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Re: Docket No. FDA-2006-P-0080

JUL 02 2019

Dear Mr. Rosen:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA or the Agency) on March 15, 2006 (Petition).<sup>1</sup> The Petition requests that FDA refrain from taking administrative action regarding the approval and/or the effective date of final approval of abbreviated new drug applications (ANDAs) for a generic version of MetroGel-Vaginal 0.75% (metronidazole vaginal gel) (MetroGel-Vaginal), new drug application (NDA) 20208, unless and until the ANDA applicant meets certain bioequivalence standards. Specifically, the Petition asks FDA to require ANDA applicants to demonstrate therapeutic equivalence to the reference listed drug (RLD), MetroGel-Vaginal, in two distinct ways:

[F]irst in a bioequivalence study that utilizes appropriate, validated clinical endpoints in patients with bacterial vaginosis; and second through the submission of evidence that the systemic absorption and pharmacokinetic profiles of both the parent drug metronidazole and its active metabolite, hydroxymetronidazole, meet the statistical criteria of bioequivalence in compliance with the applicable bioequivalence regulations and guidance documents. . .<sup>2</sup>

FDA has carefully considered your Petition and accompanying exhibits, comment to the docket, and other information available to the Agency. As explained below, we grant the Petition to the extent that the Petition asks that FDA recommend that bioequivalence for an ANDA to MetroGel-Vaginal be established through two studies (comparative clinical and pharmacokinetic endpoint studies), which is consistent with FDA's recommendations in the draft product-specific

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<sup>1</sup> The Petition was received by FDA on March 15, 2006. It was originally assigned docket number 2006P-0114/CP1; that docket number was changed in 2008 to FDA-2006-P-0080 when FDA changed to a new docketing system in <http://www.regulations.gov>.

<sup>2</sup> Petition at 2-3.

guidance for Metronidazole Vaginal Gel (draft metronidazole vaginal PSG or PSG) issued in March 2013.<sup>3</sup> The Petition is denied in all other respects.

## I. BACKGROUND

### A. Metronidazole Vaginal Gel

MetroGel-Vaginal, marketed by Medicis Pharmaceutical Corp., a Division of Valeant Pharmaceuticals North America, LLC, was approved on August 17, 1992.<sup>4</sup> MetroGel-Vaginal is indicated for the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis) in non-pregnant women. Metronidazole is a 2-methyl-5-nitroimidazole-1-ethanol, a member of the imidazole class of antibacterial agents, and is classified therapeutically as an antiprotozoal and antibacterial agent indicated for the treatment of bacterial vaginosis. Metronidazole vaginal gel is a gelled purified water solution; the intravaginal dosage form contains metronidazole at a concentration of 7.5 milligrams (mg) per gram (g) (0.75%).<sup>5</sup> Metronidazole is metabolized in the liver (and possibly other organs) to form the active metabolite hydroxymetronidazole.<sup>6</sup>

Metronidazole vaginal gel is a locally acting vaginal product where the active ingredient deposits at the site of action before it enters systemic circulation. Specifically, metronidazole gel is applied by applicator onto the vaginal mucosa, where it is absorbed into the tissue layers underneath the surface mucosa.

According to the labeling for MetroGel-Vaginal, following a single, intravaginal 5-gram dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole) to 12 normal subjects, a mean maximum serum metronidazole concentration of 237 nanograms (ng)/milliliter (mL) was reported (range: 152 to 368 ng/mL).<sup>7</sup> This is approximately 2 percent of the mean maximum serum metronidazole concentration reported in the same subjects administered a single, oral 500-mg dose of metronidazole (mean  $C_{max}$  = 12,785 ng/mL, range: 10,013 to 17,400 ng/mL).<sup>8</sup> These

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<sup>3</sup> See discussion in section I.C. When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a product-specific guidance, check the FDA guidance web page at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm>.

<sup>4</sup> Vandazole (metronidazole vaginal gel 0.75%), NDA 021806 held by Teva Pharmaceuticals, was approved on May 20, 2005 under the pathway described in section 505(b)(2) of the Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)). Although pharmaceutically equivalent, based on bioequivalence testing, FDA determined that Vandazole is not therapeutically equivalent to MetroGel and is rated "BX" to MetroGel-Vaginal 0.75% in the Agency's publication *Approved Drug Products with Therapeutic Evaluations*, 39<sup>th</sup> edition (the Orange Book), available at <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

<sup>5</sup> MetroGel-Vaginal labeling, Oceanside Pharmaceuticals, revised October 2017, available at <https://www.accessdata.fda.gov/spl/data/c2d9eedd-7f9a-4699-bffd-31a360c1d77f/c2d9eedd-7f9a-4699-bffd-31a360c1d77f.xml>.

