphasize the importance of Organon’s training program.



³⁰ *Id.* at 4.

³¹ *Id.*

³² *Id.* at 4.

³³ See [Clinical Review/Cross Discipline Team Leader Review](#), NDA 21-529/SES-007, at 19-20 (May 12, 2011) (commenting that re-training of HCPs who have already undergone training for IMPLANON should not be a condition of approval for NEXPLANON).

³⁴ See *id.* at 19.

³⁵ See *id.* at 158.

³⁶ 

C. Product-Specific Guidance for Etonogestrel Implant

On August 2, 2022, FDA issued the Draft Guidance, which “interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support [ANDAs] for the referenced drug product,” i.e., NEXPLANON.³⁹ Organon submitted a comment on this Draft Guidance.⁴⁰

The Draft Guidance states that “[t]o be eligible for the bioequivalence studies recommended in this guidance, the [generic] product should meet the following criteria”:

1. Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD)
2. Same dimensions with respect to length, diameter and skin thickness of the implant as the Reference Standard (RS) products
3. Acceptable comparative physicochemical and mechanical characteristics of the test and the RS products including: 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) crystalline form of the API; and 3) mechanical properties of the implant, including but not limited to tensile strength and hardness.⁴¹

The Draft Guidance recommends generic applicants complete one in vitro BE study with supportive characterization studies and one in vivo BE study with PK endpoints. The former should show “[a]cceptable comparative in vitro drug release of etonogestrel from the test and RS products (i.e., in water, 37°C) throughout the intended period of product use (3 years)”⁴²; however, “[a] real time release study that is shorter than 3 years may be acceptable when an accelerated dissolution method that correlates to the real-time drug release behavior is developed and validated.”⁴³ The Draft Guidance describes the recommended in vivo BE study with PK

³⁷ [REDACTED]

³⁸ [REDACTED]

³⁹ FDA, Draft Guidance on Etonogestrel, at 1(Aug. 2022).

⁴⁰ See Comment from Sandip Roy, Organon, LLC, Docket No. FDA-2007-D-0369-0691 (Oct. 5, 2022).

⁴¹ FDA, Draft Guidance on Etonogestrel, at 1-2 (Aug. 2022).

⁴² *Id.* at 2.

⁴³ *Id.*

endpoints as a “6 month[], single-dose, randomized, parallel” design study in healthy premenopausal, non-pregnant females.⁴⁴

The Draft Guidance notes that the implant and applicator are device constituents of the RLD and “recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test devices including the following characteristics”: (1) “[r]adiopaque implant”; (2) “[p]reloaded, single-use applicator”; and (3) “[g]auge and length of applicator needle.”⁴⁵ The Draft Guidance also contains the following recommendations concerning the “User Interface Assessment”:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.⁴⁶

IV. Legal Background

An ANDA generally must contain sufficient information to show that the proposed generic drug product has the same active ingredient(s), previously approved conditions of use, route of administration, dosage form, and strength as the RLD.⁴⁷ An ANDA also must contain “information to show that the new drug is bioequivalent to the listed drug,” except in the case of a suitability petition.⁴⁸ FDA may not approve a non-petitioned ANDA if “information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application.”⁴⁹ A proposed ANDA product is considered BE to the RLD if, in relevant part, “the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.”⁵⁰

⁴⁴ *Id.*

⁴⁵ *Id.* at 3.

⁴⁶ *Id.*; see also FDA, Draft Guidance for Industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan. 2017) (Human Factors Draft Guidance).

⁴⁷ FDCA §§ 505(j)(2)(A)(i)-(iii).

⁴⁸ See 21 C.F.R. § 314.127(a)(6)(i) (if “[i]nformation submitted in the ANDA is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA,” FDA may refuse to approve the ANDA).

⁴⁹ FDCA § 505(j)(4)(F).

⁵⁰ FDCA § 505(j)(8)(B); see also 21 C.F.R. § 314.3(b).

A proposed ANDA product must also have the same labeling as the RLD with certain exceptions. Section 505(j)(2)(A)(v) of the FDCA requires an ANDA to contain “information to show that the labeling proposed for the [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a [suitability petition] or because the [generic] drug and the listed drug are produced or distributed by different manufacturers.”⁵¹ If the information submitted in an ANDA “is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug” except for such allowable differences, FDA may refuse to approve an ANDA.⁵² To the extent that there are differences between the proposed ANDA labeling and the RLD labeling, any differences cannot “render the proposed [generic] drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.”⁵³

Section 505(j)(4)(H) authorizes FDA to deny an ANDA if the inactive ingredients or composition of the proposed product render it unsafe for use.⁵⁴ FDA’s regulation provides that this condition is met when there is a “reasonable basis to conclude” that the inactive ingredients or composition “raises serious questions of safety or efficacy.”⁵⁵

FDA has explained that “[d]rug products that meet the approval requirements under section 505(j) of the [FDCA] generally will be considered by FDA to be ‘therapeutically equivalent’ to the RLD.”⁵⁶ Therapeutically equivalent products “can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”⁵⁷

V. Grounds for Actions Requested

- A. FDA should require an ANDA applicant referencing NEXPLANON to conduct a three-year in vivo BE study or establish BE at three years through a validated IVIVC.

The Draft Guidance does not adequately ensure BE between a proposed ANDA product and NEXPLANON over the full duration of use, as specified in the labeling, for the RLD because it recommends an in vivo BE study with PK endpoints evaluating only six months of use.⁵⁸ FDA instead should require that an ANDA applicant: (1) conduct a three-year in vivo BE study; or (2) use a validated IVIVC model to ensure the safety and effectiveness of the product. The agency also should require ANDA applicants to submit comparative dissolution testing that includes three different pH levels for at least six months and revise the Draft Guidance, which

⁵¹ FDCA § 505(j)(2)(A)(v).

