DURAmed® RESEARCH INC.
A subsidiary of Barr Pharmaceuticals, Inc.

Duramed Research, Inc.
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004
(610) 747-2600

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VIA MESSENGER

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

CITIZEN PETITION

The undersigned hereby submits this Citizen Petition, in quadruplicate, pursuant to 21 U.S.C. § 355(j) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as well as 21 C.F.R. §§ 10.20, 10.30, 320.21, 320.23.

A. ACTION REQUESTED

Petitioner Duramed Pharmaceuticals, Inc. respectfully requests that the Office of Generic Drugs of the U.S. Food and Drug Administration ("FDA") make the determination that no Abbreviated New Drug Application ("ANDA") submitted under 21 U.S.C. § 355(j) and referencing Duramed's NDA No. 21-544 for Seasonale® (0.03 mg ethinyl estradiol/0.15 mg levonorgestrel), shall be granted final agency approval unless and until such an ANDA contains

sufficient evidence data to establish bioequivalence in accordance with 21 U.S.C. § 355(j), 21 C.F.R. § 320.21, and 21 C.F.R. § 320.23. Specifically, Petitioner requests that FDA:

1. require all applicants submitting an ANDA referencing Duramed's NDA 21-544 for Seasonale® (0.15 mg levonorgestrel/0.03 mg ethinyl estradiol) to conduct the required bioequivalence tests and studies comparing the proposed generic product to Seasonale®, the reference listed drug ("RLD"), and no other drug product;

2. refrain from granting any bioequivalence waiver for any ANDA referencing Duramed's NDA No. 21-544 for Seasonale® (0.15 mg levonorgestrel/0.03 mg ethinyl estradiol); and

3. require that the results of such tests and studies establish the bioequivalence of any generic Seasonale® product sufficient to permit final approval of any such ANDA pursuant to 21 U.S.C. § 355(j)(8)(A)(ii) and 21 C.F.R. § 320.21.

B. STATEMENT OF GROUNDS

I. Introduction.

Seasonale® is an oral contraceptive ("OC") administered to women for the prevention of pregnancy. It is unique in that it is the first extended-regimen OC ever approved by FDA, and differs from the conventional 21-day and 28-day OC regimens. Under the Seasonale® 91-day extended cycle regimen, the patient takes hormone-containing tablets for 84 days (12 weeks), followed by 7 days (one week) of placebo tablets. Women experience a menstrual-like period once every thirteen weeks, rather than once every four weeks, as with conventional OCs. Duramed spent years developing this first of its kind product, and establishing its safety and efficacy.

The active ingredients in Seasonale® are 0.15 mg of levonorgestrel (progestin) and 0.03 mg of ethinyl estradiol (estrogen). While a 28-day OC regimen might use 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol, Seasonale® is the first OC with a 91-day dosing regimen. The safety and efficacy of any drug product is critical, but it is especially important here because women rely on Seasonale® for the prevention of pregnancy. Indeed, this is one of the reasons that the Agency has deemed this product to be a narrow therapeutic range drug[1]. Thus, it is of the utmost importance to ensure that any ANDA applicant proves that its 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol generic product is bioequivalent to Seasonale®. Accordingly, Duramed respectfully requests that FDA require companies seeking approval to market a generic Seasonale® product to satisfy *all* statutory and regulatory requirements for establishing bioequivalence. Specifically: (1) that any ANDA submitted referencing Duramed's NDA 21-544 for Seasonale® (0.15 mg levonorgestrel/0.03 mg ethinyl estradiol) contain bioequivalence studies comparing the proposed generic product to Seasonale®, reference listed drug ("RLD"), and not to any other drug product; (2) that the Agency refrain from granting a bioequivalence waiver for any ANDA referencing Duramed's NDA 21-544 for Seasonale® (0.15 mg levonorgestrel/0.03 mg ethinyl estradiol); and (3) that the Agency require that the results of such tests and studies establish the bioequivalence of any generic Seasonale® product sufficient to permit final approval of any such ANDA pursuant to 21 U.S.C. § 355(j)(8)(A)(ii) and 21 C.F.R. § 320.21. Only by granting the requested relief can the Agency ensure that consumers will receive safe and effective generic equivalents of Seasonale®.

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[1] Guidance For Industry: Immediate Release Solid Oral Dosage Forms: Scale-up and Post Approval Changes: Chemistry, Manufacturing and Controls, *In vitro* Dissolution Testing, and *In vivo* Bioequivalence Documentation; Center for Drug Evaluation and Research, November 1995 (Appendix A)

II. An ANDA Applicant Must Submit Evidence That Its Proposed Generic Product Is Bioequivalent To Seasonale®, The Reference Listed Drug.

