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Food and Drug Administration
Department of Health and Human Services
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CITIZEN PETITION

The undersigned submits this Citizen Petition under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355(b) and (j)), and in accordance with 21 CFR §10.20 and §10.30 to request the Acting Commissioner of Food and Drugs refrain from taking administrative action regarding the approval and/or the effective date of final approval of any and all abbreviated new drug applications ("ANDAs") for a generic version of Metrogel-Vaginal[®] 0.75% (metronidazole vaginal gel) unless and until the ANDA applicant demonstrates the therapeutic equivalence of the proposed ANDA to the reference listed drug, Metrogel-Vaginal[®] in two distinct ways: first 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

2006P-0114

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and its active metabolite, hydroxymetronidazole, meet the statistical criteria of bioequivalence as per FDA guidelines for approaches to establish bioequivalence.

The statutory requirement to establish bioequivalence can only be met for a vaginal preparation by such a two prong approach: (1) the conduct of a bioequivalence study utilizing clinical endpoints in patients with bacterial vaginosis; and (2) through the conduct of pharmacokinetic profiles of both the parent drug metronidazole and its active metabolite, hydroxymetronidazole. Such a two prong approach is 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. Thus sufficient pharmacokinetic data must be submitted in the application to establish that the extent and rate of absorption of the generic metronidazole product is bioequivalent to the reference listed drug product. The basis for this Citizen Petition is set forth below.

A. Action Requested

The Petitioner requests that the Acting Commissioner of Food and Drugs refrain from taking administrative action regarding the approval and/or the effective date of final approval of any and all abbreviated new drug applications ("ANDAs") for a generic version of Metrogel-Vaginal[®] 0.75% (metronidazole vaginal gel) unless and until the ANDA applicant demonstrates the therapeutic equivalence of the proposed ANDA to the reference listed drug, Metrogel-Vaginal[®] in two distinct ways: first 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, specifically, 21 CFR §320, and the 2001 Guidance for Industry, *Statistical Approaches to Establishing Bioequivalence*.

Complete bioequivalence testing in a standard pharmacokinetic study will ensure that the generic drug version's systemic absorption into the bloodstream following vaginal administration will occur at virtually the same rate and to the same extent as the reference listed drug. Given the pharmacological characteristics of both metronidazole and its active metabolite hydroxymetronidazole, *i.e.*, the toxicity associated with systemic absorption, and the fact that systemic absorption can be readily measured in the serum, only ANDAs that include a comparison of the pharmacokinetic profiles for both the active parent moiety and active hydroxymetronidazole metabolite should be considered acceptable for filing and bioequivalence review.

The requested action to require a standard blood pharmacokinetic study, in addition to a bioequivalence study utilizing clinical endpoints as part of the pivotal therapeutic equivalence standards for approval of ANDAs for metronidazole vaginal gel, 0.75% is fully supported by the following points:

- Sufficient absorption of the active ingredient from metronidazole vaginal gel, 0.75% occurs resulting in readily measured blood levels of the active parent drug and its active metabolite, hydroxymetronidazole;
- Independent studies in the literature illustrate substantial variability in the extent of systemic absorption from metronidazole vaginal products;
- A minimum concentration-toxicity relationship for metronidazole has not been established;

- Clinically important systemic toxicities have been associated with use of metronidazole vaginal products; and
- Precedent exists where a locally acting topical product demonstrated clinical equivalence to the reference listed drug but differed in the amount of systemic absorption leading to a BX (not therapeutically equivalent/not substitutable) rating by the Agency.

The above listed points are explained more fully below.

B. Statement of Grounds

I. Metronidazole Vaginal Gel Background

There are currently two FDA-approved formulations of metronidazole vaginal gel 0.75% . The initial innovator product, which is also designated as the reference listed drug, MetroGel-Vaginal® 0.75%, received FDA approval on August 17, 1992, NDA 20-208, for the treatment of bacterial vaginosis. In May 2005, another new drug application (“NDA”) was approved by the FDA for metronidazole vaginal gel, 0.75%, NDA 21-806 for the same indication. These products are not AB rated (they are BX rated.)

