TEVA Women's Health

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VIA HAND DELIVERY

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting That FDA Refrain From Approving Any Abbreviated New Drug Application Referencing Paragard® T 380A (intrauterine copper contraceptive) Until Certain Conditions Are Met

Dear Sir or Madam:

On behalf of Teva Pharmaceutical Industries Ltd., Teva Women's Health, Inc. ("Teva") hereby submits this Citizen Petition pursuant to 21 C.F.R. §10.30 and section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 355(j). For the reasons that follow, Teva respectfully requests that the Commissioner of Food and Drugs refrain from approving any abbreviated new drug application ("ANDA") that references ParaGard® T 380A Intrauterine Copper Contraceptive ("ParaGard®") unless and until the conditions specified in this Petition are satisfied. Teva holds the approved New Drug Application ("NDA") for ParaGard®, which is indicated for intrauterine contraception for up to 10 years.[1]

I. Actions Requested

ParaGard® is an intrauterine device ("IUD") intended for long-term placement in healthy women that contains copper as an active ingredient. Although ParaGard® has been shown to be an extremely effective contraceptive for up to 10 years, the precise mechanism or mechanisms by which it achieves its contraceptive effects are not well understood. What is known is that ParaGard® works primarily or exclusively through local action, and ParaGard®'s copper and

[1] Teva Pharmaceutical Industries Ltd. is a global pharmaceutical company specializing in the development, production, and marketing of generic, proprietary, and branded pharmaceuticals, and active pharmaceutical ingredients. Teva is among the top 20 pharmaceutical companies and is the leading generic pharmaceutical company in the world. Teva Women's Health, Inc. is the branded women's health products subsidiary of Teva Pharmaceutical Industries Ltd. and is responsible for the clinical development, registration, and marketing of Teva's branded women's health products in North America, including Paragard®.

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non-copper components both contribute to its efficacy, although the precise contribution of each is not known.

Because of these specific characteristics, the Agency cannot be assured that a purported generic copper IUD will be as safe and effective as ParaGard® in the absence of: (a) information from one or more well-controlled clinical trials using relevant safety and effectiveness endpoints establishing *in vivo* bioequivalence; (b) a demonstration that the labeling for the proposed generic product is identical to that of ParaGard®; and (c) a demonstration that the IUD components of the proposed generic product and ParaGard® are identical. Consequently, Teva respectfully requests that the Commissioner:

1. Refrain from approving any ANDA that relies upon ParaGard® as the reference listed drug unless the application contains the results of one or more comparative clinical investigations using relevant safety and effectiveness endpoints that demonstrate the proposed generic drug is bioequivalent to, and thus as safe and effective as, ParaGard®;

2. Refrain from approving a proposed generic copper IUD unless it has the same labeling as ParaGard®, including instructions for use and a 10-year effective life span (supported by appropriate testing); and

3. Refrain from approving a proposed generic copper IUD unless its physical components are identical to those of ParaGard® in terms of, among other things, materials, design, operating principles, and performance characteristics (*e.g.*, durability, strength, etc.).

II. Statement of Grounds

A. Paragard® Is an IUD Intended for Long-Term Intrauterine Placement in Healthy Women That Acts Locally Through Mechanisms of Action That Are Not Completely Understood

1. ParaGard® Approval, Indication, and Composition

ParaGard® is an IUD that was first approved in 1984 via NDA No. 18-680 and currently is indicated "for intrauterine contraception for up to 10 years."[2] Like all IUDs, ParaGard® is intended for long-term intrauterine placement in healthy women to prevent pregnancy; it is not intended to treat or mitigate any disease or abnormal health condition. In clinical studies, the pregnancy rate of ParaGard® has been less than 1 pregnancy per 100 women each year.

[2] ParaGard® T 380A Intrauterine Copper Contraceptive prescribing information. TevaWomen's Health, Inc. Sellersville, PA. (Exhibit 1) ("ParaGard Prescribing Information").

ParaGard® is an IUD that contains copper as an active ingredient. Although non-drug or inert IUDs are regulated by FDA as medical devices, *see* 21 C.F.R. § 884.5360 (categorizing contraceptive IUDs as Class III medical devices), ParaGard® is considered to be a drug product because it incorporates copper as an active drug component. *Id.* § 310.502(a)(8).[3]

ParaGard® is comprised of a T-shaped intrauterine implant measuring 32 mm horizontally and 36 mm vertically, with a 3 mm diameter bulb at the tip of the vertical stem. A monofilament polyethylene thread is tied through the tip, resulting in two white threads, each at least 10.5 cm in length, to aid in detection and removal of the device. The T-frame is made of polyethylene with barium sulfate to aid in detecting the device via x-ray.

The T-shaped implant also incorporates a drug component – copper – to enhance contraceptive effectiveness. In particular, approximately 176 mg of copper wire is coiled along the vertical stem of each unit, and a single copper sleeve is swaged on each of the two transverse arms. Each sleeve contains approximately 68.7 mg of copper. The total exposed surface area of copper on the device is 380 ± 23 mm^2. The copper used in ParaGard® is highly purified. One ParaGard® implant weighs less than one (1) gram.

The ParaGard® implant is packaged together with an insertion tube and a solid white rod in a Tyvek® polyethylene pouch that is then sterilized. The insertion tube and rod are not intended for implantation into a patient but instead are designed to facilitate the proper insertion and placement of the ParaGard implant into the uterus. A moveable flange on the insertion tube aids in gauging the depth of insertion through the cervical canal and into the uterine cavity.

ParaGard® is available by prescription only and is intended to be inserted in the uterus only by a licensed clinician or under the supervision of a physician in accordance with detailed instructions. The placement technique for ParaGard® is different from that used for other IUDs, and physicians thus must be thoroughly familiar with the instructions for use prior to placement.

Although ParaGard® has been demonstrated to be safe and effective through both clinical trials and decades of clinical experience, it is associated with some meaningful risks. These include the possibility of longer, heavier, and sometimes painful menstrual periods, which can sometimes lead to anemia; the risk of pelvic inflammatory infection at the time of IUD insertion; perforation of the wall of the uterus by the IUD or the instrument used to insert it; embedment in the uterine wall; and the risk of expulsion, which can lead to pregnancy if the expulsion is not noticed.

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[3] Under FDA regulations, IUDs intended for contraception in humans "that incorporate heavy metals, drugs, or other active substances" are considered to be new drugs rather than medical devices. 21 C.F.R. § 310.502(a)(8). Copper is a "heavy metal" for purposes of this regulation, and ParaGard, which incorporates copper, is thus regulated as a "new drug."

2. ParaGard®'s Mechanisms of Action Are Not Well Understood

Although ParaGard® has been shown to be an extremely effective intrauterine contraceptive for up to 10 years, the precise mechanism or mechanisms by which it achieves its contraceptive effects remain unclear. Like all IUDs, ParaGard® induces a local inflammatory reaction after intrauterine placement, which may be enhanced by copper, and the associated changes to the uterine environment may interfere with events associated with the fertilization process. In addition, copper appears to have direct anti-fertility effects by interfering with the usual functioning of both sperm and ova. However, it is not known whether the efficacy of ParaGard® is due primarily to the effect of its copper component on sperm, ova or both. Also unclear is the precise site of action of these effects (assuming they exist *in vivo*) in, for instance, the cervix, the endometrium, the fallopian tubes, the fimbria or some other site or combination of sites of action. Finally, it appears that the drug and device[4] components of ParaGard® both contribute to its efficacy; however, the precise contribution of each component is not known.

