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Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket Numbers 02P-0506 and 03P-0021 (Petitions for Determination) - Submission of Comments by Merchant-Taylor International, Inc.

Dear Sir or Madam:

These comments are submitted on behalf of Hyalozyme Therapeutics, Inc. (Hyalozyme) in response to two Citizen's Petitions. The first of these petitions (02P-0506) was filed on December 5, 2002, by Lachman Consultant Services, Inc. (Lachman), and requested that the Commissioner of the Food and Drug Administration (FDA) provide a determination as to whether a formerly listed drug, Wydase (hyaluronidase) Injection USP, had been voluntarily removed from the list of approved drugs for safety or effectiveness reasons. The second petition (03P-0021) was filed on January 8, 2003, by Amphastar Pharmaceuticals, Inc. (Amphastar), and requested a similar determination by the FDA. In addition, the Amphastar petition requested that the FDA publish a notice in the Federal Register relisting Wydase (hyaluronidase) Injection USP as an approved drug.

As set forth below, the petitions must be denied based on the following grounds:

1. The regulations providing for the removal of a drug product from the list of approved drug products, 21 CFR 314.162, state that the agency will take such action based upon the presence of safety or effectiveness concerns. Given the problematic history of Wydase prior to its market discontinuation by Wyeth-Ayerst, it is reasonable to assume that the product because of safety or effectiveness

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concerns, yet neither petition provided any new evidence suggesting that their proposed versions of the product are safer or more effective than the FDA believed Wydase to be at the time it was delisted.

2. It is a matter of public record that Wyeth-Ayerst, the manufacturer of Wydase, had substantial difficulty in manufacturing Wydase in a form that was stable. The product was an uncharacterized extract of bovine testicles that, as manufactured by Wyeth-Ayerst, had typically been only about 1% pure (based upon established specific activity of the purified bovine enzyme). This product's notable impurity profile raises stability issues that Wyeth-Ayerst was never able to successfully address.

3. Wydase has proven to be an extremely difficult product to manufacture properly. FDA inspections of the Wydase manufacturing process at Wyeth-Ayerst's Marietta, Pennsylvania plant in both 1995 and 2000 indicated the presence of substantial and continuing problems with the Wydase manufacturing process. Rather than address those problems, Wyeth-Ayerst chose to discontinue manufacture of the product. Unless and until the petitioners present evidence that the version of Wydase which they would propose to manufacture, if the product is relisted as they request, can be manufactured in a form that is safer or more effective than the original delisted product, Wydase should not be relisted.

4. Since early in 2001, when Wyeth-Ayerst announced its discontinuation of Wydase, potential health concerns about crude extract products such as Wydase have increased, rather than diminished. Wydase is manufactured from bovine testicles, which are harvested from cattle that could be infected with bovine spongiform encephalopathy (BSE). The current state of scientific knowledge about BSE suggests that a product of bovine origin, if it came from an animal infected with BSE, could potentially transmit

variant Creutzfeldt-Jakob Disease (vCJD) to a patient when injected into or around the human eye. There is no evidence of which we are aware suggesting that the processes whereby petitioners' versions of Wydase would be manufactured could ensure that vCJD would not be transmitted to the patient. While these are only theoretical concerns at this point, this is a safety issue which needs to be addressed by the agency prior to any consideration being given to the relisting, and subsequent potential approval, of a new version of Wydase.

5. The presence of Wydase on the drug shortage list is not a sufficient reason to warrant relisting the product. While a safer or more effective version of Wydase may well be a "medically necessary" product, the fact that there is a shortage of a product about which there are continuing and unresolved safety or effectiveness concerns does not provide a valid basis for relisting the product, especially in the absence of any new information suggesting that the new versions of Wydase would be any more safe or effective than the original Wydase, which was delisted by the agency.

DISCUSSION

The Delisting Process

According to 21 CFR 314.62, the agency will remove a previously approved new drug product from the list when one of the following conditions are present: 1) the product presents an imminent hazard to the public health; 2) clinical or other experience, tests, or scientific data show that the drug is unsafe for use; 3) new evidence of clinical experience, not in the original application, or tests by new methods, evaluated together with evidence in the original application, reveal that the drug is not shown to be safe; 4) based upon new information not available at the time of approval, considered in conjunction with evidence from the original application, convinces the FDA that there is a lack of substantial evidence from adequate and well-controlled investigations that the drug will have the effect it is purported to have under the conditions of use suggested in the labeling; 5) the application contains any untrue statement of a material fact; or 6) the agency issues

a final decision stating that the listed drug was withdrawn from sale for safety or effectiveness reasons.

Both petitioners assert that Wydase should be relisted because its relisting will enable them to submit an application for a product which is in short supply. Neither petitioner, however, provides any substantive basis to support a finding that one or more of the conditions listed above do not still apply, as they did at the time that the product was delisted. The shortage of supply is not a substitute for providing the agency with evidence that the safety and/or effectiveness issues which led to the delisting of the product are no longer relevant. No such evidence has been provided by either petitioner.