The active ingredient metronidazole is a potent, synthetic imidazole agent classified therapeutically as an anti-bacterial and anti-protozoal agent. Following single or multiple daily intravaginal applications, metronidazole vaginal gel, 0.75% is curative in treating most cases of bacterial vaginosis. The parent drug, metronidazole, and one of its principal metabolites, hydroxymetronidazole, have *in vitro* antimicrobial activity against pathogens

associated with bacterial vaginosis including *Bacteroides* spp., *Gardnerella vaginalis*, *Mobiluncus* spp., and *Peptostreptococcus* spp.¹

Although intravaginal administration of metronidazole is believed to have prominent activity in eradicating bacterial vaginosis due to its local action, metronidazole in oral and intravenous dosage forms is similarly active against these organisms for a variety of clinical indications including gynecologic infections. However, with intravaginal administration it is unclear as to the extent to which systemically-absorbed parent drug or the principal hydroxymetronidazole metabolite may contribute to the local eradication of vaginosis.

II. Systemic Absorption of Metronidazole Vaginal Gel

HPLC assays are sufficiently robust to detect plasma or urine concentrations of metronidazole and its active metabolite, hydroxymetronidazole, throughout the typical period of a drug pharmacokinetic study. Metronidazole is absorbed systemically from vaginal products to a significant extent, though systemic absorption is well recognized to be considerably less predictable than that of oral dosing.^{2,3,4,5,6} After vaginal administration of metronidazole, systemic bioavailability is quite variable, ranging

¹ Metronidazole. In: *The Use of Antibiotics. A Clinical Review of Antibacterial, Antifungal and Antiviral Drugs*. Kucers, A., Crowe, S.M., Grayson, M.L., and Hoy, J.F. (eds.). 1997. Butterworth-Heinemann, Oxford, UK, pp. 936-958.

² Alper, M.M., Barwin, N., et al. 1985. Systemic absorption of metronidazole by the vaginal route. *Obstet. Gynecol.* 65:781-784.

³ Ralph, E.D. 1983. Clinical pharmacokinetics of metronidazole. *Clin. Pharmacokin.* 8:43-62.

⁴ Fredricsson, B., Hagstrom, B., et al. 1987. Systemic concentrations of metronidazole and its main metabolites after intravenous oral and vaginal administration. *Gynecol. Obstet. Invest.* 24:200-207.

⁵ Mattila, J., Mannisto, P.T., et al. 1983. Comparative pharmacokinetics of metronidazole and tinidazole as influenced by administration route. *Antimicrob. Agents Chemother.* 23:721-252.

⁶ Cunningham, P.E., Kraus, D.M., et al. 1994. Pharmacokinetics of intravaginal metronidazole gel. *J. Clin. Pharmacol.* 34:1060-1065.

between 20% and 56% in a number of pharmacokinetic studies. However, due to the much smaller quantity of metronidazole in the 0.75% vaginal gel (37.5 mg in a single application) compared to oral or parenteral formulations, blood concentrations achieved after intravaginal administration are relatively low: 2% and 4% of the C_{max} and AUC, respectively, compared to 500 mg oral dosing.^{7,8,9}

Inter-subject variability in systemic absorption of metronidazole following vaginal administration is considerable. The timing of mean peak plasma metronidazole concentrations has been reported as low as 7.7 hours¹⁰ and as long as 24 hours¹¹ after administration, with much larger standard errors of time-to-peak concentration for vaginal products (standard error 1.6-2.6) compared to oral dosing (standard error 0.2).^{12,13} Even poorer reproducibility is noted for vaginal applications by cream or tablet in which the rate-limiting step for systemic absorption of metronidazole is reported to be dissolution into the vaginal fluid.¹⁴ The variable rate and extent of systemic absorption of metronidazole vaginal gel, the potential risk of accumulation with long-term dosing, and differences in gel formulation creates a situation whereby systemic pharmacokinetics

⁷ MetroGel-Vaginal Summary Basis of Approval (NDA 20-208). 1992. Medical Officer's Review.