The device component of ParaGard® may contribute to its contraceptive efficacy by inducing a local inflammatory reaction in the uterus. It is well known that even non-drug, or inert, IUDs induce such a reaction, and these endometrial changes are thought to be spermicidal, inhibiting the transport of sperm through the endometrium. "It has been suggested that the antifertility action of inert IUDs is directly related to the presence of increased numbers of intrauterine leukocytes in general and macrophages in particular."[5] Nevertheless, it is not clear exactly how this local inflammatory reaction prevents pregnancy or whether there are other modes of activity in addition to the proposed spermicidal activity of increased leukocytes. According to the World Health Organization ("WHO"), it is "unlikely that any single mechanism of action accounts for the antifertility effects of IUDs."[6]

The drug component of ParaGard® – *i.e.*, its copper coil and sleeves – also contributes to its contraceptive efficacy, but the precise mechanism or mechanisms by which it accomplishes this effect are not known. One possibility is that the copper in ParaGard® induces a stronger local inflammatory reaction in the uterus than the device component alone, thereby disrupting the fertilization process to a greater degree than could be achieved by an inert IUD. Indeed, it is well known that the foreign-body reaction induced by inert IUDs is "enhanced by the addition of copper to the IUD."[7] Copper also alters the metabolism of endometrial cells.[8] Consequently,

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[4] Although ParaGard® is regulated as a drug because of its copper component, IUDs that do not contain heavy metals or other drug components are regulated as medical devices. *See* 21 C.F.R. § 884.5360. Therefore, for clarity's sake, this Petition will hereinafter refer to the non-copper components of ParaGard® as "device components" and the copper component as the "drug component." ParaGard® nevertheless remains a drug product.

[5] *Mechanism of Action, Safety and Efficacy of Intrauterine Devices: Report of a WHO Scientific Group*, World Health Organization, at 13 (1987) ("WHO Scientific Group Report") (Exhibit 2).

[6] WHO Scientific Group Report, at 68 (Exhibit 2).

[7] WHO Scientific Group Report, at 13 (Exhibit 2).

"[t]he higher inflammatory response of the endometrium in the presence of copper IUD suggests that copper IUDs may have stronger spermicidal effects on the endometrial level."[9]

In addition to enhancing the local inflammatory reaction caused by the device component of an IUD, copper is thought to play a *direct* role in preventing pregnancy by inhibiting the migration and/or viability of sperm and/or ova throughout the female reproductive system. According to ParaGard®'s approved package insert, there are several "[p]ossible mechanism(s) by which copper enhances contraceptive efficacy," including interference with sperm transport or fertilization.[10] Indeed, studies suggest that copper IUDs such as ParaGard® work primarily by preventing fertilization. Possible pre-fertilization modes of action include: (1) inhibition of sperm migration and viability in the cervix, endometrium and fallopian tubes; (2) slowing or speeding the transport of the ovum through the fallopian tubes; and (3) damage or destruction of the ovum before fertilization.[11]

The copper released from IUDs such as ParaGard® significantly increases the copper concentration in uterine fluid and cervical mucus.[12] High copper concentrations have been shown to inhibit sperm motility and may be spermicidal.[13] Because higher copper concentrations appear to be more deleterious to sperm motility than lower concentrations, IUDs containing more copper, such as ParaGard®, are often more effective than IUDs containing lower amounts of copper.[14] Moreover, copper IUDs appear to change the rheological properties and enzymatic activity of cervical mucus.[15] Although these changes in mucus properties do not completely block sperm migration through the cervix, they appear to significantly inhibit such migration.[16]

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[8] *Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action.* Ortiz & Croxatto, Contraception. S16-S30, at S17 (2007) (Exhibit 3).

[9] *Mechanisms of action of intrauterine devices: Update and estimation of postfertilization effects.* Stanford & Mikolojczyk. Am. J. Obstet. Gynecol. 1699-1708, 1700 (Dec. 2002) (Exhibit 4).

[10] ParaGard Prescribing Information (Exhibit 1).

[11] Stanford & Mikolojczyk, at 1700 (Exhibit 4).

[12] Stanford & Mikolojczyk, at 1700 (Exhibit 4).

[13] Ortiz & Croxatto, at S17 (Exhibit 3); Stanford & Mikolojczyk, at 1700 (Exhibit 4).

[14] Grimes DA, Lopez KM, Manion C, Schultz KF, Cochrane systematic reviews of IUD trials: lessons learned. Contraception 75 (2007) S55-S59 (Exhibit 5).

[15] *Effects of Non-medicated and Copper IUDs on Sperm Migration,* Aref et al. Contracept. Deliv. Syst. 4 (1983), 203-206 (Exhibit 6).

[16] Aref et al. (Exhibit 6).

Copper IUDs also appear to inhibit the migration through and viability of sperm in the fallopian tubes. Studies that evaluated the presence or absence of sperm in the fallopian tubes of IUD users compared to nonusers found evidence of fewer sperm in women using IUDs. Moreover, there is a tendency for copper IUDs to impair sperm migration to a greater extent than inert IUDs. For example, in a study of 35 women undergoing salpingectomy for sterilization (15 controls, 10 ML Cu 250 IUDs, 10 inert IUDs), no sperm were detected in the tubes or cul-de-sacs of women with copper IUDs in contrast to both the controls (11 positive) and women with inert IUDs (4 positive).[17]

In addition to the apparent effects on sperm motility and viability, data suggest that copper IUDs also have ovicidal effects or otherwise interfere with the normal reproductive functions of the ovum prior to fertilization. Studies of IUD users and control women have included flushing of excised fallopian tubes as well as of the uterus. In these studies, no ova have been recovered from the uterus in users of the Copper T-200, a precursor of ParaGard®. In addition, no ova displaying signs of fertilization have been recovered from fallopian tubes of women using the Copper T-200.[18] In a study by Alvarez and colleagues, women underwent laparotomy within 132 hours of the luteinizing hormone peak and presumed ovulation.[19] Ova were recovered from the flushings of fallopian tubes of 39% of copper T IUD users, compared to 56% recovered from control women using no contraception. None of the ova recovered from the women using the IUD showed morphological signs consistent with fertilization. Potential explanations for these findings include: (1) failure to release the oocyte from the follicle; (2) failure of oocyte pick-up by the fimbria; (3) slowing or speeding the transport of the ovum through the fallopian tubes; and (4) alterations in the biochemical and/or cellular composition of tubal fluid leading to the premature lysis of the ovum.[20]

In sum, the copper in ParaGard®, in addition to the products derived from the inflammatory reaction triggered by both the drug and device components of ParaGard®, appear

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[17] Aref et al. (Exhibit 6)

[18] Alvarez F, Brache V, Fenandez E, et al. New insights on the mode of action of intrauterine contraceptive devices in women. *Fertility & Sterility*. May 1988; 49; 768-773 (Exhibit 7); *see also* Ortiz & Croxatto (Exhibit 3)

[19] Alvarez F et al. (Exhibit 7).

[20] Additional evidence suggests that ParaGard® interrupts the fertilization process before implantation. In the most recent study examining hCG in the luteal phase of women using IUDs and controls, the sensitive assays for early pregnancy did not reveal "chemical pregnancies" in IUD users (Wilcox). Specifically, Wilcox and colleagues measured urinary hCG in 39 women using IUDs (34 copper-containing) and found only one cycle out of 107 total cycles with urinary hCG levels about 0.035 ng/ml for longer than one day. Wilcox AJ, Weinberg CR, Armstrong EG, Canfield RE. Urinary human chorionic gonadotropin among intrauterine device users: detection with a highly specific and sensitive assay. *Fertility & Sterility*. Feb 1987; 47: 265-268 (Exhibit 8). Similar findings were reported by Segal et al among 30 copper T-200 IUD users who revealed no positive hCG assays in luteal phase blood assays. Segal SJ, Alvarez-Sanchez F, Adejuwon CA, Brache de Mejia V, Leon P, Faundes A. Absence of chorionic gonadotropin in sera of women who use intrauterine devices. *Fertil Steril* 44:214, 1985 (Exhibit 9). Earlier studies using older, less specific assays, yielded more mixed results.

to be toxic to sperm and ova, thereby impacting the normal processes by which they travel and operate in the reproductive system and preventing fertilization through a variety of modes of action in the cervical mucus, endometrium and fallopian tubes. The precise mechanism or mechanisms by which ParaGard® accomplishes this effect, however, are still unclear.