While the innovator drug company must expend considerable resources demonstrating the safety and efficacy of a new drug product, the Hatch-Waxman Amendments to the FFDCA afford a manufacturer the opportunity to receive FDA approval to market a generic drug without submitting the direct evidence of the drug product's safety and effectiveness that is generally required for a New Drug Application ("NDA"). Instead, the generic company may submit an ANDA, which relies upon the FDA's prior finding that the reference listed drug ("RLD") is safe and effective.

In its ANDA, the applicant must establish, *inter alia*, that its proposed drug product is "bioequivalent" to the RLD. *See* 21 U.S.C. § 355(j)(2)(A)(iv). An ANDA applicant's demonstration of bioequivalence to the RLD referenced in the application is critical to obtaining FDA approval. As FDA has explained, "[a] major premise underlying the [Hatch-Waxman Amendments] is that bioequivalent drug products are therapeutically equivalent, and therefore, interchangeable." (Food and Drug Administration, *Approved Drug Products with Therapeutic Equivalence Evaluations*, p. xi (2005 25th ed.)). By requiring the generic version to be bioequivalent to a single RLD, FDA "avoid[s] possible significant variations among generic drugs and their brand name counterpart." (*Id.* (observing that significant variations between brand drugs and generics may occur if generic drugs are "compared to different reference listed drugs.").

The plain language of the statute requires an application submitted under 21 U.S.C. § 355(j) to establish bioequivalence to the specific RLD referenced in the application. For example, a generic drug product is "bioequivalent" when:

> (i) 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; or
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> (ii) the extent of absorption of the drug does not show a significant difference from the 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 and the difference from *the listed drug* in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

21 U.S.C. § 355(j)(8)(B) (emphasis added). Hatch-Waxman also requires an ANDA application to contain evidence sufficient to prove that the proposed ANDA product "is bioequivalent *to the listed drug*." 21 U.S.C. § 355(j)(2)(A)(iv) (emphasis added); *see also Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) ("All ANDAs submitted to the FDA pursuant to section 355(j) must contain 'information to show that the new drug is bioequivalent to the listed drug.'").[2]

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[2] A "listed drug" is "a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." 21 C.F.R. § 314.3(b). The "reference listed drug" is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." *Id.* Seasonale® is the RLD for ANDAs that reference Duramed's NDA No. 21-544. *See* www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=SEASONALE.

FDA's implementing regulations echo this statutory requirement, requiring an ANDA to include "[i]nformation that shows that the drug product is bioequivalent *to the reference listed drug* upon which the applicant relies." 21 C.F.R. § 314.94(a)(7)(i) (emphasis added); *see also* 21 C.F.R. § 320.21(b)(1) (requiring an ANDA applicant to submit "[e]vidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent *to the reference listed drug* (defined in § 314.3(b) of this chapter)" (emphasis added)).[3]

FDA's guidance documents similarly confirm that bioequivalence must be determined by comparing the proposed ANDA product to the RLD referenced in the application:

> In BE [bioequivalence] studies, an applicant c*ompares the systemic exposure profile of a test drug product to that of a reference listed drug (RLD).* For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (see 21 C.F.R. 320.1(e) and 320.23(b)).
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> BE studies are a critical component of ANDA submissions. The purpose of these studies is to demonstrate BE *between a pharmaceutically equivalent generic drug product and the corresponding reference listed drug* (21 C.F.R. 314.94(a)(7)). Together with the determination of pharmaceutical equivalence, establishing BE allows a regulatory conclusion of therapeutic equivalence.

Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Products – General Considerations, at 2, 5 (Mar. 2003) ("BA/BE Guidance") (emphasis added).

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[3] Section 320.21(b)(2) provides that an ANDA could include information sufficient to permit FDA to waive *in vivo* studies. But as discussed, *infra*, FDA should not grant a biowaiver to an ANDA applicant seeking to market a generic Seasonale® drug product.

Accordingly, the relevant statutory and regulatory authorities mandate that any ANDA application seeking to market a generic equivalent of Seasonale® must establish bioequivalence with Seasonale® – the RLD – and cannot establish bioequivalence to Seasonale® by comparing the ANDA product to any other RLD. Consequently, FDA cannot approve an ANDA seeking to market a generic equivalent of Seasonale® where the applicant compared the proposed ANDA product to a different RLD. This is true even if the proposed ANDA product is compared to a different RLD that happens to contain 0.15 mg levonorgestrel and 0.03 ethinyl estradiol.

