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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
HFA-305
Rockville, MD 20852

Re: Citizen Petition 2003P-0494

Dear Professional Staff:

The Law Offices of Gregory A. Paiva and Associates, on behalf of an unnamed client, hereby submits the following comments in opposition to the above referenced Citizen Petition pursuant to 21 CFR 10.30(d).

On October 24, 2003, Baxter Healthcare Corporation (hereinafter "Baxter") filed a Citizen Petition (hereinafter the "Baxter Petition"). The subject matter of the petition is a request that the FDA refrain from approving any New Drug Application (NDA) for a hyaluronidase product unless the conditions set forth in it's petition are satisfied. Baxter has acquired the rights to the Wydase NDA, Number 06-343, from Wyeth Pharmaceuticals. Wydase is a sterile injectable preparation of hyaluronidase extracted from bovine testicular tissue. The drug product is primarily used to enhance absorption and dispersion of other injected drugs. The most common use of the drug product is to aid in dispersion and absorption of local anesthetics during ophthalmic surgery.

2003P-0494

In its statement of grounds, Baxter states:

1. Wydase®'s safety and efficacy have been demonstrated by over 50 years of clinical use.
2. Naturally occurring hyaluronidases are heterogeneous family of glycoprotein enzymes with different amino acid sequences and species specific glycosylation, different kinetics and different sites of hyalruonic acid cleavage making efficacy and tolerability of each potential product unique and defined both by the raw material source and the production process.
3. The safety and efficacy of Wydase® cannot be extrapolated to any other hyaluronidase product unless that product utilizes the same enzyme source and a similar production process as Wydase®.

Therefore, the safety and efficacy of any new hyaluronidase product must:

1. Be proven by adequately designed and powered clinical trials.
There is significant potential for immunologic adverse events resulting from administration of a complex biological mixture (which may be caused by the presence of minor constituents of the mixture or differences in protein amino acid sequence or glycosylation). Due to the known interspecies variability of immunologic responses and the poor predictive value of preclinical models of immunogenicity, safety of new hyaluronidase products or delivery of the product by a new route of administration (such as

periorbital versus intraocular injection) cannot be assumed and must be demonstrated through properly designed clinical trials; or

2. Be shown to be equivalent to Wydase® as described in appropriately designed and sized published clinical trials through the use of properly validated models demonstrating comparable pharmacokinetics, pharmacodynamics and safety in human tissue; or
3. Be ensured by utilizing an identical raw material source and a comparable production process resulting in a finished product that can be adequately characterized and be shown to be fully equivalent to Wydase®.

For the reasons set forth below, the citizen petition should be denied.

The Baxter Petition fails to acknowledge that Hyaluronidase Injection is a compendial product, with a well established USP monograph, and an available USP reference standard.¹

I. Baxter sets forth no valid scientific or regulatory justification for its request that the FDA bar approval of ANDAs that cite Wydase or DESI Notice 6343 as the reference.

Neither science nor the applicable regulatory scheme supports the notion that FDA should withhold approval of hyaluronidase injection. To do so would be inconsistent with precedent and against public policy.

¹ USP 27/NF 22

A. Hyaluronidase Injection USP has been defined and is adequately characterized by compendia.

The FDA accepts and approves ANDAs and 505(b)(2) NDAs for “drug products that are the same as” or “represents a modification of” the reference listed, i.e., innovator drug.² A drug product is the same as a listed drug if it contains the same active ingredient, and is the same with regard to dosage form, strength and route of administration.³ Baxter argues that bovine testicular Hyaluronidase Injection, USP is not fully chemically characterized and that therefore a Hyaluronidase Injection, USP applicant will be unable to demonstrate sameness unless it uses the innovator’s manufacturing process.⁴ This is a flawed premise because bovine testicular Hyaluronidase Injection, USP, like most drugs, has been adequately defined and characterized and its specifications have been published in scientific compendia.