⁵² FDCA § 505(j)(4)(G).

⁵³ 21 C.F.R. § 314.127(a)(7).

⁵⁴ FDCA § 505(j)(4)(H).

⁵⁵ 21 C.F.R. § 314.127(a)(8)(ii)(A).

⁵⁶ FDA, Response to Citizen Petition, Docket No. FDA-2010-P-0648, at 4 (Oct. 31, 2013).

⁵⁷ 21 C.F.R. § 314.3(b).

⁵⁸ FDA, *Draft Guidance on Etonogestrel*, at 2 (Aug. 2022); *NEXPLANON Labeling* § 2 (September 2023).

cross-references non-existent information on the appropriate dissolution method, to reflect these requirements while ensuring appropriate public comment.

1. Bioequivalence

The Draft Guidance approach to BE is at odds with other FDA draft guidance and regulations. If the ANDA applicant cannot establish a validated IVIVC for the labeled duration of use, it should conduct an in vivo BE study covering that duration of use.

For single-dose in vivo PK studies conducted to show BE, FDA guidance generally recommends that drug concentrations be assessed until “the last time point with a measurable concentration.”⁵⁹ The NEXPLANON labeling notes the mean (\pm SD) serum etonogestrel concentration was 138 (\pm 43) pg/mL at the 36 months timepoint.⁶⁰ By recommending a BE study that would end long before the last time point with a measurable concentration (and the labeled duration of use), the Draft Guidance conflicts with FDA’s BE draft guidance.

We have also seen no scientific justification for the recommended six-month time point for the BE assessment. FDA’s regulations on collection of blood samples in a single-dose BE study provide that “[i]n a study comparing drug delivery systems other than oral or intravenous dosage forms with an appropriate reference standard, the sampling times should be based on valid scientific reasons.”⁶¹ The Draft Guidance provides no scientific basis to assume that BE of a generic etonogestrel implant at six months reliably predicts BE at three years. Indeed, FDA has previously rejected citizen petitions proposing required BE showings at times that were not shown to be clinically relevant. For example, FDA’s response to a citizen petition concerning Nitrolingual Pumpspray (nitroglycerin lingual spray) noted that the “relevant” PK parameters calculated from BE data are “the area under the plasma concentration vs. time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_∞),” and it rejected petitioner’s request for a generic requirement to show BE of partial AUC at five minutes because of this metric’s lack of established clinical relevance.⁶² Similarly, Organon is aware of no evidence suggesting that six-month BE data for etonogestrel implants predicts BE at three years.

Moreover, FDA’s approach appears to be in tension with other product-specific guidances for implants, none of which appear to propose a significantly shortened period for BE testing relative to the labeled duration of use or the time in which concentrations can be measured. For example, for goserelin acetate implants, guidance recommends a BE study in which “the last sampling time point ‘’ equals the dosing interval of the product used in the in vivo PK study” and advises that “for prostatic cancer patients undergoing initial therapy [in the

⁵⁹ FDA, [Draft Guidance for Industry, Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA](#), at 6 (Aug. 2021).

⁶⁰ [NEXPLANON Labeling](#) § 12.3 (September 2023)

⁶¹ 21 C.F.R. § 320.26(c)(4).

⁶² FDA, Response to Citizen Petition, Docket No. FDA-2010-P-0648, at 5, 10 (Oct. 31, 2013); see also FDA, Response to Citizen Petition, Docket No. FDA-2016-P-4094, at 9 (Apr. 21, 2017) (rejecting a request that ANDA applicants referencing Narcan be required to show BE of AUC₀₋₁₀, reasoning that “there are no data to support these specific time points”).

study] . . . the treatment should not be discontinued or delayed for a second dose,” suggesting that the study includes PK measurements for the full 28-day labeled dosing interval.⁶³ The leuprolide acetate guidance recommends submission of data on “the area under the curve from 0 to the last sampling time point with quantifiable concentration” and also states that “for prostatic carcinoma patients undergoing initial therapy, after the PK study is completed, the treatment should not be discontinued or delayed for a second dose.”⁶⁴ For testosterone pellet implants for which the RLD’s labeled implantation period is 3-6 months, the product-specific guidance recommends submission of partial AUC data “from Day 60 (2 months) to Day 90 (3 months) as *supportive* information” but does not appear to contemplate that sampling would be stopped before the last measured concentration or dosing interval conclusion.⁶⁵ Accordingly, FDA’s scientific basis for the recommended six-month duration of BE testing for generic etonogestrel implants is unclear. None of these product-specific guidances suggest that ANDA applicants can halt their BE studies before the labeled RLD duration of use and while participants still have measurable concentrations.⁶⁶

Without three-year in vivo BE or a validated IVIVC for this timeline, there is risk that the drug concentration from a generic etonogestrel implant could decrease over time, which could result in pregnancy. FDA has stated that “[t]he pharmacological activity of etonogestrel is attributed to suppression of gonadotropins and inhibition of ovulation.”⁶⁷ The concentration of etonogestrel is of critical importance to its effectiveness. Díaz et al. have suggested that a concentration of at least 90 pg/mL (0.28 nmol/L) of etonogestrel is ovulation inhibitory, and this level was used to guide the clinical development of IMPLANON.⁶⁸ As shown in Table 1 below, the mean concentration of etonogestrel in NEXPLANON decreases over time. Decreases in etonogestrel concentration also appear to depend on the subject’s body mass index (BMI). Ensuring BE concentrations over the entire labeled duration of use thus is essential to ensure that

⁶³ [Draft Guidance on Goserelin Acetate](#), at 1 (Nov. 2022); *see* [Zoladex Labeling](#) § 2 (Mar. 2023).