<sup>6</sup> See Petition Exhibit 8, Fredricsson B., et al., *Systemic Concentrations of Metronidazole and Its Main Metabolites After Intravenous Oral and Vaginal Administration*, Gynecol, Obstet Invest 24:200-207 (1987).

<sup>7</sup> MetroGel-Vaginal labeling, October 2017.

<sup>8</sup> Id.

peak concentrations were obtained 6 to 12 hours after dosing with metronidazole vaginal gel and 1 to 3 hours after dosing with oral metronidazole.<sup>9</sup>

The extent of exposure (area under the curve (AUC)) of metronidazole, when administered as a single, intravaginal 5-gram dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole), was approximately 4 percent of the AUC of a single, oral 500-mg dose of metronidazole (4977 ng\*hr/mL and approximately 125,000 ng\*hr/mL, respectively).<sup>10</sup> Dose-adjusted comparisons of AUCs demonstrated that, when comparing milligram to milligram, the absorption of metronidazole, when administered vaginally, was approximately half that of an equivalent oral dose.<sup>11</sup>

Following single and multiple 5-gram doses of metronidazole vaginal gel to four patients with bacterial vaginosis, a mean maximum serum metronidazole concentration of 214 ng/mL on day 1 and 294 ng/mL (range 228 to 349 ng/mL) on day five were reported.<sup>12</sup> Steady state metronidazole serum concentrations following oral dosages of 400 to 500 mg twice daily have been reported to range from 6,000 to 20,000 ng/mL.

## B. Statutory and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to add, among other things, section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs.<sup>13</sup> To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD is safe and effective.<sup>14</sup> The ANDA applicant must identify the listed drug on which it seeks to rely and, with certain limited exceptions, a drug product described in an ANDA must contain the same active ingredient, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.<sup>15</sup>

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.<sup>16</sup> Under section 505(j)(8)(B)(i) of the FD&C Act, a drug is considered bioequivalent to a listed drug if

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<sup>9</sup> Id.

<sup>10</sup> Id.

<sup>11</sup> Id.

<sup>12</sup> Id.

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

<sup>14</sup> An *RLD* is the “listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.” 21 CFR 314.3(b). RLDs are identified in the Orange Book.

<sup>15</sup> Section 505(j)(2)(A) and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).

<sup>16</sup> See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring “information to show that the new drug is bioequivalent to the listed drug”), § 314.94(a)(7) (requiring that an ANDA contain information to show that the drug product is bioequivalent to the RLD), and 21 CFR 314.127(a)(6)(i) (stating that FDA will refuse to approve an

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. . . .<sup>17</sup>

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and to an extent that is not significantly different from that of the RLD, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the RLD. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an effect on the rate and extent to which the active ingredient becomes available at the site of action.

As discussed further below, the statute, regulations, and case law give FDA considerable flexibility in determining how the bioequivalence requirement is met. The testing methods may include in vivo data (data from a study on human subjects), in vitro data (data from laboratory studies), or a combination of in vivo and in vitro data.<sup>18</sup> This flexibility is reflected in FDA's regulations, which describe the types of evidence that may be used to establish bioequivalence:

FDA may require *in vivo or in vitro testing, or both*, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products . . . . The selection of the method used to meet an *in vivo* or *in vitro* testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.<sup>19</sup>

The methods described in § 320.24(b) (21 CFR 320.24(b)) include (1) in vivo pharmacokinetic (PK) studies of the active ingredient, or when appropriate its active metabolites, in whole blood, plasma, serum, or other appropriate biological fluid or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary

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ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

<sup>17</sup> See also 21 CFR 314.3(b) and 21 CFR 320.23(b).

<sup>18</sup> See section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with discretion to determine whether *in vitro* or *in vivo* bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated application process").