The USP includes a monograph, which defines Hyaluronidase Injection, USP as “a sterile solution of dry, soluble enzyme product, prepared from mammalian testes and capable of hydrolyzing mucopolysacchrides of the type of hyaluronic acid...⁵” It is well settled that the FDA will not hold generic applicants to a higher standard than the innovator.⁶ Thus, a generic manufacturer 505(b)(2) applicant should be able to rely on

² 21 C.F.R. § 314.92(a)(1); 21 C.F.R. § 314.54

³ Id.

⁴ Baxter Citizen Petition at 3.

⁵ USP 27/NF22 at 913

⁶ See Serono Lab. v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (“FDA observed that Serono controls the batch-to-batch uniformity of Pergonal by

these specifications to demonstrate sameness just as Baxter's predecessor relied on these specifications for batch release.

Even if bovine testicular Hyaluronidase Injection, USP is not completely chemically characterized at this time, this does not preclude FDA from approving generic or 505(b)(2) versions. Lack of complete chemical characterization of the innovator does not bar generic or 505(b)(2) drug products. Various products that, like bovine testicular Hyaluronidase Injection, USP, are derived from natural sources, including proteins, lipids, phospholipids, and oligosaccharides "cannot be fully characterized chemically."⁷ Refusing to approve generic or 505(b)(2) drugs based on the innovator's failure to completely characterize its product would be inconsistent with Congress's intent in enacting the Hatch-Waxman Amendments:

"[I]f Congress had intended to exclude entire categories of drugs from the scope of the Hatch-Waxman Amendments . . . there would be some mention of that fact in the statute or legislative history. Instead, both are wholly silent on the subject. Thus, we conclude, that the statute does not unambiguously require the term 'same as' to be defined as complete chemical identify."⁸

using USP rat potency tests, and that Ferring does the same for Repronex. The agency concluded that 'it would be unreasonable to hold the generic menotropins product to a higher standard of uniformity than the standard used for Pergonal.' (emphasis added).

⁷ Serono Lab v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998).

⁸ Id.

Baxter also raises the issue of variability of chemical structure.⁹ As in the case of incomplete chemical characterization, variability of the chemical structure of an innovator drug does not preclude the FDA from approving generic or 505(b)(2) versions.¹⁰

The FDA's analysis and actions with regard to generic menotropins were upheld by the court and are directly on point. In deciding to approve generic menotropins products, the FDA concluded that some variability of chemical structure was acceptable. Like bovine testicular Hyaluronidase Injection, USP, menotropins products are derived from a natural source, the urine of post-menopausal women. Menotropins contain two active ingredients, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These injectable products are used to treat infertility.

Ferring's ANDA for a generic menotropin (Repronex) was approved by FDA in January, 1997. Serono, manufacturer of the innovator product (Pergonal), sued arguing that the active ingredient in the generic was not the same as the reference listed drug because of different FSH isoforms. The appellate court deferred to FDA's interpretation that FSH in the generic product was the same as that of the innovator, despite variation in chemical structure.¹¹ "In light of the fact that 'most glycoprotein products will have microheterogeneity,' the FDA determined that the relevant 'question is how much variation should be permitted.'"¹²

⁹ Baxter Citizen Petition at 3 - 4.

¹⁰ Serono Lab. v. Shalala, 158 F.3d 1313, 1318 (D.C. Cir. 1998).

¹¹ Serono Lab. v. Shalala, 158 F.3d 1313 (D.C. Cir. 1998).

¹² Serono Lab. v. Shalala, 158 F.3d 1313, 1318 (D.C. Cir. 1998) (emphasis

The chemical structure of FSH consists of a protein backbone and carbohydrate side chains. FDA concluded that the active ingredient in the generic was the “same as” that of the innovator because the protein backbones were identical, and despite variability in the structure of the carbohydrate side chains.¹³ FDA noted that most glycoprotein products would have such variability, and that the question was how much variability the agency would permit.¹⁴ FDA determined that generic menotropins products’ FSH must have the same primary structure (i.e., protein backbone) as the reference listed drug, but that differences in the carbohydrate side chains (isoforms) are acceptable, provided the degree of batch-to-batch variation in the generic is similar to variation in the reference listed drug.¹⁵ FDA approved generic menotropins despite variability in the carbohydrate side chain of FSH.