⁶⁴ [Draft Guidance on Leuprolide Acetate](#), at 2 (Nov. 2021); *see generally* [Viadur Labeling](#) (Nov. 2010).

⁶⁵ [Draft Guidance on Testosterone](#), at 2 (May 2022) (emphasis added); *see* [Testopel Labeling](#), Dosage and Administration (Aug. 2018) (“Adequate effect of the pellets ordinarily continues for three to four months, sometimes as long as six months.”).

⁶⁶ Organon is aware of a paper published by FDA staff proposing a short-term in vivo bioequivalence study in lieu of longer-term studies for a long-acting intrauterine system (IUS). Satish Sharan et al., *Application of Modeling and Simulation to Identify a Shortened Study Duration and Novel Bioequivalence Metric for a Long-Acting Intrauterine System*. 24 AAPS J. 63 (2022). The IUS discussed in this paper differs from etonogestrel implants in important aspects, and the results reported in the paper therefore cannot be extrapolated to etonogestrel implants. The primary contraceptive effect of an IUS is locally in the uterine cavity, and systemic exposure is not related to the primary effect. *See Mirena Labeling*, §§ 12.1, 12.2 (Aug. 2022). Thus, systemic bioequivalence has limited clinical relevance for an IUS. Moreover, levonorgestrel that becomes systemically bioavailable after release from an IUS is absorbed over the uterine mucosa, which is entirely different from the absorption of etonogestrel from a subdermal implant, which is largely determined by diffusion.

⁶⁷ [Clinical Review/Cross Discipline Team Leader Review](#), NDA 21-529/SES-007, at 35 (May 12, 2011); *id.* at 36 (“The contraceptive effect NEXPLANON® is achieved by several mechanisms that include suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.”)

⁶⁸ *See* S. Díaz et al., [Clinical trial with 3-keto-desogestrel subdermal implants](#), 44 CONTRACEPTION 393, 400 (1991) (noting that few subjects ovulated if etonogestrel was above this concentration, while approximately half of subjects studied did ovulate with concentrations of etonogestrel below 90 pg/mL (0.28 nmol/L)).

the generic product meets the statutory BE standard and therefore does not present a higher risk of pregnancy as compared to the RLD. The requested BE requirement is necessary to ensure that a proposed ANDA product is BE to NEXPLANON and is as safe and effective as NEXPLANON for the entire indicated duration of use.

Table 1: Data Supporting Revisions to Clinical Pharmacology Section of Labeling⁶⁹

Study		n	Etonogestrel (ENG) concentration (pg/mL) Mean (SD)
34502	Year 1 (Week 48-53)	15	260.5 (94.3)
	Year 2 (Week 98-104)	15	190.6 (64)
	Year 3 (Week 150-155)	11	177.2 (68.8)
34508	Year 1 (Day 366)	10	196
	Year 2 (Day 731)	8	194
	Year 3 (Day 1096)	6	156
069001	Year 1	16	192.1 (47.2)
	Year 2 (23 month)	12	153.6 (32.3)

[REDACTED] DA
should similarly reject such extrapolation for ANDA applicants and should update the Draft Guidance to reflect that generic applicants should show BE through either a three-year in vivo BE study or a validated IVIVC covering the three-year labeled duration of use.

⁶⁹ Addendum to Clinical Pharmacology and Biopharmaceutics Review, NDA 21-529, at 1 (June 6, 2005).

⁷⁰ [REDACTED] see also [Summary Review for Regulatory Action](#), NDA 21529/S007, at 11 (May 13, 2011).

⁷¹ [REDACTED]

⁷² [REDACTED]

Experience with similar contraceptive implants underscores the concern that six-month in vivo PK data for etonogestrel implants might not predict product PK and clinical performance over the full three-year duration of use. In the context of contraceptive implants containing levonorgestrel, a study was conducted to determine whether Sino-implant (II) could obtain a World Health Organization prequalification, which would allow the device to be used more widely across the world. This study is relevant to generic etonogestrel implants given that levonorgestrel implants have similar mechanisms of action and designs, including the use of a polymer matrix that controls rate of drug release. The study was a Phase 3 randomized open-label clinical trial comparing two 150 mg levonorgestrel implants, the Sino-implant (II) silicone contraceptive implant (N=514) and Jadelle® (N=136), for a period of four years of use.⁷³ The labeled duration of use of Sino-implant (II) in China was four years, whereas the labeled duration of use of Jadelle® was five years. The study included women aged 18 to 44 years old; 400 women completed one year of Sino-implant (II) use, and 200 women completed four years of use.⁷⁴ “The primary efficacy measure was the pregnancy Pearl Index [number of pregnancies per 100 women-years (WY) of follow-up] in the Sino-implant (II) group during up to four years of implant use.”⁷⁵ Although the study was initially designed to follow participants for up to five years, “the independent data and safety monitoring board recommend participant follow-up be truncated at month 48 due to a higher-than-expected pregnancy rate among the women who had already provided data in the fourth and fifth years of Sino-implant (II) use.”⁷⁶

