



ISO 9001 - 2000



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Certificate # 010564

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Dear Sir or Madam:

RE: **Docket No. 2003D-0206**, CDER 200275 (Draft) Guidance for Industry *Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*, Federal Register, Vol. 69, April 28, 2004 [FR Doc. 04-09653]

Please find attached our written comments regarding the aforementioned docket number.

A Microsoft word copy of this document was submitted electronically on June 28, 2004 (Temporary Comment Number 3550) and a copy of the electronic submission confirmation is attached.

If you have any questions concerning this matter please feel free to contact me at 905-689-3980 ext. 253 or by e-mail at [sindrarajah@canreg.ca](mailto:sindrarajah@canreg.ca)

Yours sincerely,

Subha Indrarajah, M.Sc., RAC  
Senior Regulatory Affairs Associate  
CanReg Inc.

2003D-0206

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Head Office, Canada: 4 Innovation Drive, Dundas, ON L9H 7P3

Tel: 905-689-3980 Fax: 905-689-1465 Toll Free (North America only): 1-866-722-6734

U.S.A.: 450 North Lakeshore Drive  
Mundelein, IL 60060  
Tel: 847-837-8824 Fax: 847-837-8825

Europe: Willeville Lodge  
Carlingford, County Louth, Ireland  
Tel/Fax: +353-42-9376740

Websites: [www.canreg.ca](http://www.canreg.ca) [www.canreg.info](http://www.canreg.info) Email: [info@canreg.ca](mailto:info@canreg.ca)

### Docket Management Comment Form

Docket: 2003D-0206 - Draft Guidance for Industry on Exocrine Pancreatic Insufficiency Drug Products--Submitting New Drug Application; Availability

Temporary Comment Number: 3550

Submitter:	Ms. Subha Indrarajah	Date:	06/28/04
Organization:	CanReg Inc. on behalf of Axcan Scandipharm Inc.		
Category:	Drug Industry		
<b>Issue Areas/Comments</b>			
<b>General</b>			
RE: Docket No. 2003D-0206, CDER 200275 (Draft) Guidance for Industry Exocrine Pancreatic Insufficiency Drug Products ? Submitting NDAs, Federal Register, Vol. 69, April 28, 2004 [FR Doc. 04-09653]			



**Print** - Print the comment  
**Exit** - Leave the application

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Dear Sir or Madam:

RE: **Docket No. 2003D-0206**, CDER 200275 (Draft) Guidance for Industry *Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs*, Federal Register, Vol. 69, April 28, 2004 [FR Doc. 04-09653]

Axcan Scandipharm (Axcan) is a leading specialty pharmaceutical company that develops, manufactures, markets and distributes a broad line of gastrointestinal products primarily in North America and Europe.

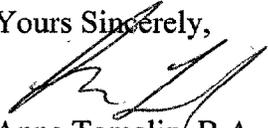
Axcan is a key player in the field of exocrine pancreatic insufficiency (EPI) with such products as VIOKASE<sup>®</sup> (US and Canada), ULTRASE<sup>®</sup>/ULTRASE<sup>®</sup> MT (US and Canada), and PANZYTRAT<sup>®</sup> (Europe, Latin America) currently on the market. As such, Axcan is keenly interested in the Agency's current views on this topic as outlined in this draft guidance document. Axcan also appreciates this opportunity to provide feedback to the Agency.

Axcan agrees with the Agency that standardization is required in the development of these products in order to minimize adverse events and therapeutic failures, and to ensure that patients receive reliable therapy that is both safe and effective.

Our comments regarding the draft guidance are organized below by subject headings as presented in the guidance document.

If you have any questions concerning these comments please feel free to contact me at 905-689-3980 or by e-mail at [atomalin@canreg.ca](mailto:atomalin@canreg.ca).

Yours Sincerely,



Anne Tomalin, B.A., B.Sc., RAC (US & EU)  
President, CanReg Inc.  
Regulatory Consultant to Axcan Scandipharm Inc.

cc: Dr. François Martin  
Senior Vice President, Scientific Affairs  
Axcan Scandipharm Inc.

Head Office, Canada: 4 Innovation Drive, Dundas, ON L9H 7P3  
Tel: 905-689-3980 Fax: 905-689-1465 Toll Free (North America only): 1-866-722-6734

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Tel: 847-837-8824 Fax: 847-837-8825

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Tel/Fax: +353-42-9376740

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**COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY - Docket No. 2003D-0206  
*Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs, April 2004***

**III. CHEMISTRY, MANUFACTURING, AND CONTROLS SECTION OF  
THE APPLICATION**

**A. Drug Substance**

*Lines 116-117*

Drug substance manufacturers have informed us that while their established manufacturing process is capable of providing viral reduction for various model viruses, the process is not effective against two specific model viruses: Porcine Parvovirus (PPV) and Encephalomyocarditis virus (EMCV). Viral clearance/inactivation methods that have been effective against the latter viruses have also resulted in the loss of enzymatic activity and the degradation of the enzymatic components. Thus far, a suitable method/technique to inactivate and/or remove these viruses that also does not compromise the integrity of the pancreatic enzyme preparations (PEPs), which are intended for oral use, has not been found. While Axcan recognizes that it is imperative to remove and/or inactivate viral agents during the manufacturing process, we request that the Agency make a realistic assessment as to the feasibility of achieving complete viral removal/inactivation. Also, as part of this assessment, an evaluation should be made concerning the potential risk a particular resistant virus poses to human subjects; for example, PPV is not known to be a human pathogen. One study demonstrated that in hemophilia patients, inadvertent and repeated concomitant injections of PPV contained within a porcine factor VIII concentrate did not yield measurable levels of anti-PPV IgG antibodies in one hundred patient sera tested. This virus is also known to be contained within food products at relatively high levels, without clinical concern or manifestations.