3. ParaGard® Acts Locally

Although its precise mechanisms of action are not fully elucidated, it is clear that ParaGard® acts locally in and around the site of placement. Possible local sites of action within the uterus and its associated reproductive structures include the cervix, endometrium, fallopian tubes, ovaries and fimbria.

Studies have demonstrated that copper levels in reproductive tissues and fluids are elevated in copper IUD users. For example, studies have observed a significant increase in the copper concentration in endometrial biopsies of copper IUD users versus controls, with elevated copper levels persisting in some studies up to one year of continuous use.[21]

Likewise, studies have observed an increase in copper content of cervical mucus, menstrual fluids and fluids in the fallopian tubes. In some studies, copper concentrations in cervical mucus ranged from two to six times higher during the menstrual cycle as compared to normal human levels.[22] In one study, investigators found that the menstrual fluids (day two of the cycle) of women using a copper IUD (3 to 24 months of use) showed a two-fold increase in their copper content as compared to controls.[23] Moreover, the concentration of copper ions in tubal fluid has been shown to increase in the presence of copper IUDs to the same level as in uterine fluid.[24]

By contrast, the use of a copper IUD does not appear to result in an increased systemic exposure to copper. In one study, serum copper levels among different ParaGard® users (10 to 12 women per group) after one, two or three years of use were within normal limits and showed no trend with increased duration of use.[25] Studies of similar copper IUDs demonstrated that mean serum copper levels did not differ significantly from normal controls with up to 48 months

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[21] Hagenfeldt K. Intrauterine contraception with the copper-T device. Effect on trace elements in the endometrium, cervical mucus and plasma. *Contraception.* Jul 1972; 6:37-54 (Exhibit 10); Moo Young, A.J., Tatum, H.j., Wan, L.S. and Lane, M.: Copper levels in certain tissues of rhesus monkeys and of women bearing copper IUDs. In Analysis of Intrauterine Contraception, Hefnawi, F. and Segal, S.J. eds., North Holland Publishing Co., New York, 1975. p. 439 (Exhibit 11).

[22] Singh, E.J.: Effect of oral contraceptives and IUDs on the copper in human cervical mucous. Obstet. Gynecol. 45(3): 328, 1975 (Exhibit 12).

[23] Moo Young et al. (Exhibit 11).

[24] Ortiz & Croxatto, at S27 (Exhibit 3).

[25] Moo Young et al. (Exhibit 11).

of use.[26] Likewise, Moo Young et al. observed that the myometrial copper levels from copper IUD users (one to six months of use) did not differ significantly from controls.[27] This suggests that the copper from ParaGard® is not absorbed into deeper uterine tissues or systemic circulation. Instead, ParaGard® appears to achieve its primary therapeutic effects through local action within the uterus, fallopian tubes and related reproductive structures.

B. Comparative Clinical Testing Using Appropriate Safety and Efficacy Endpoints Is Necessary to Ensure That Proposed Generic Copper IUD Products Are Bioequivalent To, And As Safe and Effective As, ParaGard®

Before approving a generic version of ParaGard®, FDA must require ANDA applicants to demonstrate through appropriate testing that their proposed copper IUD products are bioequivalent to ParaGard®. A rigorous showing of bioequivalence is particularly important in this case because ParaGard® is intended for long-term intrauterine placement (up to 10 years) in healthy women of child-bearing age for intrauterine contraception, not for the treatment of any disease or abnormal health condition. The approval of proposed copper IUDs that purport to be interchangeable with ParaGard® thus raises "difficult benefit-risk considerations"[28] that can be addressed only through the rigorous application of FDA's existing bioequivalence requirements.

In this case, because ParaGard® acts locally through mechanisms of action that are not fully understood, and because it is intended to remain in the uterus for up to 10 years, the usual *in vivo* and *in vitro* methods for determining bioequivalence are not appropriate. Instead, as discussed further below, the only means to ensure that a proposed copper IUD that purports to be interchangeable with ParaGard® is, in fact, as safe and effective as ParaGard® is to require a long-term, comparative clinical trial with appropriate safety and efficacy endpoints to establish that the proposed product is bioequivalent to ParaGard®. Given the factors discussed below, such a study is the most accurate, sensitive, and reproducible approach to determine whether a proposed generic product is, in fact, bioequivalent to, and as safe and effective as, ParaGard® for long-term intrauterine placement in healthy women.

1. Statutory and Regulatory Requirements Applicable to the Demonstration of Bioequivalence

In order to obtain approval of an ANDA, an applicant must demonstrate, *inter alia*, that its proposed generic product is "bioequivalent" to a reference listed drug ("RLD"). 21 U.S.C. § 355(j)(2)(iv). The FD&C Act provides that a generic drug is bioequivalent to a RLD if:

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[26] Prema et al. of India (Fertil Steril 34:32, 1980) (Exhibit 13).

[27] Moo Young et al. (Exhibit 11).

[28] 40 Fed. Reg. 27796, 27798 (July 1, 1975)(noting that the use of IUDs raises "difficult benefit-risk considerations," in part, because "they are intended to be used for long periods of time by women who are healthy").

> The rate and extent of absorption of the drug do 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 . . .

Id. § 355(j)(8)(B)(i). The FD&C Act imposes bioequivalence requirements on all drugs, even those that are not systemically absorbed. 54 Fed. Reg. 28872, 28882 (July 10, 1989). For a drug that is not intended to be absorbed into the bloodstream, the statute provides that "[FDA] may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the [RLD] in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C).

FDA's regulation defining "bioequivalence" does not distinguish between drugs that are systemically absorbed and those that are not. According to FDA, "bioequivalence" is defined (in relevant part) as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." 21 C.F.R. § 320.1(e).

Bioequivalence can be demonstrated through a variety of *in vivo* and/or *in vitro* tests depending upon the purpose of the study, the analytical methods available, and the nature of the drug product. *Id.* § 320.24(a). FDA regulations describe the following acceptable test methods in descending order of accuracy, sensitivity, and reproducibility: (1) *in vivo* pharmacokinetic ("PK") testing in humans measuring absorption into the bloodstream or an *in vitro* test that has been correlated with and is predictive of human *in vivo* bioavailability; (2) *in vivo* testing in humans measuring urinary excretion; (3) *in vivo* pharmacodynamic ("PD") testing in humans; (4) comparative clinical trials with safety and effectiveness endpoints; (5) *in vitro* studies, and (6) any other approach deemed adequate by FDA. *Id.* § 320.24(b). ANDA applicants generally are required to use the "most accurate, sensitive, and reproducible approach available" among those specified in the regulations. *Id.*

As is clear from the above list, FDA's regulations provide that *in vivo* studies typically are the "preferred method" to demonstrate bioequivalence.[29] Nevertheless, the requirement for *in vivo* studies may be waived in certain circumstances. For example, FDA considers bioequivalence to be "self-evident" – and thus will waive *in vivo* bioequivalence testing – for a "parenteral solution" intended solely for injection if the proposed generic drug product contains the same active and inactive ingredients in the same concentrations as the RLD. 21 C.F.R. § 320.22(b)(1). FDA also can waive *in vivo* bioequivalence testing "for good cause" if such a waiver is "compatible with the protection of the public health." *Id.* § 320.22(e).