<sup>19</sup> § 320.24(a) (emphasis added). In the preamble to the final rule setting forth FDA's regulations for ANDAs, the Agency explained that, depending upon the drug, it would determine the appropriate bioequivalence methodology on a case-by-case basis: "Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . is determined on a case-by-case basis, depending on the drug under study." Abbreviated New Drug Application Regulations, Final Rule (57 FR 17950 at 17972, April 28, 1992) (emphasis added).

excretion of the active moiety and, when appropriate, its active metabolite(s) are measured as a function of time; (3) in vivo studies measuring acute pharmacodynamic effect; (4) comparative clinical endpoint studies; and (5) other in vitro studies acceptable to FDA (usually a dissolution rate test) that ensure human in vivo bioavailability.<sup>20</sup> In addition, consistent with section 505(j)(8)(C) of the FD&C Act, § 320.24(b)(6) of the regulations states that FDA has the authority to use “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence.”<sup>21</sup>

For most systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. However, a traditional in vivo bioequivalence study comparing the rate and extent of absorption of the active ingredient in the blood stream is usually of limited utility for locally active, non-systemically absorbed products. Therefore, in order to demonstrate bioequivalence for topical preparations for the skin, eye, and mucous membranes, appropriately designed comparative in vivo studies with clinical endpoints may be appropriate.<sup>22</sup> The regulations also state that for drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.<sup>23</sup>

Standard bioequivalence PK studies are conducted using a two-treatment crossover study design, randomly separating a limited number of subjects into test and reference drug groups. Single doses of the test and reference drugs are administered, and blood or plasma levels of the drug are measured over time. The rate and extent of absorption are statistically evaluated. The relevant pharmacokinetic parameters calculated from these data include the area under the plasma concentration versus time curve (AUC), calculated to the last measured concentration time (AUC<sub>0-t</sub>), and AUC extrapolated to infinity (AUC<sub>∞</sub>). These parameters represent the extent of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant PK parameter is the maximum or “peak” drug concentration (C<sub>max</sub>). C<sub>max</sub> is used to reflect the rate of absorption.

For in vivo PK tests, FDA generally considers two products to be bioequivalent when the 90-percent confidence interval for the log-transformed ratio of geometric means for the PK parameters, AUC and C<sub>max</sub>, are entirely within an 80- to 125-percent acceptance interval.<sup>24</sup> The use of an 80- to 125-percent acceptance interval is a scientific judgment about the best statistical practices for bioequivalence determinations and reflects decades of scientific data on the

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<sup>20</sup> 21 CFR 320.24(b).

<sup>21</sup> § 320.24(b)(6).

<sup>22</sup> § 320.24(b)(4).

<sup>23</sup> § 320.23(b)(2).

<sup>24</sup> See FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence*, January 2001 (Establishing Bioequivalence Guidance). This guidance represents FDA’s current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

variability of product characteristics (such as potency) within and between batches, as well as biological variability in patients. From these data, FDA has concluded that the variability in PK values allowed under this acceptance interval will not adversely affect clinical outcomes because this variability is within the range of differences that can already arise because of other product-specific and biological factors.<sup>25</sup>

### C. Draft Product-Specific Recommendations for Metronidazole Vaginal Gel

FDA's guidance for industry *Bioequivalence Recommendations for Specific Products* describes the Agency's process for making available to the public FDA's guidance on the design of bioequivalence studies for specific drug products.<sup>26</sup> Currently, FDA periodically publishes notices in the *Federal Register* announcing the availability of draft, revised draft, and final versions of product-specific guidances. These documents are available on FDA's website.<sup>27</sup>

FDA considers comments received on product-specific guidances when developing its final guidances. As with Agency guidance in general, these product-specific guidances describe the Agency's current thinking and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. Applicants following our product-specific guidances have an expectation that FDA will agree that their approach to establishing bioequivalence is appropriate. However, applicants may confer with the Agency on using a different approach for establishing bioequivalence. Recommendations made in a draft or final guidance do not bind the Agency or the public. Further, even in the absence of a product-specific guidance, FDA has the authority to approve a product supported by bioequivalence data that meet the applicable statutory and regulatory requirements.