⁸ Vandazole™ (metronidazole vaginal gel, 0.75%) Professional Labeling. Accessed at http://www.upsher-smith.com/PDFs/Vandazole_PI.pdf. December 29, 2005.

⁹ Cunningham, P.E., Kraus, D.M., et al. 1994. Pharmacokinetics of intravaginal metronidazole gel. *J. Clin. Pharmacol.* 34:1060-1065.

¹⁰ Mattila, J., Mannisto, P.T., et al. 1983. Comparative pharmacokinetics of metronidazole and tinidazole as influenced by administration route. *Antimicrob. Agents Chemother.* 23:721-252.

¹¹ Ralph, E.D. 1983. Clinical pharmacokinetics of metronidazole. *Clin. Pharmacokin.* 8:43-62.

¹² Mattila, J., Mannisto, P.T., et al. 1983. Comparative pharmacokinetics of metronidazole and tinidazole as influenced by administration route. *Antimicrob. Agents Chemother.* 23:721-252.

¹³ Alper, M.M., Barwin, N., et al. 1985. Systemic absorption of metronidazole by the vaginal route. *Obstet. Gynecol.* 65:781-784.

¹⁴ Cunningham, P.E., Kraus, D.M., et al. 1994. Pharmacokinetics of intravaginal metronidazole gel. *J. Clin. Pharmacol.* 34:1060-1065.

cannot be assumed from a given vaginally-administered dose. This is the prominent reason for the pregnancy warning with these products,¹⁵ *i.e.*, advising against use in the first trimester because of undetermined risks of embryo toxicity and teratogenicity.

Regardless of route of administration, once in the blood stream, metronidazole has minimal protein binding and a large volume of distribution throughout the body.

Metronidazole readily crosses the blood brain barrier into the central nervous system, breast milk, middle ear, and abscess fluids.¹⁶ Because systemically absorbed drug is widely distributed, including potentially to the fetus and nursing infants, professional labeling for vaginal gel products specifically note that a decision needs to be made in a pregnant or nursing mother whether to discontinue the product or not depending on how important it is to treat the infection.

Biotransformation of absorbed metronidazole into hydroxyl and acid metabolites is a function of hepatic metabolism. Despite the relatively low metronidazole blood levels achieved after vaginal administration compared to oral dosing, the potential for toxic accumulation of metronidazole in hepatically-impaired subjects with slow metabolic activity is raised in the professional labeling of vaginal gel products with the Precaution that "vaginal gel should be administered cautiously" in this patient population.

III. Systemic Toxicities from Metronidazole Vaginal Gel

Metronidazole vaginal gel is usually well tolerated, with the most common adverse events being local rash at the site of application and development of *Candida* vaginitis.

¹⁵ Alper, M.M., Barwin, N., et al. 1985. Systemic absorption of metronidazole by the vaginal route. *Obstet. Gynecol.* 65:781-784.

¹⁶ Ralph, E.D. 1983. Clinical pharmacokinetics of metronidazole. *Clin. Pharmacokin.* 8:43-62.

However, systemic toxicities have been reported with the use of metronidazole vaginal gel, many of which are also seen after oral dosing. Furthermore, a variety of other clinically important adverse events are well recognized from studies and reports of oral metronidazole as described below. Certain metronidazole-associated systemic adverse events, including seizures and leucopenia, have been associated with prolonged exposure or large doses. However, a minimum threshold blood concentration has not been established for metronidazole that reduces the potential for toxicities.

Because metronidazole readily crosses the blood brain barrier, central nervous system toxicities are recognized with oral and intravenous administration of metronidazole, including seizures, cerebellar dysfunction, encephalopathy, and peripheral neuropathy.^{17,18} Other central nervous system side effects, including dizziness, headache and lightheadedness, have been seen in studies of metronidazole vaginal gels and determined to be possibly or likely related to the drug. Due to identification of the nervous system as a target for metronidazole toxicity, labeling for vaginal gel products contain a prominent **WARNING** that they “should be administered with caution to patients with central nervous system diseases” and “The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole vaginal gel therapy.”

