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Scientific Protein Laboratories LLC

June 22, 2004

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2003D-0206
"Exocrine Pancreatic Insufficiency Drug Products – Draft Guidance for Submitting NDAs", Federal Register, Vol. 69 No.02, April 28, 2004

Dear FDA Representatives:

Please allow me to introduce our company. We are Scientific Protein Laboratories LLC (hereinafter indicated as SPL) located in Waunakee, Wisconsin. SPL is an independently-owned manufacturer of the Active Pharmaceutical Ingredients (API) pancreatin and pancrelipase (Pancreatin API) from porcine pancreas glands. SPL has been manufacturing these APIs at this location for over 25 years. We also produce heparin API from porcine sources. It is worthy to note that FDA regularly reviews our heparin Drug Master File (DMF) and periodically inspects our facility and Quality Systems for our heparin products. In addition, our Pancreatin/Pancrelipase DMF (#9649) was referenced in the Cotazym NDA submitted by Organon and approved by FDA in 1996. There are about 125 employees at our location focused mainly on the heparin and pancreatin business.

SPL is routinely inspected by FDA, USDA, and other regulatory bodies, as well as by the GMP Quality Assurance audit functions of our pharmaceutical customers. We are committed to following cGMPs in our manufacturing processes and have Quality Systems in place for this purpose. We currently supply Pancreatin API to all of the drug product lines endorsed by the Cystic Fibrosis Foundation (reference *Cystic Fibrosis Foundation Newsletter*, Summer 2002.) We estimate that we supply more than 65% of the Pancreatin API used in the manufacture of drug products sold for exocrine pancreatic insufficiency (EPI). We also provide Pancreatin API for the European market.

Because we have more than 25 years of experience in the manufacture of Pancreatin API, SPL is acutely interested in the FDA publication in the Federal Register on April 28, 2004: Docket No. 2003N-0205, "Exocrine Pancreatic Insufficiency Drug Products – Draft Guidance for Submitting NDAs." This letter is intended for comment on the Draft Guidance.

2003D-0206 C6

Summary

SPL enthusiastically supports the FDA's move requiring NDAs for all pancreatin/pancrelipase products for EPI. We agree that this step will promote continued safe and effective use of pancreatic enzyme products for EPI. Marketed products will comply with recognized quality standards applied in the pharmaceutical industry and manufacturers will be expected to adhere to strict GMP guidelines.

We have already begun much of the work connected with the published draft. Because the Agency had reviewed SPL's DMF 9649 in connection with its 2003 review of the NDA filed by Solvay Pharmaceuticals, we have been aware for nearly one year of some of the elements that might be required. Both from our 25+ years of experience in manufacturing, testing and releasing Pancreatin API, and from the work we have done in these recent months, we have an excellent perspective on which of the proposed requirements are possible to implement and which requirements might actually have insurmountable problems associated with their implementation.

We have identified five specific areas to address in this letter, which I will summarize below:

1. Chemical Characterization Requirements and ICH Q6B
As a manufacturer of the drug substance, SPL is currently developing HPLC and SDS-PAGE methods for chemical identity and characterization of the Pancreatin API. The complexity of the product makes this a challenge, since numerous components (>60 peaks by HPLC and >25 bands by SDS-PAGE) have been found during methods development. But, we expect to complete development and optimization of not less than two methods for characterization. From these methods, we hope to establish appropriate release specifications to the satisfaction of the Agency. However, scientific experts with many years of experience in pancreatin analytical challenges indicate to us that the number of protein components and the associated seasonal differences in the animal source may make batch-to-batch consistency in characterization methodology extremely challenging.