In March 2013, FDA published a draft product-specific guidance on metronidazole vaginal gel, which recommended that ANDA applicants conduct two studies to establish bioequivalence to metronidazole vaginal gel.<sup>28</sup> The first recommended study is a single-dose, two-way crossover bioequivalence study with PK endpoints obtained from healthy females in the general population. The recommended study is with a product strength of 0.75% metronidazole

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<sup>25</sup> Dighe, S.V., Adams, W.P., *Bioequivalence: A United States Regulatory Perspective*, Pharmaceutical Bioequivalence (Welling PG et al., eds.), 347-380 (1991) (Regulatory Perspective on Bioequivalence Study).

<sup>26</sup> FDA guidance for industry *Bioequivalence Recommendations for Specific Products*, June 2010. This guidance states that the Agency intends to develop bioequivalence recommendations based on its understanding of the characteristics of the listed drug, information derived from published literature, and Agency research and consultations within different offices in FDA's Center for Drug Evaluation and Research (CDER) as needed based on the novelty or complexity of the bioequivalence considerations. Specific product recommendations may contain differing amounts of detail and background information depending on the product and will be revised as appropriate to ensure that the most up-to-date bioequivalence information is available to the public. Id. at 2-3.

<sup>27</sup> The Product Specific Recommendations for Generic Drug Development are available on FDA's website at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

<sup>28</sup> Draft metronidazole vaginal PSG, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345807.pdf>. As stated in the PSG, the draft guidance, once finalized, will represent the FDA's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you wish to discuss an alternative approach, contact the Office of Generic Drugs.

administered intravaginally, to be applied using one applicator full (5 grams containing approximately 37.5 mg of metronidazole) in the to-be-marketed or currently marketed applicator. The draft product-specific bioequivalence guidance recommends that applicants measure metronidazole in plasma and that the applicator weight should be measured after filling and after dosing to calculate the weight of the dose. Bioequivalence should be established based on the 90-percent confidence interval.<sup>29</sup>

The second recommended study is a comparative clinical endpoint study, which is described in detail in the draft product-specific guidance for metronidazole vaginal gel. This recommended study is a randomized, double-blind parallel, placebo-controlled *in vivo* study in otherwise healthy females with bacterial vaginosis. The strength recommended is 0.75% metronidazole in an applicator (approximately 5 grams containing approximately 37.5 mg of metronidazole) in the to-be-marketed or currently marketed applicator. The primary endpoint is therapeutic cure rate, which includes clinical cure (resolution of clinical signs and symptoms) and bacteriologic cure (Nugent score < 4), evaluated at the Test of Cure visit (study day 22-30). The draft bioequivalence protocol in the PSG discusses in detail additional recommendations for this study, and the proposed protocol also details how the study results should be computed and analyzed statistically.

## II. DISCUSSION

As stated above, the Petition requests that FDA refrain from approving an ANDA unless the applicant demonstrates bioequivalence using two specific tests: the first conducting a bioequivalence study using clinical endpoints in patients with bacterial vaginosis, and the second conducting a bioequivalence study using PK endpoints of metronidazole and its metabolite hydroxymetronidazole.<sup>30</sup> You also state in the Petition that two studies are necessary because the product's site of action is intended to be local in the vagina and toxicity has been associated with systemic absorption of the drug.<sup>31</sup>

As discussed above, FDA prepared a draft metronidazole vaginal PSG with recommendations on how applicants can design bioequivalence testing for developing an ANDA to MetroGel-Vaginal. To the extent that the Petition requests that an ANDA applicant should conduct two studies (a comparative clinical endpoint study and a PK study) to demonstrate bioequivalence of

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<sup>29</sup> See footnotes 24 and 25, and associated text (describing the 90 percent confidence interval).

<sup>30</sup> Petition at 1-2.

<sup>31</sup> Specifically, the Petition argues that a PK study should be required because: (1) both the general systemic absorption and the inter-subject absorption of vaginal metronidazole are quite variable; (2) a minimum concentration-toxicity relationship for metronidazole has not been established; and (3) there is sufficient absorption of metronidazole and its active metabolite, hydroxymetronidazole, such that they can be measured in blood levels (Petition at 3-4 and 7-13). The Petition also suggests that clinically important systemic toxicities are associated with metronidazole (Petition at 4). Finally, the Petition asserts that FDA's decision regarding Mupirocin ointment, 2 percent, provides support for its claim that systemic toxicities in metronidazole vaginal gel need to be addressed in a bioequivalence review (Petition at 13-14).

the proposed generic drug to the RLD, FDA agrees. The Agency disagrees with your request that an ANDA applicant conduct PK testing on hydroxymetronidazole.