With respect to the primary efficacy analysis, 514 women in the Sino-implant (II) group contributed 1343.9 WY of implant use, resulting in a four-year Pearl Index of 0.74 (95% CI, 0.36-1.37). A three-year Pearl Index of 0.18 (95% CI, 0.02-0.65) was based on 1117.7 WY, indicating that there was a much lower pregnancy rate during the first three years of use as compared to the fourth year.⁷⁷ In contrast, there were no recorded pregnancies in the Jadelle group (353.2 WY), resulting in a Pearl Index of 0.00 (95% CI, 0.00-1.04).⁷⁸ Overall, there were eleven pregnancies among the 650 women randomized to the study, all of which were in women assigned to the Sino-Implant (II) group.⁷⁹ Although due to “the expected rarity of pregnancy in implant trials, the study was not powered to detect, nor did it identify, significant differences in pregnancy rates between implant types,”⁸⁰ the occurrence of 11 pregnancies in the Sino-implant (II) group versus zero pregnancies in the Jadelle group, with most of the pregnancies occurring after year three, is notable.⁸¹

⁷³ See M.J. Steiner et al., *Randomized trial to evaluate contraceptive efficacy, safety and acceptability of a two-rod contraceptive implant over 4 years in the Dominican Republic*, CONTRACEPTION: X 1, 1, 2 (2019).

⁷⁴ See *id.*

⁷⁵ *Id.* at 2.

⁷⁶ *Id.*

⁷⁷ *Id.* at 1, 3.

⁷⁸ *Id.*

⁷⁹ *Id.*

⁸⁰ *Id.* at 1, 6.

⁸¹ *Id.* at 1, 4, Table 3.

Researchers also conducted a PK analysis comparing the concentration of levonorgestrel across participants in the Sino-implant (II) and Jadelle groups. The data demonstrated that concentrations of the active ingredient “were equivalent between groups at month 12, but were 19%, 22% and 32% lower in the Sino-implant (II) group at months 24, 36, and 48, respectively ($p<.001$ at each time point).”⁸² In other words, over the first 12 months, levonorgestrel levels were similar for both implant systems, but after the initial 12-month period, subjects on Jadelle® maintained higher levonorgestrel levels, and these differences manifested in differences in efficacy, as there were no pregnancies reported among users of Jadelle. Another study reports that a PK analysis “observed steadily decreasing relative total [levonorgestrel] concentrations [for Sino-implant (II)], ranging from 6% less than Jadelle® at year 1 to 32% less at year 4,” which “support[s] the conclusion that Sino-implant (II) has a shorter duration of action than Jadelle®.”⁸³ A remnant content analysis of Sino-implant and Jadelle® from a subset of participants in the same study nevertheless showed that in vivo release rates in year one were 20% lower for Sino-implant (II) than for Jadelle®, showing that in vivo release rates are not fully predictive of serum concentrations either.⁸⁴ The authors conclude that, although both implants are comprised of a similar silicone elastomeric matrix, differences in release rate could be associated with material properties such as levonorgestrel and excipient manufacturing sources, levonorgestrel particle size, levonorgestrel to matrix ratio, crosslink density of the matrix, inner core diameter, and outer membrane thickness.

These data demonstrate that similar composition and similar short-term (12 month) drug levels for a contraceptive implant are not necessarily predictive of future drug levels or clinical efficacy and that the full duration of intended use should be evaluated. Had only the first year of use been evaluated in this study, the differences between the implants may not have been apparent.

For the foregoing reasons, six-month in vivo BE data is not sufficient to establish that a generic drug is BE to NEXPLANON over the labeled duration of use. The Draft Guidance recommendation contradicts FDA guidance and regulations and FDA’s previous expectations for Organon. The recommended six-month period lacks scientific foundation, and peer-reviewed scientific publications for similar products indicate that PK parameters even at one year are not reliably predictive of PK parameters years later. [REDACTED]

[REDACTED] FDA should require ANDA applicants to show BE through an in vivo study covering the labeled duration of use or by validating an IVIVC for the labeled duration of use. This requirement is necessary to ensure that patients receiving generic etonogestrel implants receive a product that is BE across the entire labeled duration of use and thus are not exposed to an increased risk of pregnancy.

⁸² *Id.* at 1.

⁸³ Rachael Fuchs et al., *Levonorgestrel release rates measured through analysis of two-rod contraceptive explants*, 2 CONTRACEPTION X at 3 (2020).

⁸⁴ *Id.*

2. Dissolution

The Draft Guidance currently states that “[t]he dissolution information for this drug product can be found in the FDA’s Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.” This statement was not correct when the Draft Guidance was issued and remains incorrect. The Dissolution Methods database continues to lack any entries for the etonogestrel implant. Organon continues to believe that FDA should allow for public comment on the proposed dissolution method; thus, we recommend FDA make available the proposed dissolution method and accept comment on it.⁸⁵ Also, we believe that the required comparative dissolution testing should include three different pH levels for at least six months, consistent with FDA’s expectations for Organon for post-approval changes to NEXPLANON.⁸⁶

B. If the proposed BE requirements are not implemented, FDA should require the proposed generic drug to be Q3 the same to NEXPLANON.

To the extent that FDA determines that an ANDA applicant does not need to demonstrate BE as requested in section V.A, FDA should require the ANDA applicant to demonstrate Q3 (physicochemical and structural) sameness between the proposed ANDA product and the RLD to be eligible for the shorter BE study contemplated in the Draft Guidance. FDA should also revise the Draft Guidance accordingly.