Gastrointestinal adverse reactions have been reported in clinical trials with metronidazole vaginal gel and judged possibly or probably related to study drug. These reports included gastrointestinal cramps, abdominal pain, nausea, constipation or diarrhea, metallic taste and decreased appetite. Since these and other toxicities have also been

¹⁷ Ralph, E.D. 1983. Clinical pharmacokinetics of metronidazole. Clin. Pharmacokin. 8:43-62.

¹⁸ Kasten, M.J. 1999. Clindamycin, metronidazole, and chloramphenicol. Mayo Clin. Proc. 74:825-833.

associated with oral or intravenous metronidazole, it is clear that vaginal gel products can produce sufficient blood levels to result in systemic adverse gastrointestinal reactions.

IV. Systemic Plasma Levels Associated With Metronidazole Vaginal Gel and Other Formulations and Drug Interactions

As discussed above, Metronidazole is absorbed systemically from vaginal products. Metronidazole vaginal gel professional labeling identifies three potential drug interactions of concern. These include psychotic disulfiram-like reactions with alcohol; potentiation of warfarin anticoagulation effects; and lithium toxicity.

A metronidazole-ethanol "disulfiram-like" reaction can include headache, nausea, gastric burning, flushing, and cold sweats following administration of metronidazole in the setting of concomitant alcohol ingestion. Such a reaction has been associated with use of a metronidazole vaginal insert.¹⁹ This was a report of headache, nausea, gastric burning, and flushing that occurred approximately one hour after a 68 year old woman, who had in the previous several hours consumed several alcoholic drinks, applied a metronidazole vaginal insert. The reaction had occurred after the 5th vaginal application. In the absence of any other possible causes of such symptoms, the author attributed the reaction to a significantly high blood metronidazole level. Disulfiram-like reactions including a fatal outcome also

¹⁹ Plosker, G.L. 1987. Possible interaction between ethanol and vaginally administered metronidazole. Clin Pharm. 6:189-191.

have been associated with the use of intravenous metronidazole²⁰ and oral metronidazole²¹,²² in the setting of ethanol ingestion.

Two literature citations described a contrary opinion that a metronidazole-ethanol “disulfiram-like” reaction has not been conclusively established. One such conclusion is based on the finding that experimental subjects given metronidazole tablets, 200 mg t.i.d., for five days followed by ingestion of 0.4 g/kg ethanol did not develop significant blood acetaldehyde concentrations.²³ However, the subjects also did not develop any symptoms suggestive of a disulfiram-like reaction, and the authors acknowledge that such reactions could occur in vulnerable subgroups. The other paper is a review of the literature, from which the authors remained unconvinced that a metronidazole-ethanol interaction has been scientifically established, suggesting that alcohol reactions alone, or possibly adverse effects secondary to concomitant illnesses, might have been responsible for the observed adverse disulfiram-like effects.²⁴ However, the authors also conclude that until evidence is obtained proving that ethanol and metronidazole is a safe combination, it “would seem unwise to change the time-honored advice” to avoid the concomitant use of these drugs. We agree with the latter sentiment, and suggest that since the existence of a metronidazole-ethanol “disulfiram-like” reaction remains controversial, it is prudent to document the

²⁰ Edwards, D.L., Fink, P.C., and Van Dyke, P.O. 1986. Disulfiram-like reaction associated with intravenous trimethoprim-sulfamethaxazole and metronidazole. *Clin. Pharm.* 5:999-1000.

²¹ Krulewitch, C.J. 2003. An unexpected adverse drug effect. *J. Midwif. Women’s Health* 48:67-68.

²² Cina, S.J., Russell, R.A., and Conradi, S.E. 1996. Sudden death due to metronidazole/ethanol interaction. *Am. J. Forensic Med. Pathol.* 17:343-346.

²³ Visapaa, J-P., Tillonen, J.S., et al. 2002. Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann. Pharmacother.* 36:971-974.

²⁴ Willams, C.S., and Woodcock, K.R. 2000. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann. Pharmacother.* 34:255-257.

extent of systemic absorption of all metronidazole drug products, including generic formulations of vaginal gel.