[29] Letter to William A. Rakoczy, FDA-2007-P-0418, at 4 (May 7, 2008) (Exhibit 14).

On the other hand, FDA may require *in vivo* bioequivalence testing for any product, even one otherwise eligible for a waiver, if "the agency determines that any difference between the drug product and [the RLD] may affect the bioavailability or bioequivalence of the drug product." *Id.* § 320.22(f). Likewise, FDA may require *in vivo* bioequivalence testing at any time if the agency has evidence that a proposed generic product: (1) may not produce comparable therapeutic effects to the RLD; (2) may not be bioequivalent to the RLD; or (3) has greater than anticipated potential toxicity related to PK or other characteristics. *Id.* § 320.24(c).

2. FDA Should Require *In Vivo* Bioequivalence Testing for Proposed Generic Copper IUD Products

In this case, FDA should require *in vivo* bioequivalence testing for generic copper IUD drug products because (1) such products are not eligible for a waiver under 21 C.F.R. § 320.22; and (2) differences between ParaGard® and a proposed generic drug could significantly affect the bioequivalence of the proposed generic, thereby negatively impacting safety, efficacy or both. Indeed, since passage of the Hatch-Waxman Act, Teva is not aware of any situation in which FDA has granted a biowaiver for an implantable drug product, particularly a locally acting drug product like ParaGard®. Accordingly, *in vivo* testing is necessary to assess whether proposed generic copper IUDs perform equivalently to ParaGard® during long-term placement and use in healthy women.

Generic copper IUD products are not eligible for a waiver of *in vivo* bioequivalence testing pursuant to 21 C.F.R. § 320.22 because they do not fall within any of the categories eligible for mandatory waiver. In particular, copper IUDs are not parenteral, ophthalmic or otic solutions, inhalation gases, oral or nasal solutions, or solutions for aerosolization or nebulization. 21 C.F.R. § 320.22(b). Nor are they solid oral dosage forms or reformulated products that are similar to products marketed by the same manufacturer. *Id.* § 320.22(c), (d)(2), (d)(4). Moreover, to Teva's knowledge, there is no *in vitro* test that has been correlated with *in vivo* data for copper IUDs. *Id.* § 320.22(d)(3). Accordingly, there is no basis under FDA's regulations to grant a mandatory waiver of *in vivo* bioequivalence testing for proposed generic versions of ParaGard.

It also would be inappropriate for FDA to grant a waiver under its regulatory authority to grant discretionary waivers "for good cause" because such a waiver would not be "compatible with the protection of the public health." *Id.* § 320.22(e). As mentioned above, ParaGard® is intended for long-term placement up to 10 years in healthy women of child-bearing age for intrauterine contraception, not for the treatment of any disease or abnormal health condition. Moreover, ParaGard® acts locally through mechanisms of action that are not fully elucidated, and the precise contribution of its device component to safety and effectiveness is not known. Consequently, the effects of minor design, structural or compositional changes, particularly the long-term effects of such changes on, *inter alia*, drug exposure, local irritation, expulsion rates and bleeding risk, cannot be adequately assessed in the absence of *in vivo* testing. Given the "difficult benefit-risk considerations" posed by copper IUDs such as ParaGard®, the risks associated with approving a purported generic product in the absence of *in vivo* bioequivalence

data are not "compatible with the protection of the public health." On the contrary, FDA should require *in vivo* testing because even minor differences between ParaGard® and a proposed generic could significantly affect bioequivalence, particularly given ParaGard®'s extended life span.

In similar situations involving implantable drug products, FDA has refused to waive *in vivo* bioequivalence testing. For example, FDA has indicated that ANDA applicants seeking approval of a generic version of Viadur (leuprolide acetate implant) are required to conduct a single-dose, parallel, cross-over bioequivalence study in prostatic carcinoma patients.[30] Likewise, for ANDAs for generic versions of Testopel Pellets (testosterone), an implantable drug product, FDA is requiring, among other things, a single dose, two-arm, parallel, *in vivo* bioequivalence study in healthy, hypogonadal male patients.[31] Indeed, Teva is not aware of any modern example in which FDA has approved an implantable drug product in the absence of data from one or more *in vivo* bioequivalence studies.[32]

In addition, FDA routinely requires *in vivo* bioequivalence testing for vaginal drug products, including vaginal inserts. For example, FDA is requiring *in vivo* bioequivalence studies with clinical endpoints for ANDAs seeking approval of generic versions of Cervidil (dinoprostone), a vaginal insert indicated for the initiation and/or continuation of cervical ripening in patients at or near term.[33]

ParaGard®, of course, not only is similar to implants like Viadur and Testopel Pellets and vaginal inserts like Cervidil but also acts locally through mechanisms of action that are not completely understood. This is an important, distinguishing characteristic that further underscores the need for *in vivo* bioequivalence testing in this case. In a similar situation involving a locally acting drug product, FDA refused to waive *in vivo* bioequivalence testing for an ANDA applicant seeking approval of a generic sucralfate product that used an active ingredient produced by a new supplier. FDA explained that a waiver was inappropriate because "sucralfate does not exert its therapeutic action by systemic absorption, and we do not know which chemical and physical features of sucralfate are essential to provide ulcer healing."[34] ParaGard® likewise does not rely upon systemic absorption to achieve its clinical effect, and, as noted above, the chemical and physical features essential to its safety and effectiveness may be

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[30] Draft Guidance on Leuprolide Acetate (May 2010) (Exhibit 15).

[31] Draft Guidance on Testosterone (Aug. 2011) (Exhibit 16).

[32] It appears that the ANDA for Testopel pellets was approved without *in vivo* bioequivalence data. However, the ANDA was approved in 1972 as part of the Drug Efficacy Study Implementation program and is not relevant to ANDAs approved under the Hatch-Waxman Act.

[33] Draft Guidance on Dinoprostone (Nov. 2011) (Exhibit 17).

[34] *See* ANDA No. 70-848, Request for Conducting an In-Vivo Bioavailability Study for Biocraft's Sucralfate (Sept. 18, 1989) (Exhibit 18).

even more complex and poorly understood than with sucralfate. A waiver of *in vivo* bioequivalence testing, therefore, is similarly inappropriate.

Consequently, FDA should refrain from approving any ANDA for a generic copper IUD product unless it contains acceptable results from *in vivo* bioequivalence studies.

3. Neither PK Nor PD Studies Are Capable of Establishing the Bioequivalence of Proposed Copper IUD Products and ParaGard®

In this case, because of the unique characteristics of ParaGard®, bioequivalence cannot be established through either PK or PD testing. PK testing is not appropriate because ParaGard® is primarily a locally acting drug product, and the active ingredient, copper, does not appear to be absorbed into the systemic circulation and thus cannot be measured in whole blood, plasma, serum or urine. Moreover, although there are some PD changes associated with ParaGard® treatment, none have been validated to correlate with the availability of the active moiety at the site or sites of drug action. Accordingly, neither PK nor PD testing is an acceptable method to establish bioequivalence under the FD&C Act or FDA regulations because neither would be expected "to detect a significant difference between the [proposed generic] drug and the listed drug in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C).

a. PK Studies Cannot Demonstrate Bioequivalence

For drug products whose primary mechanism of action depends on systemic absorption, the determination of bioequivalence generally rests on PK studies; *i.e.*, "a comparison of drug and/or metabolite concentrations in an accessible biological fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers."[35] PK studies, however, often are inadequate to demonstrate bioequivalence for drug products that act locally, like ParaGard®. This is because such drugs may not produce measurable concentrations of the active ingredient, active moiety, or metabolites in an accessible biological fluid, and even when measurable concentrations are produced, there is a lack of evidence of "any correlation between these systemic concentrations and concentrations at the site of drug action."[36]

Although ParaGard®'s primary mechanism of action is not fully understood, it nevertheless is clear that ParaGard® acts locally rather than through systemic absorption. Indeed, as discussed in section II.A.3 above, the copper in ParaGard® does not appear to be absorbed into systemic circulation in any measurable quantities. Accordingly, traditional PK studies cannot demonstrate bioequivalence to ParaGard®.