The Draft Guidance recommends “[a]cceptable comparative physicochemical and mechanical characteristics of the test and the RS products including: 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) crystalline form of the API; and 3) mechanical properties of the implant, including but not limited to tensile strength and hardness.”⁸⁷ It does not, however, define “acceptable.” Moreover, the recommendations in the Draft Guidance fall short of full Q3 sameness because they do not ensure equivalence with respect to the polymer and the microstructure of the implant.⁸⁸

FDA should apply Q3 sameness requirements if the generic applicant does not conduct a BE study for the labeled duration of use or validate an IVIVC over that time period. Complete characterization of the physical and structural qualities that define the generic product, including

⁸⁵ See [Comment from Sandip Roy, Organon, LLC](#), Docket No. FDA-2007-D-0369-0691, at 7 (Oct. 5, 2022) (“Organon requests that FDA reopen the public docket on the Draft Guidance after FDA publishes the dissolution method for etonogestrel implants and before the Agency publishes a revised draft or final version of the Draft Guidance.”).

⁸⁶ See Mem. of Teleconference Minutes, IND 42877/NDA 21529, at 3 (Sept. 18, 2007).

⁸⁷ FDA, [Draft Guidance on Etonogestrel](#), at 1-2 (Aug. 2022) (emphasis added).

⁸⁸ Cf. FDA, [Draft Guidance for Industry: Physicochemical and Structural \(Q3\) Characterization of Topical Drug Products Submitted in ANDAs](#), at 9-10 (Oct. 2022) (defining Q3 sameness to mean that each relevant Q3 attribute of the test product, characterized in multiple batches, is either shown “to be within the range characterized for that Q3 attribute of the reference standard for the topical product” or “determined by the Agency to be within the acceptable variability for the reference standard for the topical product,” and “[t]here is no difference in the components or composition of the test topical product and reference standard for the topical product that may significantly affect systemic or local availability”); FDA, [Equivalence of Locally-Acting Drug Products](#), at 6 (May 3, 2017) (referring to Q3 as “[s]ame components in [the] same concentration with the same arrangement of matter (microstructure)”).

its critical excipients, is important to ensure that these generic products are BE and can be expected to have the same clinical effect and safety profile as NEXPLANON for the labeled duration of use. Demonstrating Q1/Q2 sameness does not ensure that the release rate of the active ingredient is also the same; yet release of the drug from the polymer matrix is a critical aspect to ensuring safety and effectiveness of the drug.

[REDACTED] Such effects may not be evident based on the finished product or information in the public domain. The literature supports the potential for polymer attributes to affect bioavailability. For example, the Sino-implant (II) and Jadelle implants had a similar silicone elastomeric matrix but differed in PK profile and release rate, which "could be associated with material properties such as [active ingredient] and excipient manufacturing sources, [levonorgestrel] particle size, [levonorgestrel] to matrix ratio, crosslink density of the matrix, inner core diameter and outer membrane thickness."⁸⁹

[REDACTED]

Particularly

where the ANDA applicant has not conducted a BE trial spanning the labeled duration of use, FDA should require the applicant to show Q3 sameness to ensure that the product meets the statutory requirements of sameness and BE to NEXPLANON. Item 3 in the Draft Guidance should be amended to recommend a showing of an equivalent comparative degree of substitution of the rate controlling polymer and equivalent microstructure between the test and the RLD product.

Q3 sameness is also an appropriate requirement to ensure that the generic drug does not present a higher risk of breakage than NEXPLANON. Differences in the polymer matrix and manufacturing can affect the brittleness of an etonogestrel implant and, therefore, its potential for breakage. For example, in a comparison of Sino-implant (II) and Jadelle with different polymer properties, there was "a higher than expected breakage rate for Sino-implant (II) at the time of removal": Sino-implant (II) had a breakage rate of 16.3%, and Jadelle had a breakage rate of 3.1% ($p < .001$).⁹¹ Although breakage rates in China were comparable to the breakage rates

⁸⁹ Rachael Fuchs et al., *Levonorgestrel release rates measured through analysis of two-rod contraceptive explants*, 2 CONTRACEPTION: X at 3 (2020).

⁹⁰ See *Review of Chemistry, Manufacturing and Controls, Chemistry Review #1*, NDA 21529/SES-007, at 5 (261/484) (Apr. 19, 2010).

⁹¹ M.J. Steiner et al., *Randomized trial to evaluate contraceptive efficacy, safety and acceptability of a two-rod contraceptive implant over 4 years in the Dominican Republic*, CONTRACEPTION: X 1, 6 (2019).

observed for other contraceptive implants (5.0%, 16 of 318 removals evaluated), “laboratory testing conducted during the trial showed that the tensile integrity of Sino-implant (II) was less robust than Jadelle[®], s.”⁹²

Finally, extractables and leachables are an important component for an equivalent safety profile to the RLD and should be included as part of the Q3 characterization. This requirement is consistent with FDA’s draft guidance on generic drug-device combination products, which states that “[t]he delivery device constituent part should be shown to be compatible for use with the final formulation of the drug constituent part through appropriate studies, including, for example, extractable/leachable studies, performance testing, and stability studies.”⁹³ FDA also generally expects NDAs to include extractable and leachable study data for injectable drug products regardless of the material used for the container closure system, and this expectation should apply equally to an implanted product.⁹⁴

The testing of extractables and leachables should be conducted as per current FDA guidance ‘Use of International Standard ISO10993-1, “Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process”, specifically Section VII. Chemical Assessment, conducting chemical characterization in relevant polar, semi-polar and non-polar solvents as part of the Q3 characterization; and require safety and biocompatibility testing for the generic drug product. Furthermore, as per recently stated expectation from the FDA⁹⁵, in order to establish chemical equivalence, it is critical to demonstrate that the proposed device have the same or fewer extractable constituents as compared to the reference product and there should not be any new constituents in the proposed device.