**A. FDA's Draft Product-Specific Recommendations for Metronidazole Vaginal Gel are Consistent with the Petition's Request for Two Bioequivalence Studies**

As set forth above, the draft metronidazole vaginal PSG recommends that ANDA applicants conduct two studies on a proposed generic drug and MetroGel-Vaginal, the RLD, to establish bioequivalence: a bioequivalence study with clinical endpoints in patients with bacterial vaginosis; and a PK study that compares metronidazole in plasma from subjects taking MetroGel-Vaginal, the RLD, to subjects taking the proposed generic drug.<sup>32</sup> This is consistent with the request in the Petition for two studies.

FDA agrees with the Petition that an ANDA applicant should conduct a comparative clinical endpoint study to demonstrate bioequivalence of the proposed generic metronidazole vaginal gel to the RLD, MetroGel-Vaginal.<sup>33</sup> The draft metronidazole vaginal PSG describes in detail the comparative clinical endpoint trial for demonstrating bioequivalence.<sup>34</sup> As stated in the regulations on bioequivalence, appropriately designed comparative clinical studies provide acceptable evidence to demonstrate the bioequivalence of a proposed generic drug for dosage forms intended to deliver the active moiety locally (e.g., topical preparations for the skin, eye, and mucous membranes).<sup>35</sup> Metronidazole vaginal gel is applied locally on the surface mucosa of the vagina and absorbed into the tissue layers underneath. There is significant variability in absorption of drugs delivered by vaginal application, including inter-subject variability, making bioequivalence difficult to demonstrate solely through PK studies.<sup>36</sup> Therefore, as stated in the draft metronidazole vaginal PSG, we recommend a comparative clinical endpoint study of the test drug to compare with the RLD to establish bioequivalence.

While a comparative clinical endpoint study may be sufficient to establish bioequivalence in certain instances, our review of data regarding metronidazole vaginal gel determined that a PK endpoint study should also be conducted as part of the bioequivalence demonstration of a proposed generic drug to the RLD. We recommend a PK endpoint study in the PSG because a

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<sup>32</sup> Draft metronidazole vaginal PSG (2013). Background in the notice of availability (NOA) for the draft PSG acknowledged this Petition and stated the Agency was reviewing the issues raised in the Petition and would consider any comments on the PSG when responding to the Petition. 78 FR 19271 (March 29, 2013). There were no comments filed in response to the NOA and publication of the draft PSG.

<sup>33</sup> Draft metronidazole vaginal PSG (2013).

<sup>34</sup> Id.

<sup>35</sup> § 320.24(b)(4).

<sup>36</sup> As discussed in the literature, consistent systemic delivery of drugs from a vaginal source is known to be substantially modified by cyclic changes in epithelial thickness, composition, pH, amount of vaginal secretions, and variation in local endopeptidases as influenced by hormonal fluctuations. See Vermani, K., Garg, S., *The scope and potential of vaginal drug delivery*, PSTT 3:359-64 (2000); Lamp, K.C., et al., *Pharmacokinetics and Pharmacodynamics of the Nitroimidazole Antimicrobials*, Clin Pharmacokinet 36:353-73 (1999); see also Petition at 5-6 discussing systemic absorption and inter-subject variability of metronidazole vaginal gel.

difference in pharmacokinetics may reflect performance differences between a proposed product and the RLD with respect to local vaginal delivery.<sup>37</sup> Formulation differences may cause differences in systemic absorption as the rate and extent of drug absorption from vaginal fluid can be altered by differences in gel composition and manufacturing.<sup>38</sup> This second study is recommended to confirm the bioequivalence of metronidazole in the proposed generic drug and the RLD in plasma and to detect significant differences (e.g., whether metronidazole is present in potentially toxic levels) between the drug products. FDA recommends that this study meet statistical criteria for bioequivalence.<sup>39</sup> Therefore, FDA agrees with the Petition and recommends that bioequivalence for an ANDA to MetroGel-Vaginal be established through two studies: a comparative clinical endpoint study and a PK study for metronidazole, as described in FDA's draft metronidazole vaginal PSG.