2. Viral Clearance Requirements and ICH Q5A
The current SPL manufacturing processes each contain one step that produces some viral reduction for six model viruses. At the request of the Agency, SPL has been working diligently to try to find one or more additional suitable robust, orthogonal viral clearance steps for the Pancreatin API manufacturing process that will not adversely impact the API's chemical, physical, or pharmaceutical properties. This is a severe challenge and one that we are not convinced can be achieved by SPL or any Pancreatin API manufacturer without creating a drug

substance different from currently marketed product in terms of composition with an unknown safety and efficacy profile. Since all of the viral clearance process changes SPL has tried have resulted in the significant degradation of the critical lipase component, we are not certain 1) if the potency of the enzymes is still sufficient to be efficacious and 2) if the "new" API, containing the degradation products from these new processes will match the good safety profile of the product that has been on the market for decades. Since the FDA repeatedly emphasizes the "extensive use of marketed PEP products" in stating that no new toxicology and/or pharmacology studies are necessary, it is critical that we, as the drug substance manufacturer in the United States, point out that the inclusion of new viral clearance steps in the manufacturing process will most likely result in a drug product significantly different – in physical, chemical, pharmacological, stability, and safety characteristics – from the drug as we know it today. It is absolutely critical that the Agency and the industry perform an accurate risk-assessment analysis with regard to absolute viral clearance of the most highly resistant virus against the risk of dramatically changing the important properties of the drug before the guidance document is finalized.

3. <u>Residual Solvents and ICH Q3C</u>

SPL employs two main separate manufacturing processes for Pancreatin API used for EPI, as described in the SPL Drug Master File (DMF) #9469 submitted to the FDA. As a result of the FDA review of the SPL DMF in 2003 in connection with the Solvay NDA submission for their Creon product, SPL has established that the manufacturing processes are capable of reducing the isopropyl alcohol (IPA) concentration to not more than (NMT) 1.0% for one process and NMT 2.5% for the other process. We have instituted IPA release specifications for these limits, effective March 2004. Revising the process to achieve the ICH Q3C requirement of NMT 0.5% may not be achievable. We take the opportunity to mention that the use of the IPA, a Class 3 solvent with low toxicity, is a step that contributes to viral clearance.

4. <u>Stability and the 90-110% Proposed Specification</u>

Although we manufacture the Pancreatin API, as opposed to formulating the drug product, we must state categorically that compliance with a drug product formulation target of 100% of label claim and a typical solid-oral-dosage-form stability specification of 90-110% is not achievable for this product. We believe that it may be possible to tighten the specifications from those currently allowed by USP, as some of our customers already do. But we expect that our customers will also respond to the Agency that the 90-110% range is unlikely to be achieved, particularly if they must formulate at 100% Label Claim. We will leave it to the drug product manufacturers to propose a more reasonable range.

5. Cost Considerations

In the FDA News announcement (P04-48) of April 27, 2004 and in the *"Questions & Answers on Exocrine Pancreatic Insufficiency Drug Products"* section of the FDA announcement on the FDA website, the comment was made that these changes should not impact the cost of the product. We do not know exactly to which costs the FDA was referring in that comment. However, it is clear from the draft guidelines that there will be additional analytical testing required for the chemical characterization of both the API and the finished drug product. The FDA has also asked for a modification of the manufacturing process, if possible, to accomplish an increased level of viral clearance. Just the additional testing alone for the chemical characterization for both the API and the finished drug product, not to mention the analytical development costs, will increase the cost of the API. If manufacturing process modifications are required for viral clearance, there will be major additional expenses related to production costs and production yield losses. Therefore, SPL must state unequivocally that the new requirements for chemical characterization, viral clearance, and stability will definitely increase the cost of manufacturing and testing of these API products.

Above, we have mentioned our five major areas of concern. It is important that the Agency understand that SPL has a considerable body of data available to support the points made regarding chemical characterization, viral clearance, setting of specifications, and the potentially significant ramifications of process modification. Due to the public nature of this document, however, we do not provide the details here. However, SPL will provide this information to the FDA on a confidential basis as needed, or if requested by the FDA.

SPL continues to work diligently to meet the requirements set forth by the FDA in the 2003 review of our DMF and in this recent FDA Draft Guidance. The comments that follow are more general in nature in response to the guidance document.

Detailed Line-By-Line Response to the Draft Guidance Document

Lines 104-105
These lines recommend referencing the ICH guidances Q1A, Q2A, Q2B, Q3C, Q5A, Q5C, and Q6B.

Comment: Add "ICH Q7A" to the list of pertinent guidances.