The ability of metronidazole to potentiate warfarin anticoagulation has been established both by a case report and in an experimental study of the interaction. The case report was a 31 year old woman adequately and well controlled with an anticoagulant (5.0-7.5 mg warfarin daily for many years) who developed lower extremity hemorrhages several days after beginning oral metronidazole for vaginosis.²⁵ The prothrombin time was massively elevated at 147 seconds (normal therapeutic level identified by the author as 17-19 seconds). Reversal of the over-anticoagulation was accomplished with vitamin K but at the expense of the formation of a cerebral embolus. This case report illustrates the dual dangers of warfarin potentiation: a presenting hemorrhagic event followed by risk of thrombosis during emergency correction of the coagulopathy. The experimental study was conducted after recognition that disulfiram can augment warfarin anticoagulation, and that metronidazole and disulfiram may act similarly to create the disulfiram-ethanol reaction.²⁶ Eight adult volunteers were administered warfarin (either the racemic mixture or resolved R(+) or S(-) enantiomorphs) plus metronidazole 250 mg t.i.d. or placebo (cross-over design), with determinations of plasma levels of warfarin and prothrombin times. All subjects demonstrated statistically greater peak prothrombin times and AUC values for the usual racemic warfarin mixture or S(-) warfarin, the 2-5 times more potent enantiomer (but not for R(+) warfarin) in the presence of metronidazole. The authors suggest it would be

²⁵ Kazmier, F.J. 1976. A significant interaction between metronidazole and warfarin. *Mayo Clin. Proc.* 51:782-784.

²⁶ O'Reilly, R.A. 1976. The stereoselective interaction of warfarin and metronidazole in man. *N. Engl. J. Med.* 295:354-357.

prudent to decrease warfarin doses, or use only R(+) warfarin, in the setting of concomitant use of metronidazole.

Finally, renal retention of lithium leading to toxic blood levels has been described in case reports of oral metronidazole use. In one report,²⁷ stable serum lithium levels increased by 20% and greater than 100% in two patients placed on metronidazole 250 mg t.i.d. and metronidazole 500 mg b.i.d., respectively. The two patients experienced symptoms of lithium toxicity including polyuria, nocturia, nephrogenic diabetes insipidus, confusion and difficulty walking. In one case the lithium dose was decreased as a result of the observed toxicity, in the other case lithium was discontinued. The authors suggest that tapering or even discontinuing lithium would be prudent when metronidazole is being administered. In a second case report,²⁸ stable serum lithium levels increased in a patient by approximately 50% following a 1-week course of oral metronidazole 500 mg b.i.d., accompanied by symptoms consistent with lithium toxicity including ataxia, impaired concentration, dysarthria, malaise and weakness. Hospitalization was required.

Based upon review of the metronidazole vaginal gel professional labeling, and the literature discussed above, it is clearly evident that systemic absorption from vaginal gel products can at times be sufficient to potentially cause any of several concomitant drug interactions. These interactions can be clinically significant and potentially very dangerous, and substantial dosage adjustments of the concomitant medications may prove necessary. Since systemic absorption of vaginal metronidazole is known to be quite

²⁷ Teicher, M.H., Altesman, R.I., et al. 1987. Possible nephrotoxic interaction of lithium and metronidazole. *J. Am. Med. Assoc.* 257:3365-3366.

²⁸ Ayd, F.J. 1982. Metronidazole-induced lithium intoxication. *Int. Drug Ther. Newsl.* 17:15-16.

variable, and there is no known blood level threshold for risks of systemic toxicity, in order to establish bioequivalence, systemic absorption data for both the parent drug metronidazole and the active metabolite, hydroxymetronidazole should be obtained, in addition to data generated from a bioequivalence study employing clinical endpoints, for all metronidazole vaginal gel products including generic versions.