This requirement is necessary to ensure that the generic application contains appropriate manufacturing information and that the generic drug product composition does not render it unsafe for use over the duration of use and for the entire shelf-life.⁹⁶ For the same reason, FDA should require biocompatibility testing for the proposed generic product.⁹⁷

⁹² *Id.* Steiner also notes that a “reduction in breakage rate after retraining suggests removal technique is an important factor that can lead to varying breakage rates across and within studies.” *Id.*; see *infra* Section V.D.

⁹³ Human Factors Draft Guidance, at 3.

⁹⁴ FDA Response to IDRS Labs Private Limited, Docket No. FDA-2021-P-0389 (Aug. 25, 2021), at 8.

⁹⁵ [REDACTED]

⁹⁶ Human Factors Draft Guidance, at 3; FDCA § 505(j)(4)(H); 21 C.F.R. § 314.127(a)(8)(ii)(A).

⁹⁷ Cf. FDA, Guidance for Industry and Food and Drug Administration Staff, *Use of International Standard ISO 10993-1, “Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process”* (Sept. 2020).

C. FDA should require proposed ANDA products to have equivalent device constituents to NEXPLANON in performance, operating principles, and critical design attributes.

In alignment with FDA precedent, generic etonogestrel implants should be required to have equivalent device constituents to NEXPLANON in terms of performance, operating principles, and critical design attributes. FDA should update the Draft Guidance accordingly.

FDA addressed device requirements for generic drug-device combination products in a comprehensive citizen petition response to King Pharmaceuticals and subsequently reaffirmed these principles in a response to Dey Pharma.⁹⁸ Per the King response, FDA's ANDA review process "for combination products considers whether any difference in materials, design, or operating principles introduces a new risk," "includ[ing] . . . both risks intrinsic to the new product and risks associated with switching from one product to the other without additional physician intervention or training."⁹⁹ FDA said that "[s]ome design differences may be acceptable as long as they do not significantly alter product performance or operating principles and do not result in impermissible differences in labeling."¹⁰⁰ Per the King response, the agency requires ANDA applicants "to provide details on attributes such as [device] design, materials, operating principles, and comparative performance tests between the [device] constituent of the RLD and the [device] constituent of the product described in the ANDA."¹⁰¹ "If FDA determines that the [device] constituent of a product proposed in an ANDA is not equivalent to the [device] constituent of the RLD in terms of performance and critical design, FDA will refuse to approve the ANDA for that product."¹⁰² A subsequent 2017 draft guidance, discussed further below, briefly reiterates several of these principles while focusing on user interface issues.¹⁰³

The King response explains that the requirement to submit supportive information for a device constituent of a generic drug-device combination products stems from several statutory requirements for ANDAs, including the requirement that the generic applicant: (1) submit information to show that its product has the same labeling as the RLD other than permissible differences; (2) submit information to show that its product is BE to the RLD; (3) submit information to show that its product is the "same" as the RLD; and (4) provide appropriate chemistry, manufacturing, and controls information to support the ANDA.¹⁰⁴ FDA also notes

⁹⁸ King Response, at 6; FDA Response to Dey Pharma L.P., Docket No. FDA-2009-P-0578 (May 27, 2010) (Dey Response).

⁹⁹ King Response, at 6.

¹⁰⁰ *Id.* at 6.

¹⁰¹ *Id.* at 7.

¹⁰² *Id.*

¹⁰³ See, e.g., Human Factors Draft Guidance, at 4 ("FDA intends to consider whether the generic combination product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the generic combination product.").

¹⁰⁴ King Response, at 6-9; see also Dey Response, at 8 ("Our criteria for evaluating sameness were described in the King Petition response, which indicates that an ANDA and its RLD may have some auto-injector design differences as long as these differences 'do not significantly alter product performance or operating principles and do not result in impermissible differences in labeling'") (citation omitted).

that differences between device release mechanisms “would satisfy criteria under 21 CFR 314.127(a)(8)(ii)(A) for refusing to approve an ANDA because ‘there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy.’”¹⁰⁵ Finally, FDA notes that it will consider the information submitted in the ANDA regarding the device constituent in determining whether the generic drug product is therapeutically equivalent to the RLD, i.e., whether the generic drug product is a “pharmaceutical equivalent[] [to the RLD] for which [BE] has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”¹⁰⁶

Consistent with these principles, FDA should require any ANDA applicant for a proposed generic etonogestrel implant to characterize and provide details about the implant and applicator device design and materials and operating principles, as well as comparative performance tests. If a device for the proposed ANDA product is not equivalent to the NEXPLANON device in performance, operating principles, or critical design attributes, FDA should deny approval of the ANDA.¹⁰⁷ FDA should also consider device-related information appropriately submitted in the ANDA to determine if the generic drug product is therapeutically equivalent to the RLD.¹⁰⁸

The Draft Guidance does not articulate these principles. It states that “[t]he implant and the applicator are device constituents used to administer the drug.”¹⁰⁹ It then recommends that prospective applicants “examine the size and shape, external critical design attributes, and external operating principles of the RLD devices when designing the test devices.”¹¹⁰ It is not sufficient for ANDA applicants to simply “examine” these characteristics. FDA should require, and the Draft Guidance should be revised to reflect, that generic device constituents must be equivalent to those of NEXPLANON in performance, operating principles, and critical design attributes. It should also provide that the ANDA needs to contain details about the design of the applicator device design, its materials, operating principles, and comparative performance tests.

These determinations are important from a public health perspective. If the generic drug’s device constituents were not equivalent to the NEXPLANON devices in these respects, there would be a reasonable basis to conclude that the composition of the generic drug raises

¹⁰⁵ King Response, at 10 (citation omitted).