The Petition states that metronidazole vaginal gel is well tolerated, with the most common adverse events being local rash at the site of application and development of *Candida* vaginitis.<sup>40</sup> However, it raises a number of safety issues regarding the use of metronidazole in support of its position that an ANDA applicant should conduct two studies in order to demonstrate bioequivalence of the proposed generic drug to the RLD.<sup>41</sup> We agree that there is a potential for systemic toxicities with use of metronidazole vaginal gel, and the PK testing is designed to detect a significant difference between MetroGel-Vaginal and a generic drug product. The PK study confirming the product composition and manufacturing is expected to also ensure that patients are protected from potential systemic toxicities with the use of vaginal metronidazole gel when the test product is compared to the RLD.

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<sup>37</sup> Differences in drug formulation can exert a physiological effect depending on the concentration, target population, route of administration, and duration of drug use. See Rayavarapu, S., et al., *Comparative Risk Assessment of Formulation Changes in Generic Drug Products: A Pharmacology/Toxicology Perspective*, Toxicological Sciences 146(1):2-10 (2015). See also discussion in footnote 38, below, which describes approval of Vandazole and the decision to rate the drug as BX to MetroGel-Vaginal. In reviewing that drug product, the Medical Review found that the proposed drug was virtually identical to the RLD save for a high pH for the study drug and a substitution of one inactive ingredient. The Division of Special Pathogens and Transplant Products (DSPTP) (Clinical Pharmacology) in the Office of Antimicrobial Products (OAP) thought it was possible that the alternative ingredient in the formulation may have improved the muco-adhesive properties of the applicant's formulation, which led to a longer retention or contact time with the vaginal mucosa, affecting absorption.

<sup>38</sup> The Petition notes the approval of NDA 21806 for Vandazole (metronidazole) vaginal gel, 0.75%, held by Teva Pharmaceuticals (Teva), in May 2005 and that on approval, it was designated as BX rated in comparison to MetroGel vaginal gel (Petition at 4). Review documents by FDA posted after approval of Vandazole contain relevant information on how different inactive ingredients in this metronidazole vaginal gel product may have affected its absorption. NDA 21806 was originally submitted as an ANDA relying on MetroGel-Vaginal, NDA 20208. FDA's Office of Generic Drugs refused to receive the application because the clinical bioequivalence of the proposed product to the RLD was not established. See Vandazole Drug Approval Review Documents 21806 Medical Review by DSPTP within OAP, available at <https://www.accessdata.fda.gov/scripts/cder/daf> (Medical Review) at 2. Teva then submitted an application for its product under the 505(b)(2) pathway, which was approved. In 2011, OAP was reorganized, and the metronidazole product was transferred to the Division of Anti-Infective Products.

<sup>39</sup> Draft metronidazole vaginal PSG (2013); see footnotes 24 and 25 and associated text for a discussion of statistical significance.

<sup>40</sup> Petition at 7.

<sup>41</sup> See Petition at 7-12.

Although systemic levels of metronidazole from vaginal administration are significantly lower than metronidazole levels from oral doses,<sup>42</sup> there is no clinical data directly comparing metronidazole administered orally to metronidazole administered vaginally demonstrating that the same safety issues are not present when administered vaginally.<sup>43</sup> Therefore, in our opinion, the absorption and systemic pharmacokinetics of metronidazole vaginal gel have not been fully evaluated. Thus, although the lower levels of exposure that are seen with vaginally administered products are less likely to produce the serious adverse reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded. A statement on this is included in the labeling for MetroGel-Vaginal,<sup>44</sup> along with specific warnings and precautions. Approved labeling for metronidazole vaginal gel includes the same or similar safety warnings as an oral route of administration.<sup>45</sup>

In the PSG, FDA recommends that an applicant support its ANDA for generic metronidazole vaginal products with a single-dose PK bioequivalence study of metronidazole in plasma in addition to a comparative clinical endpoint study. A demonstration of the bioequivalence of metronidazole in the proposed generic product and RLD is expected to provide sufficient information on both systemic metronidazole levels to support the comparative clinical bioequivalence determination and to ensure patients are protected from potential toxicities associated with metronidazole in approved ANDAs comparable to the RLD.<sup>46</sup> Therefore, to the

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<sup>42</sup> See discussion in section I.A. Blood concentrations of metronidazole after intravaginal administration are relatively low (2 percent and 4 percent of the C<sub>max</sub> and AUC, respectively, compared to 500-mg oral dosing). Dose-adjusted comparisons of AUCs demonstrate that, when comparing milligram to milligram, the absorption of metronidazole when administered vaginally is approximately half that of an equivalent oral dose.