V. An Important Precedent: Mupirocin Ointment

Mupirocin Ointment, 2% (Centany™) was approved for impetigo based in part on equivalent clinical efficacy to Bactroban Ointment® (mupirocin ointment, 2%). However, as part of the Centany™ safety evaluation, a comparative human pharmacokinetic study was also conducted. This was a cross-over study in 23 subjects, with systemic absorption measured by 24-hour urinary excretion of the principal metabolite of mupirocin. A difference between products in systemic absorption of more than 4-fold was described by the sponsor: 0.29% vs. 1.29% for Bactroban vs. Mupirocin Ointment, respectively.²⁹ Calculations performed by the Agency's Clinical Pharmacology reviewer concluded that there were even greater absorption differences between the products, as high as 10-20 fold depending on the method of comparison (major differences in approach centered around selection of the lower level of quantitation, and resultant inclusion of different sets of subjects in the analyses). Consequently, Centany™ has a BX therapeutic equivalence code.

This study clearly highlighted very substantial differences in systemic absorption for two mupirocin 2% topical products that could significantly affect the systemic toxicity

²⁹ Mupirocin Ointment, 2% Summary Basis of Approval (NDA 50-788). 2002. Medical Officer's and Clinical Pharmacologist's Reviews.

risk profiles of these two drugs. It is important to recognize that without conducting the systemic bioavailability comparison, these two drugs with virtually identical clinical efficacy (94% and 95% resolution of infection rates at the test of cure follow-up visit) would have been considered therapeutically equivalent without any suspicion of the large difference in systemic toxicity risk.

VI. **Conclusions**

In conclusion, based upon the foregoing information, the Petitioner hereby requests that the Acting Commissioner of Food and Drugs refrain from taking administrative action regarding the approval and/or the effective date of final approval of ANDAs for a generic version of Metrogel-Vaginal[®] 0.75% (metronidazole vaginal gel) unless the ANDA applicant demonstrates the therapeutic equivalence of the proposed ANDA to the reference listed drug, Metrogel-Vaginal[®] by a two prong approach: (1) the conduct of a bioequivalence study utilizing clinical endpoints in patients with bacterial vaginosis; and (2) through the conduct of a study establishing equivalent pharmacokinetic profiles of both the parent drug metronidazole and its active metabolite, hydroxymetronidazole.

There is sound scientific reasoning for requiring that systemic absorption of both the parent drug metronidazole and its active metabolite, hydroxymetronidazole, be determined for all ANDAs for a metronidazole vaginal gel, 0.75%. Many independent sources have documented that measurable quantities of metronidazole are systemically absorbed after administration of vaginal products, but that the extent and timing of systemic absorption can be quite variable. The blood levels, while substantially lower compared to oral or intravenous dosing, can be clinically significant and can even result in

serious toxicities, principally neurological side effects and drug interactions that potentially require major dosage adjustments.

Knowing the extent of systemic absorption for a new vaginal gel product formulation is important because the demonstration of clinical efficacy based on local eradication of bacterial vaginosis, which may mimic the efficacy of marketed metronidazole vaginal gel, 0.75% preparations, does not predict a product's systemic toxicity profile. Vaginal gel preparations that are clinically equivalent may or may not show equivalent safety profiles. While clinically equivalent, the proposed metronidazole vaginal gel formulations may exhibit different pharmacokinetic profiles with respect to both the parent drug and the active metabolite. The most sensitive and informative way to evaluate and put into perspective clinical trial safety data related to systemically circulating drug would be to quantify systemic exposures with blood level determinations of both the parent drug metronidazole and its active metabolite, hydroxymetronidazole, and subject the data to generally accepted statistical criteria for bioequivalence.

C. Environmental Impact

Pursuant to 21 CFR § 25.31(a), this Citizen Petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic Impact

Pursuant to 21 CFR §10.30(b), Petitioner will, upon request by the Commissioner, submit economic impact information.

E. 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 representative data and information known to the Petitioner which are unfavorable to the Citizen Petition.

Respectfully submitted,

A handwritten signature in black ink that reads "David L. Rosen". The signature is written in a cursive style with a large, prominent "D" and "R".

David L. Rosen, B.S. Pharm, J.D.

cc: Gary Buehler, Director, Office of Generic Drugs

Janice Soreth, MD, Director, Division of Anti-Infective and Ophthalmologic Drug Products