¹⁰⁶ *Id.* at 7; 21 C.F.R. § 314.3(b).

¹⁰⁷ King Response, at 10 (“[W]e agree that the auto-injector constituent in an ANDA for a combination product should be equivalent to that of the RLD product in terms of performance, operating principles, and critical design attributes”).

¹⁰⁸ *Id.* at 7 (“FDA considers the auto-injector constituent part along with the drug constituent part when determining therapeutic equivalence ratings for a drug/auto-injector combination product.”).

¹⁰⁹ Draft Guidance, at 3. FDA has previously characterized the implant as part of the drug product. See [Summary Review for Regulatory Action](#), NDA 21529/S007, at 13 (May 13, 2011). (“The final drug product (the implant) and the inserter applicator are sterilized”). In any case, because FDA has noted that it applies the provisions of the statute and FDA regulations concerning generic inactive ingredients and compositions to device constituents, differences in the implant composition that raise new safety or effectiveness issues would not be permissible in an ANDA. See King Response, at 10 (citation omitted).

¹¹⁰ Draft Guidance, at 3 (emphasis added).

serious questions of safety and efficacy.¹¹¹ Differences in the applicator or implant's critical design attributes, operating principles, or performance could lead to errors in implantation and removal. These errors in turn could lead to both efficacy concerns, e.g., by increasing the risk of insertion failures that may lead to an unintended pregnancy, as well as safety concerns, such as increasing the risk of deep insertions that could result in adverse events. The Draft Guidance should therefore be revised as described.

- D. To ensure the safe and effective use of the proposed generic product, FDA should require ANDA applicant to implement measures to ensure appropriate training and instruction on the use of the generic product.

NEXPLANON's labeling includes extensive information about the need to train HCPs who insert, localize, and remove the product, and its training program has been the subject of extensive discussion with FDA. This labeling information and training are critical to safe and effective use of the product. Because a generic drug may be substituted for NEXPLANON, it is important that the generic drug meet the therapeutic equivalence standard, i.e., it "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."¹¹² To meet this standard and satisfy the "same labeling" requirement, the generic drug must include the same language regarding training as found in the NEXPLANON labeling, except for differences necessary to refer to different product names, manufacturer names, or manufacturer contact information. The generic labeling also should include the same instructions as the NEXPLANON labeling with regard to implant insertion, localization, and removal except for similarly *de minimis* differences. Consistent with the agency's emphasis on the importance of training throughout its communications with Organon, FDA should also require that a generic manufacturer implement a training program to cover the same information as the NEXPLANON training and limit access to the product to trained prescribers. Without these steps, there would be a significant risk that patients could receive unsafe or ineffective treatment with the generic drug due to insertion, localization, and/or removal errors, thereby negatively impacting the interests of patient safety and the public health.

From the time of the original submission of the IMPLANON application the FDA had concerns regarding implant IRRE that may result from inadequate training of HCPs. Therefore, a clinical training program was developed and deployed to address this concern. Hence, as a public health matter, it is crucial that generic drug labeling includes the same content as the NEXPLANON labeling regarding training, with the minor exceptions discussed above. [REDACTED]

[REDACTED] Omission of the training-focused content from generic labeling would "render the proposed [generic] drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."¹¹⁴ For example, the generic labeling must state that "[a]ll healthcare professionals should

¹¹¹ FDCA § 505(j)(4)(H); 21 C.F.R. § 314.127(a)(8)(ii)(A)(5).

¹¹² FDA, [Orange Book Preface](#) (discussing therapeutic equivalents).

¹¹³ See *supra*, notes 36-38.

¹¹⁴ 21 C.F.R. § 314.127(a)(7).

receive instruction and training prior to performing insertion and/or removal of the generic drug.¹¹⁵ It also must advise the prescriber that “videos demonstrating insertion and removal are available online for trained healthcare professionals.” FDA has noted that “the need for training, and the characteristics of such training, are product-design specific determinations.”¹¹⁶ Experience with contraceptive implants has indicated the importance of training, as reflected in the NEXPLANON labeling and our discussions with FDA over the years. If HCPs are not properly trained on how to use the generic product, patients would be at higher risk of IRREs with the generic drug.

Experience with other contraceptive implants also supports the importance of training to ensure the safe and effective use of a generic etonogestrel implant. For example, in the study discussed above, there was a significantly higher breakage rate for Sino-implant (II) compared to Jadelle (16.3% vs. 3.1%), and this complication required a second visit “to ensure that the Sino-implant (II) was completely removed in 13 (2.7%) instances.”¹¹⁷ “One of the identified explanations for the high breakage rate was that the site was not following the removal instructions.”¹¹⁸ After HCPs received additional training, “[t]he breakage rate in the Sino-implant (II) group generally decreased with each intervention: 33.3% prior to training, 17.6% after training to minimize twisting/torque and 8.3% after the site began using Crile forceps,” which are larger and less sharp than the previously used forceps.¹¹⁹ Testing found that, although the composition of the implant was a factor,¹²⁰ “the reduction in breakage after retraining suggests removal technique is an important factor that can lead to varying breakage rates across and within studies.”¹²¹ This publication shows that training plays a critical role in ensuring safe use of contraceptive implants, with concrete implications for patients in terms of the risk of breakage and risk of associated adverse events. Given the importance of training to safe and effective use of NEXPLANON, deleting the labeling text on training would render the generic drug less safe and effective than the RLD. This labeling is necessary to ensure that patients receiving the generic product can expect the generic drug to have the same clinical effect and safety profile as NEXPLANON.