Comment: Compliance with ICH Q3C for residual solvents (not more than 0.5% by weight for IPA) is not achievable on a routine basis with the current SPL manufacturing processes. Changes to the processes to achieve this level of IPA residual will have a definite impact on the drug product formulations of our customers. Since any process change to drive off the residual IPA is likely to include drying with additional heat, it is likely that such a process change will reduce the enzyme levels and change the ratios of the enzymes. Therefore, we respectfully suggest that the guidance document clarify that the applicant should consult the indicated guidance documents and provide data and justification to support the systems and specifications developed for the PEP named in the submission.

Line 105-106
"*Information unique to PEPs that should be provided in NDAs is described below.*"

Comment: After "*NDAs*", add "*or the referenced Drug Master Files (DMFs).*"

Lines 116-117
"*The manufacturing ... process should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A.*"

Comment: Section V of ICH Q5A provides for the "*Rationale and Action Plan for Viral Clearance Studies and Virus Tests on Purified Bulk*". Based upon this section, Pancreatin API meets the "Case C" criterion in that a relevant virus, porcine parvovirus (PPV) "*for which there is no evidence of capacity for infecting humans,*" is known to be present in all porcine-sourced Pancreatin API from all manufacturers (reference SPL DMF 9649). PPV is a small, non-enveloped virus known to be extremely resistant to viral clearance techniques. PPV is not a human pathogen. It has been detected by quantitative polymerase chain reaction (PCR) testing in Pancreatin API made by all major manufacturers.

SPL has demonstrated through the use of viral spiking studies that one step in the SPL manufacturing process is capable of reducing various model viruses by a reduction of up to 6 logs. However, this step is not capable of reducing the relevant virus, PPV. Therefore, SPL has been conducting research on viral clearance steps that could be added to the current manufacturing process in order to produce effective viral clearance of PPV.

SPL has investigated the scientific literature and conducted tests on processing options that could demonstrate inactivation of viral agents. We believe that our scientific investigation has been thorough. We have investigated solvents, oxidizers, pH extremes, detergents, wet heat, dry heating by various means, gamma irradiation, electron-beam, macrowave, and nanofiltration. In our investigation we have not found any viral inactivation method that can successfully demonstrate acceptable PPV viral clearance without also degrading or reducing the pancreatic enzymes, particularly lipase, to unacceptable levels. In addition, because the enzymes do not degrade at the same rate, changes in the ratios of lipase, protease, and amylase will occur. Due to the limitations associated with analytical testing of such a complex biological API, it will be difficult to determine what degradants may be introduced into the product by any added viral clearance steps. In conclusion, process steps that can be effective against PPV have a high potential for changing the nature of the Pancreatin API that has been on the market for many years.

SPL is concerned that the implementation of any of the potential processing steps for further viral clearance would increase risk to the patient population due to the unknown nature of the degradation products and changes in enzyme ratios. First, as the Agency wisely points out, due to the complexity of the pancreatic extract product, it is unlikely that currently available physiochemical and biological analytical tools – or even with the characterization methods currently in development – will be able to demonstrate with clarity the nature of the degradants that may be produced and/or the effects of these in a clinical setting. Second, SPL has observed that lipase degrades more rapidly than amylase or protease when subjected to viral clearance steps. This results in a change in the enzyme ratios.

In spite of SPL's concerns about the potentially significant effects on the Pancreatin API that could be generated due to process modifications to effect viral clearance, we have continued researching possible viral clearance steps. Our goal is to find

effective clearance steps that do not significantly impact the enzyme composition of the drug substance. SPL has evaluated the multiple potential viral clearance steps and research into an achievable clearance continues to date. SPL will provide information on this research on a confidential basis to the FDA, if requested. The significance of this SPL research to the FDA Draft Guideline is that it may be impossible for any manufacturer to meet the requirements of ICH Q5A to include two robust, orthogonal viral clearance steps into the manufacturing process for Pancreatin API without significant impact on the quality of the drug substance as we know it.

Therefore, SPL recommends that the Agency qualify the requirement for meeting ICH Q5A requirements. We recommend that Lines 116 – 117 be revised to read, *"The manufacturing process (extraction and purification) process should be evaluated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A, where possible. A full viral risk assessment should be made and justified."*

<u>Lines 119-123</u>
"The drug substance should be fully characterized (based upon ICH Q6B) using appropriate ...testing..."