*Lines 119-130*

Axcan agrees with the Agency that a better characterization of PEPs is necessary. However, the extent of such a characterization should not be excessive due to the innate limitations of working with biological tissues as opposed to recombinant biological products. For example, since PEPs are derived from a mixture of different porcine gland extracts, variability in the relative quantities of each enzyme from sub-batch to sub-batch is expected prior to potency adjustments in the final blending step. The Agency has commented on this very fact on *Line 85 Because of the complexity of pancreatic extract products, it is unlikely that currently available physiochemical and biological analytical tools would be able to demonstrate that the active ingredients in pancreatic extract products from two different manufacturers are the same.* This statement also holds true for different batches from the same manufacturer.

*Lines 132-134*

The Agency has proposed that specifications for the drug substance include various tests with appropriate acceptance factors. Due to the biological nature of the drug substance and the inherent challenges that this poses, establishment of release or stability specifications for purity and impurities that are typical for chemical synthetic products is neither practical nor realistic. Drug substance manufacturers are currently attempting to develop appropriate characterization methods. Initial evaluations by these methods have confirmed the complex nature of these products, i.e., a very high number of peaks were revealed by HPLC analysis and numerous bands were observed by SDS-PAGE analysis. Identifying these peaks and establishing correlations with enzymatic activity is a challenge for drug substance manufacturers and it is unlikely that any attempt to distinguish purity or impurities by means of chemical testing would be successful. Also, any method that would discriminate the minor impurities not identified by HPLC would be very difficult to manage and may prevent the release of product systematically. Axcan requests that the Agency take these factors into consideration prior to the finalization of this guidance document.

**B. Drug Product**

*Lines 138-142*

The challenge of working with complex biological materials carries forward to the finished drug product, and the same issues as outlined above under *Lines 132-134* are also applicable under this section.

**C. Stability**

*Lines 153-156*

Axcan agrees with the Agency that primary stability studies should be carried out according to ICH Q1A and Q5C. However, with respect to the issue of batches formulated to be released at 100 percent of the label-claimed potency, please see comments below under *D. Overages*.

**D. Overages**

*Lines 162-165*

While Axcan agrees with the Agency that tightening the release potency of the finished drug product may reduce variability in the potency of the final product, we would like to point out that (as the Agency comments on *Line 146*) *due to the inherent lability that has been observed with PEPs* it is not feasible or realistic to formulate PEPs to be released at 100 percent of the label-claimed potency. Based on our extensive experience with these products, we have found that in order to maintain a reasonable shelf-life, an overage of at least 25% is needed.

### **E. Dissolution Method**

No comments.

## **IV. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION**

### **A. Toxicology**

No comments.

### **B. Pharmacology**

No comments.

## **V. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION**

### *Lines 204-211*

The requirement to conduct studies to determine the bioactivity and/or bioavailability of the active ingredients at the site of action for all PEP NDAs may not be realistic. Intestinal perfusion studies are extremely challenging to perform for various reasons. Patient recruitment will be problematic due to the inconvenience posed to the subject and the inherent risks involved with the technique. As a result, such studies will present ethical dilemmas especially in children. Additionally, centers qualified to perform these studies are limited with only three such sites in the United States. Results obtained from these studies will also be subject to interpretation as gastrointestinal transit time is very variable from patient to patient. If a PEP has been shown to be effective in clinical trials, then it is not critical to demonstrate the *in vivo* release profile of the product in addition to the *in vitro* one. Therefore, it is our recommendation that these studies should not be mandatory.

## **VI. CLINICAL STUDIES FOR NEW PEPS (SECTION 505(b))**

### **A. Considerations for Clinical Trial Development**

### *Lines 235-237*

While dose ranging studies are generally conducted for pharmaceutical products, such studies should not be required for PEPs as enzyme replacement doses are determined based on individual patient body weights and lipase needs. Furthermore, it is well established that the more enzymes you administer, the more substrate is digested.

## **B. Patient Populations in Clinical Studies**

*Lines 244-250*

Axcan recognizes that in certain population groups there is a greater clinical need for PEPs. However, it should not be mandatory to conduct studies in pediatric patients with cystic fibrosis. The nature of the clinical studies conducted should be to support the indication sought. Therefore, a sponsor should only be required to conduct clinical studies in pediatric patients with cystic fibrosis if an indication in cystic fibrosis is being pursued.

## **C. Endpoints (Outcome Measures) Efficacy**

*Lines 254-271*

Axcan recognizes that the 72-hour fecal fat test (FFT) is the current gold standard. However, other less cumbersome tests should be encouraged as long as they are validated; for example, the steatocrit test and the C13 triglyceride test.

## **D. Safety**

No comments.

## **E. Design**

No comments.

## **VII. PEDIATRIC STUDIES FOR PEPS**

No comments.