Similarly, the labeling information on implant insertion, localization, and removal instructions is integral to ensure safe and effective use of an etonogestrel implant. Omitting this information would make the generic drug both less safe and less effective than the RLD. The labeling indicates that errors in insertion, localization, and removal can result in safety issues (including bleeding, infection, neural or vascular injury, compromised fertility, ectopic

¹¹⁵ [NEXPLANON Labeling](#) §§ 2, 2.2 (September 2023).

¹¹⁶ FDA, Response to Citizen Petition from US WorldMeds, LLC, Docket No. FDA-2015-P-2626, at 7 (Sept. 22, 2017) (US WorldMeds Response).

¹¹⁷ M.J. Steiner et al., *Randomized trial to evaluate contraceptive efficacy, safety and acceptability of a two-rod contraceptive implant over 4 years in the Dominican Republic*, CONTRACEPTION: X 1, 5 (2019).

¹¹⁸ *Id.*

¹¹⁹ *Id.*

¹²⁰ See *supra*, Section V.B.

¹²¹ M.J. Steiner et al., *Randomized trial to evaluate contraceptive efficacy, safety and acceptability of a two-rod contraceptive implant over 4 years in the Dominican Republic*, CONTRACEPTION: X 1, 6 (2019).

pregnancy, chest pain, and/or respiratory disorders) and necessitate surgery.¹²² Further, “[f]ailure to appropriately insert or remove the implant can result in inadequate contraception.”¹²³ Specifically, “[o]f the 1814 medically confirmed reports of [insertion and removal related events (IRRE)] to Organon, 561 reported an unintended pregnancy.”¹²⁴ Insertion failures can include insertion too deep into the inner arm, difficulty inserting the implant, failure to insert the implant, and a broken or cut implant.¹²⁵ Each of these failures can result from inadequate instructions. The labeling on insertion, localization, and removal of the implant contains detailed instructions necessary to guide these provider activities that are directly tied to safe and effective use. Without the instructions within the NEXPLANON labeling, HCPs would be more likely to experience issues with proper insertion, localization, and removal of the implant with safety and effectiveness implications. Similarly, substantial changes to these instructions could cause procedural errors that could reduce safety or effectiveness.

To ensure that the generic drug can be expected to have the same clinical effect and safety profile as NEXPLANON and to comply with the language regarding training in the labeling, an ANDA applicant referencing NEXPLANON must also implement its training program as described in the labeling.¹²⁶ As evidenced by FDA’s emphasis on the importance of training to safe and effective use of etonogestrel implants since the original approval of IMPLANON to present day experience with NEXPLANON, adequate training is required for the safe and effective insertion, localization, and removal of an etonogestrel implant. The training program should cover all three activities and include hands-on elements with a model arm, as in the NEXPLANON training program. The ANDA applicant should develop “videos demonstrating insertion and removal . . . for trained healthcare professionals” for use in these trainings as well as for online display to trained HCPs. Further, the ANDA applicant should be required to assess the effectiveness of such training (as was done in the NEXPLANON Observational Risk Assessment Study (NORA)).¹²⁷ Finally, the proposed ANDA product should be available only to trained healthcare providers, with the ANDA applicant having a process in place to ensure that the product will be released only to trained individuals. Without these steps, the risk of errors in insertion, localization, or removal that could lead to safety or effectiveness concerns would be higher with the generic drug. For example, if untrained healthcare providers could access the generic drug, or if the generic program did not involve any hands-on training, the risk of IRRE with related safety and effectiveness implications would be higher. This outcome is incompatible with the statutory standard for generic approval and the public health need for a generic drug to have the same clinical effect and safety profile as the RLD.

¹²² See [NEXPLANON Labeling](#) § 5 (September 2023).

¹²³ [Risk Assessment and Risk Mitigation Review](#), NDA 21529, at 2 (July 20, 2005).

¹²⁴ *Id.* at 4.

¹²⁵ See *id.*

¹²⁶ Even though the NEXPLANON training program was not a condition of approval, this case differs from that of Apokyn, where the approved labeling contained no reference to training on a pen injector device. US WorldMeds Response, at 7. The NEXPLANON labeling instead emphasizes the need for training.

¹²⁷ See [Clinical Review/Cross Discipline Team Leader Review](#), NDA 21-529/SES-007, at 158 (May 12, 2011); Reed S, Minh TD, Lange JA et al. Real world data on Nexplanon® procedure-related events: final results from the Nexplanon Observational Risk Assessment study (NORA). *Contraception* 2019;100:31-6.

As articulated above, if a generic did not demonstrate BE, equivalent device constituents and have a comparable training program then, in totality, the generic would have a different safety and efficacy profile than NEXPLANON. Accordingly, generics should be required to meet these attributes.

VI. Conclusion

For the reasons set forth in this petition, Organon requests that FDA take the above stated actions with respect to ANDAs citing NEXPLANON or IMPLANON.

C. Environmental Impact

This petition is categorically exempt from the requirement for an environmental assessment or environmental impact statement under 21 C.F.R. § 25.31(a) & (g).

D. Economic Impact

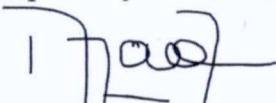
An economic impact statement will be submitted at the request of the Commissioner per 21 C.F.R. § 10.30(b).

E. 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: August 2022 (when the FDA issued its draft product-specific guidance on etonogestrel (Draft Guidance)); [REDACTED]

[REDACTED] 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: regular compensation received as an employee of Organon. 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,



Juan Camilo Arjona Ferreira

Head, Organon Research & Development
and Chief Medical Officer