Comment: It is interesting to note that ICH Q6B, in Section 1.3 *Scope* states:

> "The principles adopted and explained in this document apply to ... proteins and polypeptides ... produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.
>
> The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues ... To determine applicability, manufacturers should consult with the appropriate regulatory authorities.
>
> This document does not cover antibiotics, synthetic peptides and polypeptides, heparins..."

We understand, of course, that the FDA is certainly the pertinent regulatory authority in this case. However, as manufacturers of heparin, as well as Pancreatin API, we are wondering why one drug substance sourced from porcine tissue (heparin) is not covered under ICH Q6B, but the FDA is asking us to meet these requirements for another drug substance, also isolated and purified from porcine tissue. We would appreciate an explanation for this seemingly contradictory requirement.

Please also note the comments under lines 132-134, which indicate SPL's concerns regarding our concerns regarding the analytical challenges of chemical characterization for pancreatin.

Line 122-123

"Identity may be demonstrated by fingerprint analysis using (but not limited to) the following methods:

- *Chromatography...*
- *SDS-PAGE...*
- *Isoelectric focusing..."*

Comment: SPL recommends a slight change to the verbiage. As written, this statement may be interpreted to *require* the use of all three techniques indicated, which may or may not be feasible for this product. We believe that the intent of the verbiage is to suggest these three techniques as the starting place for chemical characterization, without limiting development to these three method types. Therefore, we suggest a revision, such as:

"Identity should be demonstrated by fingerprint analysis. Consider using the following types of methods:

- *Chromatography...*
- *SDS-PAGE...*
- *Isoelectric focusing...*
- *Appropriate new analytical technology that can be shown to be appropriate to meet the requirements of the guidelines.*

Lines 132-134

"*Specifications for the drug substance should include tests for identity, biological activity of different classes of enzymes, purity, and other relevant attributes. Appropriate acceptance factors (e.g. limits and ranges) should be established and justified."*

Comment: Of particular concern to SPL (and, we expect, to all manufacturers of Pancreatin API) is the statement in the guidance document stating that specifications should be set for purity. ICH Q6B also indicates that specifications should be set for purity and impurity requirements (Section 2.1.4.). The ICH document acknowledges that determination of absolute or relative purity presents *"considerable analytical challenges."* It further states, "*Historically, the relative purity of a biological product has been expressed in terms of*

specific activity... which is also highly method-dependent." In the case of impurities, the ICH document identifies product-related and process-related impurities. Given the state of knowledge of Pancreatin API that has been marketed for in excess of 50 years, it is difficult, if not impossible, to determine which components are active and which "do not have properties comparable to those of the desired product..."

SPL is in the process of having appropriate chemical characterization methods developed. We have had some success with SDS-PAGE and Reversed Phase-HPLC. We are also evaluating ion-exchange and size exclusion HPLC. It is extremely important to note that initial evaluation by these types of methods has produced in excess of 60 peaks (HPLC) or 25 bands (SDS-PAGE). We are continuing to develop and optimize these methods. However, it is important to note that establishment of typical release or stability specifications for purity and/or impurities based upon such methods, given the complexity of this drug substance, may be extremely difficult.

It is also important to note that in ICH Q7A, Section 11.21, it states, *"Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin."* It is apparent that the developers of that guidance, along with those who developed ICH Q6B and eliminated heparins in the scope of the document, understood the difficulties associated with separation and identification of the large number of components that may be present in such APIs.

ICH Q6B indicates that acceptance criteria for purity and for impurities should be set, as appropriate. Given the sheer number of peaks or bands we are already finding in our characterization development, we expect to find it difficult or impossible to distinguish purity or impurities by means of chemical testing. Given this history and complexity of the API, as well as the probable limits of the chemical characterization methods currently in development, it will be extremely difficult to determine which components are truly impurities and which supply pharmacological effect. Therefore, we suggest that the guidance document make some allowances for the nature of the Pancreatin API with respect to ICH Q6B requirements.

We also respectfully submit that complete characterization for chemical purity and impurity may not be a completely value-added exercise for this product. Given the historical fact that pancreatin drug products have been on the market for over 50 years, it is

apparent that some impurity differences are likely to have existed without significant safety hazard to the patient population during that time.