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[35] *See* Letter to Izumi Hara and Jeffrey Jonas, M.D., FDA-2010-P-0111, at 5 (Aug. 20, 2010) (Exhibit 19); *see also* 21 C.F.R. §§ 320.24(b)(1), (2).

[36] *See* Letter to Izumi Hara and Jeffrey Jonas, M.D., FDA-2010-P-0111, at 5 (Exhibit 19).

Although copper concentrations have been shown to be elevated in other biological fluids, such as uterine and tubal fluids, these are not appropriate biological fluids for purposes bioequivalence testing. First, because the mechanism or mechanisms of action of ParaGard® are not fully known, no correlation between concentrations in these biological fluids and concentrations at the sites of drug action has been established. For example, copper concentrations in the cervical mucus, endometrium or even the ovaries may be more important than, and not completely correlated with, concentrations in uterine and tubal fluids.

Second, because even non-drug IUDs have contraceptive effects, ParaGard®'s efficacy may be due in large part to the local inflammatory reaction triggered by its device component.[37] Although copper is believed to enhance this local inflammatory reaction, it is not clear how copper does so and/or how copper interacts with a user's immune system to stimulate the infiltration of intrauterine leukocytes. Copper concentrations in uterine and tubal fluids thus may be poorly correlated with the clinical effect of a proposed generic product or its comparative safety and efficacy versus ParaGard.

Third, Teva does not believe that feasible test methods could be developed for measuring copper concentrations in uterine or tubal fluids for purposes of bioequivalence testing. While testing of tubal fluids is theoretically possible, it likely would require medical procedures, such as hysteroscopy, laparoscopy and/or anesthesia, that would involve an unacceptable level of risk for purposes of bioequivalence testing. Moreover, studies using uterine or tubal fluids likely would involve high intra- and inter-subject variability that would make the results difficult, if not impossible, to validate.

In sum, PK studies are incapable of demonstrating bioequivalence because: (a) ParaGard® is primarily a locally acting drug product, (b) the active ingredient, copper, does not appear to be absorbed into systemic circulation and thus cannot be measured in whole blood, plasma, serum or urine, and (c) even though copper concentrations can be measured in some biological fluids (*e.g.*, uterine fluid), testing may be unethical, and no correlation has been established between copper concentrations in these fluids and concentrations at the site or sites of drug action. Accordingly, PK studies are not appropriate for demonstrating bioequivalence because they would not be expected "to detect a significant difference between the [proposed generic] drug and the listed drug in safety and therapeutic effect." 21 U.S.C. § 355(j)(8)(C).

b. PD Studies Cannot Demonstrate Bioequivalence

Likewise, PD testing is not an appropriate method for demonstrating bioequivalence between ParaGard® and proposed generic copper IUD drug products. When PK testing is not informative, alternative measures may be sought to demonstrate bioequivalence. One such alternative is PD testing; *i.e.*, measuring an appropriate acute pharmacological effect of the active moiety or, when appropriate, active metabolites, as a function of time. 21 C.F.R. § 320.24(b)(3). FDA considers this approach to be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution. *Id.* Under the statute

[37] *See* WHO Scientific Group Report, at 13 (1987) (Exhibit 2).

and FDA regulations, however, the choice of study design to demonstrate bioequivalence must be based upon the ability of the study "to compare the drug delivered by the two products at the particular site of action of the drug."[38]

In this case, PD testing is of limited utility in demonstrating bioequivalence because, although there are some known PD effects associated with ParaGard®, none have been validated to correlate with the availability of the active moiety at the site or sites of drug action. For example, copper IUDs have been shown not only to elevate the copper concentration of cervical mucus, but also to change its rheological properties and enzymatic activity. Copper also alters the metabolism of endometrial cells. These PD parameters, however, have not been validated to serve as markers of bioavailability of ParaGard®, or as markers of bioequivalence between ParaGard® and other proposed generic copper IUD products. Indeed, it is not even clear whether these qualitative PD changes could be quantified or compared for purposes of bioequivalence testing, particularly since it is not clear whether the device component of ParaGard® contributes to these PD changes and, if so, to what degree.

Moreover, because the mechanisms of action of ParaGard® are not fully understood, the possibility cannot be excluded that PD testing measuring the above-described parameters will fail to capture critical information about the availability of copper at other important sites of action. In other words, given the complexity of the reproductive system and the lack of information regarding ParaGard®'s mechanisms or sites of action within that milieu, PD testing is not an accurate or sensitive method for measuring the availability of copper at the site or sites of drug action, many of which may be unknown. Because PD testing would not be expected "to detect a significant difference between the [proposed generic] drug and the listed drug in safety and therapeutic effect," 21 U.S.C. § 355(j)(8)(C), it, too, is not an appropriate method for demonstrating bioequivalence between ParaGard® and proposed generic copper IUD drug products.

c. Neither PK Nor PD Studies Can Assess Differences Attributable to Device Components

Finally, neither PK nor PD testing would be expected to detect a difference in the safety or effectiveness of a proposed generic copper IUD that is attributable to a difference in the materials, design, operating principles, performance or manufacturing of its device component. Because the mechanism or mechanisms by which copper IUDs prevent pregnancy is not fully elucidated, and because the relative contributions of the device and drug components are not known, it is not possible to predict whether even small differences in the device component of a copper IUD will have a significant impact on safety or effectiveness. Indeed, studies have shown meaningful differences in effectiveness rates and safety parameters between IUDs with different design characteristics.[39]

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[38] Letter to William A. Rakoczy, FDA-2007-P-0418, p. 4 (Exhibit 14).

[39] Grimes et al. (Exhibit 5).

For example, in one trial, the TCu-220 C, a T-shaped, copper IUD, proved to have significantly lower failure rates than the TCu-200, another T-shaped, copper IUD, even though the difference in copper content was only 20 mg.[40] While this significant difference in efficacy may have been due in part to the different copper levels, it also likely was attributable, at least in part, to differing designs with respect to the placement of copper on each device.[41] Differences in design and/or device components between ParaGard® and a proposed generic copper IUD likewise could result in different safety and effectiveness profiles, including different rates of contraceptive efficacy, ectopic pregnancy, bleeding, infection or expulsion. Because neither PK nor PD testing would be expected to detect these types of design or device-related differences, neither is an appropriate method for demonstrating bioequivalence in this case.

4. A Comparative Clinical Trial Using Appropriate Safety and Effectiveness Endpoints Is the Most Sensitive, Accurate, and Reproducible Method for Demonstrating the Bioequivalence of Proposed Generic Copper IUD Products to ParaGard®

Although comparative clinical studies generally are not considered to be as sensitive, accurate, and reproducible in determining bioequivalence as PK or PD studies, FDA long has recognized that well-controlled clinical studies are acceptable when, as here, PK and PD approaches are "infeasible."[42] Indeed, FDA regulations provide that comparative trials with appropriate clinical endpoints may be considered "sufficiently accurate for . . . demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally." 21 C.F.R. § 320.24(b)(4). Further, FDA officials have stated that "most" locally acting drugs "require clinical endpoint studies" to demonstrate bioequivalence.[43]

Because ParaGard® is intended to act locally in the female reproductive system following placement in the uterus, comparative clinical trials are an acceptable method for demonstrating bioequivalence. In fact, comparative clinical trials are the *only* acceptable method for demonstrating bioequivalence because of (1) the complexity of the reproductive system; (2) the uncertainty regarding ParaGard®'s mechanisms and sites of action; and (3) the uncertainty

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[40] WHO Scientific Group Report, at 21 (Exhibit 2).