Wydase Had Unresolved Stability Issues

The Hyaluronidase manufactured using Wyeth-Ayerst's process contained less than 1% hyaluronidase enzyme. As described in the original patent (Singher et.al, US2806815), 1000 units of the product contained an average of 1.33 mg., or 750 units/mg of protein. This compares to the known specific activity of bovine hyaluronidase, which is approximately 100,000 units/mg protein under similar assay conditions. Thus, Wydase, as described in its original specifications, contained approximately 0.75% hyaluronidase, and there is evidence suggesting that this lack of purity is directly connected to the lack of stability in the finished Wydase product.

Over 30 years ago, Biorex Laboratories developed a more purified form of bovine testes hyaluronidase (Pope, et.al., US4410531). This product, which was tested in a clinical trials setting but was never commercially available, had specific activity at least 60 fold higher than that reported for Wydase. This material retained over 85% of its activity for up to 21 months, despite the absence of chelating agents and preservatives of the type used with Wydase. Wydase, even with chelating agents and preservatives, lost all activity under similar conditions within 30 days.

Indeed, in 1991, 88,000 vials of Wydase, in its lyophilized form, were subject to a recall because a loss of potency was observed 24 hours after reconstitution. To summarize, a product with perennial stability problems is not an appropriate product for relisting.

Persistent Manufacturing Difficulties

Wydase was a product that had proven consistently difficult to manufacture properly. As noted earlier, on two separate occasions, in 1991 and 1995, the manufacturing facility at Marietta, Pennsylvania where Wyeth-Ayerst manufactured Wydase, as well as other drug products, was inspected by the FDA. A number of the inspectional observations were related specifically to Wydase manufacturing issues. Rather than address those issues, Wyeth-Ayerst chose to discontinue the manufacture and distribution of Wydase. The agency should carefully consider whether it is appropriate to relist a product on the approved products lists when the original manufacturer chose to discontinue the product rather than address key manufacturing issues.

As noted earlier the fact that Wydase is on the drug shortage list is certainly something that the agency should take into consideration when it is making a relisting decision. However Wydase was removed from the approved products list because of agency concerns about its safety and/or its effectiveness. In addition Wydase is difficult to manufacture properly. These factors should receive even greater weight.

New Health Concerns Since Delisting

Thankfully, to date the concern that a product such as Wydase, which is manufactured from bovine testicles, could cause vCJD in patients if they were to receive a product manufactured from a bull infected with BSE, is only a theoretical concern, as there have been no reported cases. On the other hand, given the current state of knowledge about the transmission of vCJD from infected animals, there is

little doubt that a product manufactured from such a bovine source and injected directly into the human eye is capable of causing vCJD. In determining whether or not there is sufficient evidence to warrant the relisting of Wydase, the agency should factor into its decision-making process the increasing knowledge about the dangers associated with the presence of BSE, and the associated safety issues related to products of bovine origin, especially when those products are injected around the human eye.

The Drug Shortage List

FDA's stated policy is to help prevent or alleviate the shortages of medically necessary drug products. This is an important FDA initiative, and one that is worthy of support. Wydase is on the drug shortage list, and it is therefore fully appropriate for the agency to actively consider approaches that might be utilized to make Wydase, or an acceptable version of it, available for medical use.

It is important to realize, however, that there is nothing in the agency's current Drug Shortage Program, nor in the Federal Food, Drug, and Cosmetic Act itself, which requires or indeed permits the FDA to disregard legitimate safety or effectiveness issues with respect to a drug product in short supply. The same standards with respect to a demonstration of safety and effectiveness for its intended use still apply to a product, regardless of whether or not the product is in short supply.

As noted earlier, it appears that Wydase was delisted by the agency, by regulation, because there were legitimate safety or effectiveness issues concerning its clinical use. The product has a demonstrated record of stability problems, is difficult to manufacture properly, and is derived from a bovine source that has the potential to cause vCJD in humans. Until such time as these issues are addressed to the satisfaction of the agency, it would be inappropriate, indeed it would be an abuse of agency discretion, to relist the product. Certainly, neither Lachman Consultant Services nor Amphastar Pharmaceuticals, the petitioners seeking the relisting of Wydase, have provided the FDA with any evidence whatsoever that the issues which led to the delisting of Wydase have been addressed.

CONCLUSION

For the reasons set forth above, the petitions of Lachman Consultant Services and Amphastar Pharmaceuticals, both of which sought an agency determination as to whether Wydase had been voluntarily removed from the list of approved drugs for safety or effectiveness reasons, should be answered by the agency in the affirmative. If either of the petitioners have any new information which would suggest otherwise, they should be requested to submit it to the agency for review and consideration. With respect to the request by Amphastar that the FDA publish a notice in the Federal Register relisting Wydase (Hylaluronidase) Injection as an approved drug, that request should be denied, pending the submission of the requested new information.

Very truly yours,

Bruce Merchant

Bruce Merchant, M.D., Ph.D.
Merchant-Taylor International, Inc.