<sup>43</sup> We note that adverse events consistent with systemic metronidazole toxicity were not reported in the clinical trials of MetroGel-Vaginal, Vandazole, or Metronidazole vaginal gel 1.3%.

<sup>44</sup> The MetroGel-Vaginal labeling includes the following statement in the PRECAUTIONS section of labeling: "Metronidazole Vaginal Gel affords minimal peak serum levels and systemic exposure (AUCs) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded presently. Data from well-controlled trials directly comparing metronidazole administered orally to metronidazole administered vaginally are not available."

<sup>45</sup> Note that the labeling for MetroGel-Vaginal, Vandazole and Metronidazole vaginal gel 1.3% contain similar WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS as approved labeling for oral and intravenous metronidazole formulations based on the potential for systemic toxicity. The package insert for Vandazole includes a CONTRAINDICATION for administration of disulfiram, citing an association of oral metronidazole with psychotic reactions in alcoholic patients who have taken disulfiram within the previous two weeks. Although not a contraindication, the MetroGel-Vaginal labeling contains similar statements in the WARNINGS AND PRECAUTIONS section. The WARNINGS section mentions systemic toxicities including convulsive seizures and peripheral neuropathy, and the PRECAUTIONS section acknowledges that a "disulfiram-like reaction to alcohol has been reported with oral metronidazole, thus the possibility of such a reaction occurring while on metronidazole vaginal gel therapy cannot be excluded." Precautions are also stated for patients with severe hepatic disease who metabolize metronidazole slowly.

<sup>46</sup> The Petition cites the approval of Mupirocin Ointment 2% as support for its argument that in addition to a comparative clinical endpoint study, a PK study evaluating systemic bioavailability must be conducted to establish bioequivalence for MetroGel-Vaginal (Petition at 13-14). The Agency's approval decision regarding mupirocin ointment is distinguishable from any approval decision relating to metronidazole vaginal gel. However, because we

extent the Petition requests that FDA recommend that ANDAs referencing MetroGel-Vaginal contain bioequivalence data from two separate studies—a comparative clinical endpoint study and a PK study for metronidazole—the Petition is granted.

#### B. Bioequivalence Testing of the Metabolite is Unnecessary

The PSG recommends that an ANDA applicant conduct a PK test of metronidazole (but not the metabolite, hydroxymetronidazole) in plasma from subjects using its proposed generic product and the RLD to demonstrate bioequivalence.<sup>47</sup> FDA generally recommends that generic applicants measure only the parent drug (the moiety released from the dosage form) rather than the metabolite during bioequivalence testing because the “concentration-time profile of the parent drug is more sensitive to changes in formulation than a metabolite, which is more reflective of metabolite formation, distribution, and elimination.”<sup>48</sup>

FDA’s current scientific thinking is that the parent drug in the dosage form should be measured in biological fluids collected in bioequivalence studies unless accurate assay quantitation is not possible using state-of-the-art technology.<sup>49</sup> The Petition does not suggest that metronidazole cannot be measured; in fact, it implicitly concedes that it is measurable by asking for bioequivalence testing for metronidazole and its metabolite.<sup>50</sup> Under such circumstances, FDA generally recommends that primary metabolites be measured only if a primary metabolite is both formed substantially through pre-systemic metabolism (first pass, gut wall, or lumen metabolism) *and* contributes significantly to the safety and efficacy of the product.<sup>51</sup>

Available data and literature demonstrate that hydroxymetronidazole is not formed pre-systemically.<sup>52</sup> Clinical testing has shown that following a single dose of metronidazole vaginal

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agree with the Petition that two studies are recommended for bioequivalence demonstration for metronidazole vaginal gel, a further discussion of mupirocin ointment is not necessary in response to this Petition.

<sup>47</sup> Draft metronidazole vaginal PSG (2013).

<sup>48</sup> These recommendations are consistent with FDA’s draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) at 12 (*Bioequivalence Studies with PK Endpoints draft guidance*). For the most recent version of a guidance document, check the FDA guidance webpage, available at <https://www.fda.gov/Drugs/GuidancecomplianceRegulatoryInformation/Guidances/default.htm>.

<sup>49</sup> Id. at 12.