In the case of menotropins, FDA said that to be considered to have the same active ingredients as the reference listed drug, the generic product must have the same primary structure (which was assured by using the same natural source), the same potency, and the same batch-to-batch uniformity as measured via rat potency tests as specified in the U.S. Pharmacopeia (“USP”).¹⁶ Similarly, FDA should approve generic or 505(b)(2) bovine testicular Hyaluronidase Injection, USP even if there is variability of structure. Nothing precludes FDA from relying on other valid scientific standards: “FDA

added).

¹³ Id. at 1318 (citing Letter from J. Woodcock to Serono, June 17, 1997).

¹⁴ Id.

¹⁵ Id.

¹⁶ See Serono, 158 F.3d 1313, 1318 (citations omitted).

will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia (USP).”¹⁷

B. Baxter erroneously asserts that generic or 505(b)(2) applicants can only satisfy the “sameness” requirement in one of three ways.

Baxter claims that in order to satisfy the sameness requirement, a generic applicant must do one of three things:

1. Be proven by adequately designed and powered clinical trials.

There is significant potential for immunologic adverse events resulting from administration of a complex biological mixture (which may be caused by the presence of minor constituents of the mixture or differences in protein amino acid sequence or glycosylation). Due to the known interspecies variability of immunologic responses and the poor predictive value of preclinical models of immunogenicity, safety of new hyaluronidase products or delivery of the product by a new route of administration (such as periorbital versus intraocular injection) cannot be assumed and must be demonstrated through properly designed clinical trials; or

2. Be shown to be equivalent to Wydase® as described in appropriately designed and sized published clinical trials through the use of properly

¹⁷ 57 Fed. Reg. 17,950, 17,959 (1992) (emphasis added).

validated models demonstrating comparable pharmacokinetics, pharmacodynamics and safety in human tissue; or

3. Be ensured by utilizing an identical raw material source and a comparable production process resulting in a finished product that can be adequately characterized and be shown to be fully equivalent to Wydase®.¹⁸

1. Requiring generic and 505(b)(2) applicants to demonstrate safety and effectiveness through clinical trials is inconsistent with the regulatory scheme.

Baxter's suggestion that bovine testicular Hyaluronidase Injection, USP applicants be required to conduct full clinical trials to demonstrate safety and effectiveness simply ignores the regulatory scheme for approval of generic drugs and section 505(b)(2) of the FD&C Act. Baxter is asking that FDA require more than FDA may legally require in an ANDA. See 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)."). To grant Baxter's request would mean that generic and 505(b)(2) applicants would be required to submit full reports (i.e., a new drug application (NDA)) in order to market a generic version of a drug. Baxter's request is literally impossible. To require clinical studies of safety and effectiveness for approval of an ANDA or 505(b)(2) would mean that the application is no longer an ANDA or a 505(b)(2) application.

¹⁸ Baxter Citizen Petition at 2 - 3

2. Requiring generic or 505(b)(2) applicants to demonstrate safety and effectiveness through clinical trials is inconsistent with the regulatory scheme.

Baxter's suggestion that generic bovine testicular Hyaluronidase Injection, USP applicants be required to conduct full clinical trials to demonstrate safety and effectiveness simply ignores the regulatory scheme for approval of generic drugs. Baxter is asking that FDA require more than FDA may legally require in an ANDA. See 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)."). To grant Baxter's request would mean that generic and 505(b)(2) applicants would be required to submit full reports (i.e., a new drug application (NDA)) in order to market a generic or modified version of an approved drug. Baxter's request is literally impossible. To require clinical studies of safety and effectiveness for approval of an ANDA would mean that the application is no longer an ANDA, and a 505(b)(2) application would in fact become a 505(b)(1) application.

3. Duplicating the innovator's manufacturing process is not required by law; it is not the standard for demonstrating "sameness."