Therefore, we respectfully suggest that the guidance document state clearly that 1) impurity profiles and/or specifications for release or stability are not suitable for this product, and 2) that purity be evaluated by appropriate biological activity assays.

SPL plans to prepare a package detailing our chemical characterization work (along with the viral risk assessment research) for submission to the FDA - along with a request for a meeting – in the third quarter 2004. At our joint meeting, we expect to provide more detailed information on feasibility of full compliance with ICH Q6B and ICH Q5A and the future of Pancreatin API.

<u>Lines 154-155 & 162-163</u>
"Primary stability studies should be performed with batches that are formulated to be released at 100 percent of the label-claimed potency. The proposed shelf-life should not depend on the existence of a stability overage."

Comment: Although these lines do not directly impact SPL, since we do not formulate the drug product, this is such a critical issue for the pancreatin drug market that we feel compelled to comment on this requirement. We understand the Agency's concern with regard to inconsistent dosing of the patient due to large overages allowed by the USP monograph. However, compliance with a drug product formulation target of 100% of label claim, with a typical synthetic solid oral dosage form stability specification of 90-110% is not achievable for this product. Although it may be possible to tighten the specifications from those currently allowed by USP (as some of customers currently do), we expect that our customers will also respond that the 90-110% range is unlikely to be achieved, particularly if they must formulate at 100% Label Claim. We will leave it to the drug product manufacturers to propose a more reasonable range based upon their stability data that will assure a more consistent dosing for patients, without leaving them without a viable product.

Stability studies for the drug substance may be made to comply with ICH Q5C, with one notable exception. Please note that, at the request of the FDA during review of SPL's DMF #9649 last year, SPL has instituted a stability evaluation comparing the potency of each batch as reported at Time Zero, with potency at successive timepoints. Once characterization methods have been developed

and evaluated for their usefulness in stability studies, SPL will institute the appropriate tests and limits or specifications for the drug substance. However, the same issues that were raised earlier with regard to purity and impurities apply to stability studies, as well.

Detailed Response to the FDA "*Questions and Answers on Exocrine Pancreatic Insufficiency Drug Product*"

#18.
"We do not expect prices to change as a result of this action. Our economic analysis of this action found that, although some firms may choose to leave the market, enough manufacturers would continue producing pancreatic enzyme products that the market would remain competitive."

Comment: SPL agrees with the final sentence, which indicates that more than one company will continue to market the products. However, we must also wholeheartedly disagree with the statement that the prices will not be expected to change as a result of the increased regulatory requirements for the pancreatin drugs.

SPL, as the sole major U.S. manufacturer of APIs for pancreatic insufficiency products, will incur significant increases in manufacturing costs due to the new regulatory requirements indicated in the draft guidance document. These cost increases will be passed on to the manufacturers of these drugs. These manufacturers will presumably increase their prices to reflect their increased costs.

SPL has calculated that the projected increase in costs to SPL, excluding major changes to the manufacturing process for additional viral clearance steps, will exceed 20%.

Conclusion

This concludes SPL's comments on the draft guidance and the Q&A report. We appreciate the opportunity to provide input to the process of improving consistency in the dosage forms provided to EPI patients. We ask that the Agency seriously consider our comments as provided herein with particular attention to the five major areas of concern to SPL in the Guidance document and/or the FDA publications:

1. Chemical Characterization Requirements and ICH Q6B
2. Viral Clearance Requirements and ICH Q5A.
3. Residual Solvents and ICH Q3C

4. Stability and the 90-110% Proposed Specification
5. Cost Considerations

SPL will continue to work to meet the requirements that are scientifically based and achievable. As stated previously, SPL has a considerable body of data available to support the points made above regarding chemical characterization, viral clearance, setting of specifications, and the potentially significant ramifications of process modification. SPL will provide this information to the FDA on a confidential basis as needed, or if requested by the FDA.

If you have questions or would like to discuss the points presented, please contact me by telephone at (608) 849-5944 or by email at koisc@splpharma.com. SPL is ready and willing to send a representative to further discuss our concerns, if the Agency would benefit from such a discussion. Please note that we at SPL have notified our customers, the drug product manufacturers, of this response to the FDA publications. We look forward to working with you.

Sincerely,

Christine E. Kois
Director, Quality and Regulatory Affairs

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