<sup>50</sup> The Petition states that both metronidazole and its metabolite can be accurately measured using HPLC assays (Petition at 5). HPLC refers to high performance liquid chromatography.

<sup>51</sup> This recommendation is also consistent with the *Bioequivalence Studies with PK Endpoints draft guidance* at 12 (emphasis added). There is some indication in the literature that hydroxymetronidazole contributes to the efficacy of metronidazole; however, its contribution has not been quantified and any contribution would be made after systemic absorption, not before. Pendland, S., et al., *In Vitro Activities of Metronidazole and Its Hydroxy Metabolite against Bacteriocides*, Antimicrobial Agents and Chemotherapy, 38(9):2106-2110 (1994). As noted above, for purposes of bioequivalence determinations, a parent drug provides more relevant information on formulation differences than a metabolite, which will reflect metabolite formation, distribution, and elimination.

<sup>52</sup> In the Petition’s Exhibit 8, the authors conclude that there is no pre-systemic formulation of the hydroxyl metabolite. Fredricsson, B., et al., *Systemic Concentrations of Metronidazole and Its Main Metabolites After*

gel 0.75%, the first measurable plasma concentrations for metronidazole and hydroxymetronidazole were observed at 1 hour and 6 hours post-dosing, respectively. This PK profile confirms that the metabolite is formed after the drug is absorbed into the systemic circulation, not pre-systemically.

Because the Petition has not demonstrated that the metabolite is formed pre-systemically, we need not address whether and to what extent it contributes to the safety and efficacy of the product. In addition, the Petition presents no data indicating that systemic absorption of this metabolite could be associated with toxicities that are independent from those associated with metronidazole.<sup>53</sup> Clinical trial data reviewed by FDA support the conclusion that plasma levels of hydroxymetronidazole, when quantifiable,<sup>54</sup> are considerably lower than plasma levels of metronidazole following vaginal administration of metronidazole gel. Based on available information, it is our opinion that measurements of metronidazole in plasma will be adequate to assess safety of the drug product. Because hydroxymetronidazole is not formed pre-systemically, we disagree that metabolite testing is necessary to demonstrate bioequivalence. Therefore, we do not address the argument in the Petition that metabolite testing must meet statistical criteria for establishing bioequivalence.<sup>55</sup>

Accordingly, your request that PK testing on hydroxymetronidazole be required for bioequivalence studies on MetroGel-Vaginal is denied.

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*Intravenous Oral and Vaginal Administration*, Gynecol, Obstet Invest 24:200-207 (1987). After intravenous, oral, or vaginal administration, the relationship between parent and metabolite is consistent, indicating that metabolic degradation of the drug mainly takes place systemically (in the liver and possibly other organs) and not in the vagina. The Petition also acknowledges that “[b]iotransformation of absorbed metronidazole into hydroxyl and acid metabolites is a function of hepatic metabolism” (Petition at 7).

<sup>53</sup> The Petition argues that to establish bioequivalence, FDA should consider systemic absorption data for both parent and active metabolite in addition to a [comparative] clinical endpoint study because “systemic absorption of vaginal metronidazole is known to be quite variable, and there is no known blood level threshold for risks of systemic toxicity” (Petition at 12-13). However, even accepting that argument, the Petition does not demonstrate that the metabolite is formed pre-systemically.

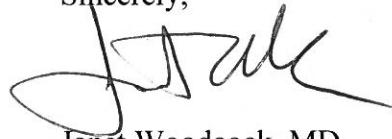
<sup>54</sup> There is some evidence in the literature that following administration of intravaginal metronidazole gel 0.75%, plasma concentrations of hydroxymetronidazole may not be reliably measured. See Cunningham, F.E., Kraus, D.M., Brubaker, L., et al., *Pharmacokinetics of intravaginal metronidazole gel*, J Clin Pharmacol 34:1060-65(1994).

<sup>55</sup> Petition at 2 and 15.

### III. CONCLUSION

For the reasons discussed above, FDA grants your Petition to the extent that it requests that the Agency recommend that ANDA applicants conduct two studies for bioequivalence testing for MetroGel-Vaginal. FDA denies your request that the Agency require that ANDA applicants conducting bioequivalence testing include a PK endpoint study measuring the metabolite hydroxymetronidazole.

Sincerely,



Janet Woodcock, MD  
Director  
Center for Drug Evaluation and Research