Baxter attempts to equate the requirement that a generic or 505(b)(2) drug product "the same as" the reference listed drug or represents a modification to a listed drug to its premise that the manufacturing process must be the same. This is not the standard set forth by law. The requirements that a generic applicant demonstrate "sameness" and describe its manufacturing process are two separate and distinct requirements, which are addressed at two different sections of the statute: 21 U.S.C. §§ 355(j)(2)(A)(ii)(I)

(sameness) and 355(j)(2)(A)(vi) (description of the manufacturing process).¹⁹ There is no requirement that to achieve “sameness” or the manufacturing process for the innovator and the generic or 505(b)(2) manufacturer be exactly the same.

Even if FDA were to conclude that a generic or 505(b)(2) applicant should duplicate Baxter’s manufacturing process, Baxter has not identified the differences in the manufacturing process that would be unacceptable. Baxter fails to make the case for requiring FDA to hold a generic or 505(b)(2) applicant to a higher standard.

The Baxter Petition specifically addresses Vitase®, an ovine based hyaluronidase. The petition does not specifically request that approval be withheld for any bovine based hyaluronidase.

Baxter states, “Spontaneous reporting of adverse events, including potentially immunologically mediated events, for Wydase® from 1986 to 2003 has demonstrated an acceptable safety profile.”²⁰ The proposed product, 505(b)(2) Hyaluronidase Injection USP, is sourced from the same animal tissues, bovine testicles, as is Wydase®. The Baxter Petition discusses hyaluronidase differences among different species and among differing tissues within a species, but makes no claim of differences between hyaluronidase processed from the same species and tissues.²¹

¹⁹ For parenteral products, such as bovine testicular Hyaluronidase Injection, USP, FDA typically waives the requirement to submit in-vivo bioequivalence data. 21 C.F.R. § 320.22(b)(1).

²⁰ The Baxter Citizen Petition at 7

²¹ *id.*, at 3-4

The Baxter Petition specifically suggests that “ovine-sourced hyaluronidase” as contained in Vitrase®, manufactured by ISTA Pharmaceuticals, Inc., cannot be considered equivalent to bovine testicular based hyaluronidase, such as that contained in Wydase® and a proposed 505(b)(2) Hyaluronidase Injection, USP. At page 5, the Baxter Petition states, “[d]ue to the species-specific as well as the intraspecies, site-specific variability of hyaluronidase, this product (Vitase®) clearly differs from the bovine-derived product, Wydase®, already approved in the United States. Our client does not disagree with the position taken by Baxter in regard to Vitase®. However, there is clearly no indication that a proposed 505(b)(2) Hyaluronidase Injection, USP is different in any manner from Wydase®. Therefore, a proposed 505(b)(2) bovine based Hyaluronidase Injection, USP will demonstrate the same “acceptable safety profile” as seen with Wydase® since both are manufactured from the same starting material, bovine testicles.

The Baxter Petition discusses comparison of Wydase® with a new drug, however the proposed 505(b)(2) Hyaluronidase Injection, USP is not a new drug when compared to Wydase®. The proposed 505(b)(2) Hyaluronidase Injection, USP is a purified enzyme derived from bovine testicular material, processed in a similar manner as Wydase®, and yielding the same drug product. Both Wydase® and the proposed 505(b)(2) Hyaluronidase Injection, USP comply with the USP monograph for Hyaluronidase Injection USP, and the characterization of the proposed 505(b)(2) Hyaluronidase Injection, USP has been much more rigorous than the initial characterization of Wydase®. The Baxter Petition further notes that Wydase® experienced over 50 years of safe and effective clinical use. The efficacy was confirmed by the Drug Efficacy Study

Implementation (DESI) program findings published in the Federal Register on September 23, 1970; 25(185) 14800-1.

For all the aforementioned reasons, the undersigned respectfully requests that FDA deny the Baxter Citizen Petition.

Sincerely,

A handwritten signature in cursive script, appearing to read "Stephen A. Campbell".

Stephen A. Campbell, Esq.
The Law Offices of Gregory A. Paiva & Associates