III. A Manufacturer Seeking To Market A Generic Seasonale® Product Cannot Avoid Having To Establish Bioequivalence To The RLD By Seeking A Biowaiver.

In certain limited instances, an ANDA applicant may request a biowaiver, which eliminates the requirement that an applicant submit evidence demonstrating the *in vivo* bioequivalence of its generic drug product to the RLD. *See* 21 C.F.R. §§ 320.21(b)(2) and 320.22(a). FDA cannot grant a biowaiver allowing an ANDA applicant seeking to market a generic version of Seasonale® to establish bioequivalence by reference to an RLD other than Seasonale®.

For solid, oral dosage forms, FDA may grant a biowaiver to an ANDA applicant only in the following circumstances:

> FDA shall waive the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence of a solid oral dosage form (other than a delayed release or extended release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation [DESI] notice or which is identical, related, or similar to

> such a drug product under § 310.6 of this chapter unless FDA has evaluated the drug product under the criteria set forth in § 320.33, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential bioequivalence problem. A drug product so rated reflects a determination by FDA that an in vivo bioequivalence study is required.

21 C.F.R. § 320.22(c). Seasonale®, approved in 2003, has not been the subject of a DESI notice, nor is it "identical, related, or similar to such a drug product under [21 C.F.R.] § 310.6."

Section 320.22(d) permits a biowaiver for different strength products where the specified criteria are satisfied; where an application contains evidence that the drug product is "shown to meet an in vitro test that has been correlated with in vivo data"; or to a reformulated product that contains different color, flavor, or preservatives where the specified criteria are met. 21 C.F.R. § 320.22(d). To Duramed's knowledge, none of these situations apply to Seasonale®, which has but a single approved strength.[4]

Consequently, Duramed sees no basis under FDA's regulations for the Agency to permit an ANDA applicant referencing Duramed's Seasonale® NDA to obtain a biowaiver. This is true even if an applicant has evidence its ANDA product is bioequivalent to a drug product, other than Seasonale®, that contains 0.15 mg levonorgestrel/0.03 ethinyl estradiol mg.

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[4] The biowaiver provisions of 21 C.F.R. § 320.22(b) do not apply to solid, oral dosage forms, and Duramed is unaware of information that would allow FDA to utilize § 320.22(e) to grant a biowaiver to an ANDA applicant seeking to market a generic Seasonale® product.

As previously discussed, while other drugs approved by FDA may contain 0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol, none are administered using the Seasonale® 91-day extended cycle dosing regimen. Thus, any comparison by an ANDA applicant to a non-Seasonale® drug product containing 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol RLD should not form the basis for obtaining a biowaiver. As FDA has acknowledged, significant variations between brand drugs and generics may occur if generic drugs are "compared to different reference listed drugs." (Food and Drug Administration, *Approved Drug Products with Therapeutic Equivalence Evaluations*, p. xi (2005 25th ed.)).

If the FDA were to approve a generic for Seasonale® based on a bioequivalence study comparing the generic product with a 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol product other than Seasonale®, the generic might very well not be bioequivalent to Seasonale® due to the well-known problem of "bioequivalence creep". This situation can arise when one product ("Product A") is bioequivalent to, but slightly *less well* absorbed than a comparator product ("Product B"), and another product ("Product C") is also bioequivalent to, but slightly *better* absorbed than the same comparator product ("Product B"). In such a case, Product A is not necessarily bioequivalent to Product C. In order to avoid such a situation, which could result in the distribution of a generic version of Seasonale® that is not bioequivalent to the RLD, Seasonale®, the FDA should grant the relief requested herein.

IV. Conclusion.

Seasonale® is the first extended-cycle oral contraceptive containing 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol product with an FDA approved 91-day dosing regimen. This innovative OC not only is a reliable method of birth control, it also reduces the number of menstrual cycles experience by women. The intricacies of this combination drug product require that any generic formulation satisfy all the statutory and regulatory requirements for bioequivalence. Requiring that all ANDA applicants establish bioequivalency by compared to Seasonale® is mandated by the relevant statutory and regulatory authorities.

C. ENVIRONMENTAL IMPACT

Under 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. ECONOMIC IMPACT

According to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

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 that it includes representative data and information known to the petition that are unfavorable to the petition.

Respectfully submitted,

DURAMED PHARMACEUTICALS, INC.

By: _____

Joseph A. Carrado, M.Sc., R.Ph.
Vice President
Clinical Regulatory Affairs
Duramed Research, Inc.