[41] For example, the TCu-200 incorporates copper only on the vertical stem, whereas the TCu-220 C has copper on both the vertical stem and the horizontal arms.

[42] Letter to Izumi Hara and Jeffrey Jonas, M.D., FDA-2010-P-0111, at 6 (Exhibit 19); *see also Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (hereinafter *BA/BE Guidance*), at 9-10 (March 2003).

[43] *See Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs*, Dena Hixon, M.D., Assoc. Dir. Medical Affairs, FDA Office of Generic Drugs, presented at the Pharmaceutical Science Advisory Committee (March 12, 2003) (Exhibit 20), *available at* http://www.fda.gov/ohrms/dockets/ac/03/slides/3926S1_18_Hixon.ppt.

regarding the relative contributions to safety and efficacy made by ParaGard®'s drug and device components.

In the highly analogous situation of locally acting vaginal drug products, FDA routinely requires *in vivo* bioequivalence studies with clinical endpoints. For example, for proposed generic versions of Cervidil (dinoprostone), a vaginal insert indicated for the initiation and/or continuation of cervical ripening in patients at or near term, FDA recommends that ANDA applicants conduct a randomized, double-blind, parallel, placebo-controlled clinical trial in appropriate pregnant female patients comparing the proposed generic product against both the RLD and placebo with respect to both "treatment success," the recommended primary endpoint, and safety, including vaginal irritation.[44] Likewise, FDA requires bioequivalence studies with appropriate clinical endpoints for ANDAs seeking approval of estradiol vaginal tablets; estradiol 0.01% vaginal cream; terconazole vaginal suppositories; tioconazole vaginal ointment; miconazole nitrate vaginal suppositories; butoconazole nitrate vaginal cream; clotrimazole vaginal cream; and clindamycin phosphate vaginal cream.[45]

The FDA's consistent requirement that ANDAs for locally acting vaginal drug products be supported by bioequivalence studies with clinical endpoints reflects the complex nature of the interactions between these types of drug products and the vagina. As FDA has recognized, the safety and efficacy of these products depends upon, *inter alia*, the anatomy of the organ, surface properties of the epithelium, mechanical properties of the tissues, and the presence of different fluids.[46] Because these types of issues are just as relevant, if not more so, for drug products, like ParaGard®, that are intended to be placed into the uterus to affect the complex, human reproductive system over a multi-year time frame, FDA likewise should require *in vivo* bioequivalence studies with clinical endpoints.

The fact that ParaGard®'s mechanisms of action are not well understood further supports the need for clinical endpoint studies. In a situation with similarities to ParaGard®, FDA required ANDA applicants seeking approval of generic sucralfate products to conduct a "clinical safety and efficacy trial" to demonstrate bioequivalence to Carafate®, the RLD. Sucralfate, like ParaGard®, is a locally-acting drug product with a variety of mechanisms of action that are not well-understood. Given this complexity, generic applicants were not able to correlate the chemical properties of their proposed drugs with all of the postulated modes of action of the

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[44] Draft Guidance on Dinoprostone (Nov. 2011) (Exhibit 17). Under the draft guidance, "treatment success" is defined as attainment of an increase of at least 3 in a Bishop score during the 12-hour observation period, the attainment of a Bishop score of ≥6 during the 12-hour observation period, or vaginal delivery occurring during the 12-hour observation period.

[45] The bioequivalence guidances for the products identified are available on FDA's website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[46] Methods for Assessing Bioequivalence of Topical Products: How Should FDA Redirect its Research Program?, presentation by Ajaz Hussain, Ph.D., Acting Director, FDA Office of Testing and Research, OPS, CDER (Nov. 17, 2000) (Exhibit 21).

RLD. The Agency explained that, "[g]iven the number and complexity of [the RLD's] postulated modes of action and in the absence of data that demonstrates equivalence of formulations in producing each of these effects," a comparative clinical trial with safety and effectiveness endpoints would be required to demonstrate bioequivalence.[47]

Moreover, the integral role played by the device component of ParaGard® to the product's overall safety and efficacy necessitates a bioequivalence study with clinical endpoints. Non-drug IUDs are regulated as Class III medical devices subject to premarket approval application ("PMA") requirements,[48] and FDA historically has required new non-drug IUDs to undergo rigorous Phase II and Phase III clinical trials in several hundred patients prior to approval.[49] The Agency should not relax these scientific standards simply because an IUD incorporates copper as an active ingredient. Rather, the Agency should ensure that, at a minimum, the safety and effectiveness of the device component of a proposed generic copper IUD product is assessed in rigorous bioequivalence studies with appropriate clinical endpoints.

Finally, as noted above, ParaGard® is intended for long-term intrauterine placement up to 10 years in healthy women. Given that an ineffective or unsafe product can lead to significant public health consequences, including unwanted pregnancies and infections and their attendant risks, the manufacture, chemical composition, and clinical activity of intrauterine contraceptives warrant rigorous scrutiny that can be provided only by clinical testing. Consequently, the FDA should require well-controlled comparative trials with clinical endpoints, as it does with vaginal drug products, sucralfate, and non-drug IUDs, to satisfy the bioequivalence requirement under the FD&C Act and ensure that proposed generic copper IUD products are as safe and effective as ParaGard®. Given the factors discussed above, a comparative *in vivo* study with clinical endpoints is the most sensitive, accurate, and reproducible method for demonstrating the bioequivalence of proposed generic copper IUD products to ParaGard®.

5. A Bioequivalence Study Should Be Conducted in the Relevant Patient Population, Use Appropriate Clinical Endpoints, and Be of Sufficient Duration to Support a Ten-Year Indication for Contraception

The comparative clinical studies required by FDA to demonstrate bioequivalence should utilize appropriate safety and effectiveness endpoints based upon the endpoints used in the clinical studies supporting approval of ParaGard® and other modern IUDs (e.g., Mirena). Specifically, FDA should require ANDA applicants to conduct clinical studies in patients that are adequately powered to demonstrate comparable safety and efficacy between the proposed

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[47] *See* ANDA No. 70-848, Response to Consultation re Biocraft Submission of April 27, 1988 (May 2, 1988) (Exhibit 22), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/96/070848.PDF.

[48] 21 C.F.R. § 884.5360.

[49] *See* Guidelines for Evaluation of Non-Drug IUDs (Sept. 26, 1976) (Exhibit 23), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm083716.pdf.

generic product and ParaGard®. This likely will require well-controlled clinical studies comparable in size and duration to those for a new molecular entity seeking a ten-year efficacy claim. FDA officials previously have explained that the trial design and efficacy and safety endpoints of a "clinical endpoint" bioequivalence study are similar to those required for an NDA.[50]

Sponsors typically are required to conduct a 3-arm comparative trial comparing the proposed generic product versus the RLD versus placebo. The endpoints should be similar to those required for an NDA and should include outcomes of drug effects on the approved indication in a comparable patient population according to the labeled dosing of the RLD. Moreover, both the generic and RLD typically must be statistically superior to placebo ($p<0.05$) in order to assure that the study is sensitive enough to show a difference between products, and the endpoints must meet established bioequivalence limits (*e.g.*, a difference of ±20% in a 90% confidence interval).

For copper IUDs, ANDA applicants should be required to conduct one or more well-controlled clinical investigations of their proposed generic products in parous and nulliparous women seeking intrauterine contraception. Although use of a placebo arm may be challenging in this case, FDA nevertheless should consider the feasibility of a placebo arm (*e.g.*, women not using any birth control) to ensure sensitivity or, at the very least, a control arm using an inert IUD.[51] If FDA determines that a placebo (or inert IUD) arm is not feasible or appropriate in this case, the clinical study should incorporate other design features that ensure the study is sensitive enough to show a difference between products if they exist.

The clinical trial or trials should be designed so that one of the clinical endpoints is the pregnancy rate at various time points throughout the total period of intended use (*e.g.*, measured annually though year 10 – the approved indication for ParaGard®). Other clinical endpoints, including safety endpoints, should include, among other things, expulsion rates, overall discontinuation rates, discontinuation rates due to bleeding and pain, rates of ectopic pregnancy, perforation rates, embedment, infection rates, difficult removals, and an assessment of any mechanical failures (*i.e.*, by examining removed devices). Endpoints should be chosen to assess whether the generic product is performing in a similar manner through all potential modes of action. For example, if the rate of ectopic pregnancy is higher for a proposed generic product than for ParaGard®, this may indicate that, because of design or performance differences, the generic product is not as effective at disrupting the fertilization process in the ovaries, fimbria or fallopian tubes as ParaGard®. This could indicate a lack of bioequivalence, and a major safety concern, even if the products have similar overall or non-ectopic pregnancy rates.

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[50] *See Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs*, Dena Hixon, M.D. (Exhibit 20).

[51] If FDA requires an arm using an inert IUD, the design of the inert IUD should be identical to that of the device portions of both ParaGard® and the proposed generic copper IUD product, since design features can significantly affect the safety and effectiveness of an inert IUD. *See* section II.B.3.c above.

Moreover, any bioequivalence trial should be of sufficient duration to support the approved indication of contraceptive efficacy through ten years. This is necessary to ensure that drug exposure remains comparable throughout the labeled implantation period. Studies have demonstrated that the rate of daily copper loss from ParaGard® is not constant throughout its intended ten year use period but rather decreases gradually over time, averaging 50 micrograms over the first year of use and decreasing to about 27 micrograms per day over a five-year period.[52] If a purported generic product were to release copper *in utero* at a different or lower rate over time than ParaGard®, this could compromise the safety or effectiveness of the proposed generic product, particularly in later years if, because of design or performance differences, more copper is lost from the proposed generic products as a result of fragmentation.

In an analogous situation, FDA required the sponsor of IMPLANON (etonogestrel implant), a contraceptive implant, to conduct a three year bioequivalence trial to support approval of NEXPLANON (etonogestrel implant), its next generation implant containing barium sulfate as a radiopaque component.[53] Although the two formulations were highly similar and were manufactured by the same company, a three year study duration was required because (a) both products are labeled for use up to three-years; and (b) pharmacokinetic studies demonstrated that the mean serum concentrations of etonogestrel following IMPLANON implantation gradually decreased over the three-year implantation period. Although NEXPLANON was not approved or intended to be a generic substitute for IMPLANON, the duration of the required bioequivalence study nevertheless is relevant to the bioequivalence study requirements for proposed generic versions of ParaGard®.

In this case, because ParaGard® is approved for intrauterine contraception for up to ten years, the duration of any bioequivalence trial should be sufficient to support a ten year indication. Moreover, given the unique risks associated with a long-term IUD intended for intrauterine contraception in healthy women, including the risks of contraceptive failure in later years, these studies must be completed and demonstrate equivalent performance *before* ANDA approval.

C. FDA Should Not Approve a Proposed Generic Copper IUD Product Unless It Has Identical Labeling to ParaGard®, Including Instructions for Use and a 10-Year Effective Lifespan

Under the FD&C Act, FDA generally cannot approve an ANDA for a generic drug unless it has the same labeling as the RLD.[54] This requirement helps to ensure that an approved generic drug product is as safe and effective as the RLD. Although there are some exceptions to this general rule, they are narrow. In particular, a generic drug can have different labeling from the

[52] Data on file.

[53] *See* Package Insert for Nexplanon, § 12.3 (Exhibit 24).

[54] 21 U.S.C. §355(j)(4)(G); 21 C.F.R. §314.127(a)(7)

RLD if: (a) the ANDA is submitted pursuant to a suitability petition; (b) labeling is omitted because it is protected by exclusivity or a listed patent; or (c) minor labeling changes reflect permissible differences between the ANDA and its RLD (*e.g.*, different inactive ingredients, container-closure systems, shape or color).[55] Labeling changes that introduce new or increased risks or that otherwise render the proposed generic less safe or effective than the RLD, however, are not permitted and will result in refusal to approve the ANDA.[56]

In this case, FDA should require proposed generic copper IUD products to have the same labeling as ParaGard®, particularly with respect to instructions for use and the 10-year effective life span. According to ParaGard®'s FDA-approved labeling:

> The placement technique for ParaGard® is different from that used for other IUDs. Therefore, the clinician should be familiar with the following instructions.[57]

A clinician seeking to implant a purported generic version of ParaGard®, however, may be unfamiliar with the new device and encounter difficulties inserting it in a safe and effective manner if the instructions for use are different than those for ParaGard®. If such healthcare professionals are not re-trained before using a generic copper IUD with different instructions for use, they reasonably (albeit incorrectly) may assume that the generic product should be implanted in exactly the same manner as ParaGard®. Indeed, FDA itself has recognized that "[u]sers will expect devices and device components to operate in ways that are consistent with their experience with other similar devices or device interface components."[58]

A physician's failure to properly implant a generic IUD could compromise the effectiveness of the product and/or render the proposed generic product less safe than ParaGard®. For example, improper placement could increase the risks of, *inter alia*, uterine perforation, IUD expulsion, pelvic infection, or even contraceptive failure. Physicians with extensive experience with ParaGard® may be particularly susceptible to these risks. Because different instructions for use invariably will raise safety and effectiveness concerns, FDA should refuse to approve an

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[55] 21 U.S.C. §§355(j)(2)(A)(v), (j)(2)(A)(viii), (j)(4)(G); 21 C.F.R. §§314.94(a)(8)(iv), 314.127(a)(7); *see also* FDA Response to Xyzal Petition, Docket No. FDA-2010-P-0545, pp. 7-8 (Feb. 24, 2011).

[56] 21 C.F.R. §314.127(a)(7); *see also* FDA Response to King Petition, Docket Nos. FDA-2009-P-0040 and FDA-2007-P-0128, at 7 (July 29, 2009) (Exhibit 25) (hereinafter referred to as "King Petition Response").

[57] ParaGard Prescribing Information (Exhibit 1).

[58] *FDA Guidance on Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, at 13 (July 18, 2000) ; *see also FDA Draft Guidance on Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, at 14 (June 22, 2011) ("[u]sers will expect devices and device components to operate in ways that are consistent with their experience with other similar devices or user interface elements.").

ANDA for a generic copper IUD product unless its labeled instructions for use are identical to those of ParaGard®.[59]

Likewise, FDA must refrain from approving an ANDA unless it is labeled for use up to ten (10) years. According to its FDA-approved labeling, ParaGard® is indicated "for intrauterine contraception *for up to 10 years*,"[60] and there is no basis for an ANDA applicant to carve out or change this time frame. The omission of labeling information is permissible only if exclusivity or a listed patent protects it.[61] In this case, the 10-year language is not protected by any exclusivity period or by a listed patent. In addition, simply omitting this language would either falsely suggest that the generic product is safe and effective indefinitely and never needs to be removed or replaced or that the generic product is safe and effective for the same 10 year period as ParaGard®. Likewise, a generic product indicated for intrauterine contraception for less than ten years could not be approved because it would be less safe and effective than ParaGard®.[62] Accordingly, there is no legal basis for FDA to permit ANDA applicants to "carve out" or modify labeling indicating that the product is effective up to ten years. A ten-year labeling claim, of course, must be supported by appropriate clinical testing of sufficient duration to support the ten-year indication, as discussed in section II.B.5 above.

D. FDA Should Not Approve a Proposed Generic Copper IUD Product Unless Its Device Component Is Identical to ParaGard®'s

Finally, the device component of a proposed generic copper IUD product must not be merely the "same" as ParaGard®'s device component; it must be identical. Although this standard is more stringent than the one FDA has adopted for drug products that incorporate an autoinjector, it is justified here because of the unique characteristics of the device component in a copper IUD. In this case, the device component (a) is intended to be implanted in the patient for up to ten years; and (b) appears to make a direct and substantial contribution to the safety and

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[59] Although FDA may be able to approve a 505(b)(2) application for a product that has different instructions for use, this would require, among other things, clinical studies to establish safety and effectiveness and a communication plan under 21 U.S.C. § 355-1(e)(3) to educate physicians on the different instructions for use.

[60] ParaGard Prescribing Information (emphasis added) (Exhibit 1).

[61] 21 U.S.C. §§355(j)(2)(A)(v), (j)(2)(A)(viii), (j)(4)(G); 21 C.F.R. §§314.94(a)(8)(iv), 314.127(a)(7).

[62] FDA also should refuse to approve a 505(b)(2) application for a copper IUD that relies upon ParaGard® as the listed drug if the proposed effective life span of the new product is less than ten years. First, if the proposed product is a duplicate of ParaGard®, it should be submitted as an ANDA rather than a 505(b)(2) application and have the same labeling as ParaGard®, including a ten-year effective life span. *See* 21 C.F.R. § 314.101(d)(9). Second, a product with a shorter life span would be less effective (and possibly less safe) than ParaGard®, and FDA should not use section 505(b)(2) to approve a drug product that is less safe or less effective than the listed drug. *See Draft Guidance on Applications Covered by Section 505(b)(2)*, at 6 (Oct. 1999) (noting that "a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards of bioequivalence.").

effectiveness of the product as a whole. In other words, the device component of a copper IUD doesn't just *deliver* the intended treatment; it *is* part of the intended treatment.

Although ParaGard® is regulated as a drug product, it is analogous to a "combination product" because of its durable, non-copper components. When reviewing an ANDA that seeks approval of a combination product, FDA's policy is to evaluate both the drug and device components to ensure that the proposed generic product is the "same" as the RLD. For example, in the context of drugs that incorporate an autoinjector, FDA has explained that the Agency "must evaluate the auto-injector constituent part of the combination product for which ANDA approval is sought to ensure that its performance characteristics and critical design attributes will result in a product that will perform *the same as* the RLD."[63] Although FDA does not require all design features of the device constituent to be exactly the same as the RLD, design differences will be permitted only if "they do not significantly alter product performance or operating principles and do not result in impermissible differences in labeling."[64] In sum, FDA's review process for ANDAs for combination products "considers whether any difference in materials, design, or operating principles introduces a new risk. . . . This review considers the RLD as a whole and its individual constituent parts."[65]

In this case, FDA should refuse to approve a proposed generic copper IUD product unless its device component is *identical* to ParaGard®'s in terms of materials, design, operating principles, and performance characteristics. In other words, FDA should require ANDA applicants to use exactly the same materials, design features, and operating principles as ParaGard® and ensure that the proposed generic product meets the same performance standards. Although this requirement is more stringent than FDA's announced policy with respect to autoinjectors, heightened vigilance is justified in this case because of the special safety and efficacy concerns associated with copper IUDs.

As mentioned above, the device component of a copper IUD, unlike an autoinjector, is intended for intrauterine placement for up to 10 years in healthy women. Its materials, design features and performance characteristics thus could have a much more pronounced effect on safety and effectiveness than an autoinjector, which simply delivers the medication and does not contact the body for more than a brief period of time.

Moreover, the device component appears to make a direct and significant contribution to the efficacy of the product, albeit through mechanisms of action which are not fully understood. This last point is particularly important. Because the mechanism or mechanisms by which copper IUDs prevent pregnancy is not fully elucidated, and because the relative contributions of

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[63] King Petition Response, p. 6 (emphasis added) (Exhibit 25).

[64] *Id.*

[65] *Id.*

the device and drug components are not known, it is not possible to predict whether even small design differences in the device component of a copper IUD will have a significant impact on safety or effectiveness, particularly over the course of the entire 10-year time period for which ParaGard® is indicated.

Studies have shown meaningful differences in effectiveness rates and safety parameters between IUDs with different design characteristics. For example, in a double blind study comparing ParaGard® and the TCu-200, ParaGard® "showed a statistically significant increase in effectiveness in comparison with the TCu 200, but the TCu-200 had significantly lower termination rates attributable to bleeding and pain."[66] Although differences in copper content may have contributed to the differing safety and effectiveness profiles seen in this study, design differences also likely played a significant part. Indeed, unlike ParaGard®, the TCu-200 does not have copper sleeves on either of its two transverse arms.

Consequently, FDA should determine that *any* difference in materials, design, operating principles, or performance characteristics between a proposed generic copper IUD and ParaGard® introduces a potential new risk that cannot be assessed without clinical trials. Even for combination products like autoinjectors, FDA has agreed that changes to the device component of a proposed generic product "may require further clinical data because potential clinical consequences might be unknown."[67] In this case, because of the complexity of the human reproductive system and the lack of a specific mechanism of action of ParaGard®, the potential clinical consequences of *any* change to the device component of a copper IUD remain unknown. Potential risks from such modifications include, among other things, higher failure rates, higher expulsion rates, higher discontinuation rates, and an increased risk of bleeding, pain, perforation and pelvic infection.

Accordingly, FDA should refuse to approve a proposed generic copper IUD product unless its device component is identical to ParaGard®'s in terms of materials, design, operating principles, and performance characteristics. If the device component is not identical to ParaGard® in these respects, FDA should require adequate and well-controlled clinical studies demonstrating that the modified product is safe and effectiveness. The duration of these studies should extend throughout the total period of the intended use of the device but in no event should it be less than ten years.[68] Moreover, because these types of safety and effectiveness studies are not permitted in an ANDA submission,[69] FDA should advise applicants seeking approval of

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[66] *See* Paragard Summary Basis of Approval, at 5, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/018680_original_approval.pdf .

[67] King Petition Response, p. 8.

[68] *See supra* note 62.

[69] 21 U.S.C. § 355(j)(2)(A) ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).").

modified devices that they must proceed via the full NDA or 505(b)(2) pathways rather than the ANDA pathway.

E. Conclusion

For the foregoing reasons, no ANDA application that references ParaGard® as the reference listed drug should be approved unless and until the conditions set forth above have been satisfied.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31(a).

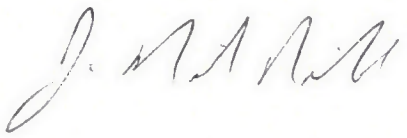
IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.[70]

Respectfully submitted,



J. Michael Nicholas, Ph.D.,
Sr. Director

cc: Gregory Geba, M.D.
Director, Office of Generic Drugs

Hylton V. Joffe, M.D., M.M.Sc.
Director, Division of Reproductive and Urologic Products

[70] This petition includes the certification required by 21 C.F.R. § 10.30 rather than the certification required by 21 U.S.C. § 355(q) because, despite robust due diligence, Teva has not identified any information suggesting that an ANDA or 505(b)(2) application referencing ParaGard® is currently pending before FDA. If FDA has information indicating that this petition is subject to the requirements of 21 U.S.C. § 355(q), we ask that you notify the undersigned promptly so that this petition can be withdrawn and a new petition meeting the requirements of 21 U.S.C. § 355(q) can be submitted.