



**Eurand S.p.A.**  
Via Martin Luther King, 13  
20060 Pessano con Bornago  
Milano (Italy)  
Phone +39 02 954281  
Fax +39 02 95745012 - +39 02 95745018  
www.eurand.com

June 25, 2004

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

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**“Exocrine Pancreatic Insufficiency Drug Products – Draft Guidance for Submitting NDAs”**  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

Dear Sir or Madam:

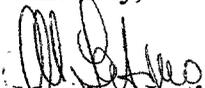
Enclosed please find comments from Eurand for the Draft Guidance for Submitting NDAs on Exocrine Pancreatic Insufficiency Drug Products, published in the Federal Register on April 28, 2004, Docket No. 2003N-0206. The comments to the various sections are presented in the order in which they appear in the guidance.

Eurand is an Italian-based company, owned by the US private equity investment firm, EM Warburg Pincus. The Company is specialized in bioavailability enhancement of poorly-soluble drugs, modified-release oral dosage forms and taste-masking. Eurand’s principal operating offices are in Milan, Italy and in Vandalia, Ohio. The Company has research, development and manufacturing facilities in Italy, the United States and France. Since the early 1990s, Eurand has developed a Drug Product consisting of capsules filled with delayed-release minitablets containing Pancrelipase to obtain different labeled enzymatic amounts of lipase, amylase and protease. This Drug Product has been licensed to the US Company Axcan Scandipharm Inc. (22 Inverness Center Parkway, Birmingham, AL 35242) and has been marketed under the name “Ultrase MT”. Eurand has been manufacturing this Drug Product at its location in Italy for over 12 years.

Eurand appreciates the opportunity to provide feedback and suggestions for this guidance. If you have any questions about our comments, please do not hesitate to contact me at the following e-mail address: [mlatino@eurand.it](mailto:mlatino@eurand.it).

Thank you for your consideration.

Sincerely,



**Massimo Latino**

Director  
Regulatory Affairs Europe

2003D - 0206

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## Comments on the Guidance

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

#### Lines 116-117

***“The manufacturing process should be validated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A.”***

Assessment of viral clearance capability to remove and/or inactivate viral agents, as recommended in ICH Q5A, plays an important role in establishing the safety of PEP products. Two API manufacturers have conducted appropriate process evaluation studies of viral clearance in which “relevant” and/or specific “model” viruses have been used to determine the ability of the manufacturing process to remove and/or to inactivate these viruses. They have demonstrated through the use of viral spiking studies that their established manufacturing process is capable of removing specific model enveloped viruses. However, the process is not capable of reducing two specific “model” non-enveloped viruses, in particular, Porcine Parvovirus (PPV) and Encephalomyocarditis virus (EMCV). As a result, they have conducted studies on viral clearance steps that could be added to their current manufacturing process in order to produce effective viral clearance of non-enveloped viruses. Their efforts include the use of solvents, oxidizers, pH extremes, detergents, wet heat, dry heating by various means, gamma irradiation, electron-beam, microwave, and nanofiltration. Unfortunately, neither manufacturer thus far has found any viral inactivation method that can successfully demonstrate acceptable PPV or EMCV clearance without also degrading or reducing the pancreatic enzymes, particularly lipase, to unacceptable levels. 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 as a result of any added viral clearance steps. In conclusion, process steps that can be effective against non-enveloped viruses have a high potential for changing the nature of the Pancrelipase API that has been extensively marketed for many years, thus having a potentially serious impact on the drug’s quality, safety and efficacy.

We are concerned that the implementation of any potential processing steps for further viral clearance would increase the risk to the patient population due to the unknown nature of the degradation products formed as a direct result of the inactivation process.

We recommend that Lines 116 – 117 be revised to read, *“The manufacturing process (extraction and purification) should be evaluated for its capability to remove and/or inactivate viral agents as recommended in ICH Q5A, where possible. A viral risk assessment should be made and justified.”*

#### Lines 122-123

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

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

This statement may be interpreted to require the use of all three techniques indicated, which may or may not be feasible. We agree that these three techniques should be considered the starting point for fingerprint analysis. We recommend that Lines 122-123 be revised to read, *“Identity may be demonstrated by fingerprint analysis using an appropriate methodology (e.g., ion-exchange or reversed phase HPLC, SDS-PAGE, isoelectric focusing). Other analytical methodologies should be used when appropriate”*.

**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.”***

Two API manufacturers are developing appropriate chemical characterization methods. They are having some success with some of the techniques proposed in this guidance. Establishment of typical release or stability specifications for purity and/or impurities based upon such methods, given the complexity of the API, may be extremely difficult. Given the very high number of peaks or bands already found in ongoing API characterization studies, it may be difficult if not impossible to distinguish purity from impurities by means of biochemical testing. Furthermore, given the use of Pancrelipase Drug Products in the world for over 50 years, it is reasonable to assume that some impurity differences are likely to have existed without significant safety hazard to the patient population.

We recommend that Lines 132-134 be revised to read, *“Specifications for the drug substance should include tests for identity, biological activity of different classes of enzymes, purity, and other relevant attributes. When appropriate, acceptance factors (e.g., limits and ranges) should be established and justified.”*

**Lines 138-140**

***“Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradants, dissolution, and other relevant attributes. Appropriate acceptance factors should be established and justified.”***

For the Drug Product, we are developing appropriate chemical characterization methods based on the same techniques and methodologies developed for the API. The same comments given above for the Drug Substance are applicable also to the Drug Product.

We recommend that Lines 138-140 be revised to read, *“Specifications for the drug product should include tests for identity, biological activity of different classes of enzymes, degradants, dissolution, and other relevant attributes. When appropriate, acceptance factors (e.g., limits and ranges) should be established and justified.”*

**Lines 154-155 & 162-163**

***“Primary stability studies should be performed with batches that are formulated to be released at 100 percent of the label-claimed potency.”***

***“The finished product should be formulated to be released at 100 percent of the label-claimed potency ...”***

This is a very critical issue for all Pancrelipase Drug Product manufacturers. We have worked with these formulations for 15 years and it has been our experience that an overage is required to achieve a reasonable shelf-life. 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 at release, with a typical solid oral dosage form stability specification of 90-110%, may not be achievable for this product. The USP Monograph for Pancrelipase-based products allow overages of up to 65%. This is because the nature of these enzymatic preparations is such that there is a rapid decline of activity that makes it difficult to maintain a reasonable shelf-life without an overage. According to the ICH Q6B requirements (Chapter III Justification of the Specification), *“specifications should account for the stability of drug substance and drug product”*. In particular, it is stated that *“Degradation of drug substance and drug product, which may occur during storage, should be considered when establishing specifications”*. Stability results for two different formulations of Pancrelipase Drug

Product over a period of 24 months have clearly demonstrated the need for an overage, although not necessarily as high as what is allowed in the USP Monograph. If requested, we are able to provide to the Agency the relevant supportive documentation.

#### **IV. NON CLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION**

##### **Lines 235-237**

***“For NDA approval of any particular PEP, clinical studies should demonstrate a relationship between the extent of the clinical benefit and the amount of PEP administered (e.g., empirical demonstration of dose-response relationships in clinical trials).”***

In Cystic Fibrosis (CF), the dose of pancreatic enzymes is always titrated by the physician on a per-kilogram body weight basis. Furthermore, it is a known fact that CF patients usually learn to self-adjust their dose also on the basis of their daily dietary intake. It is therefore our opinion that, in CF trials, proof of a “dose-response relationship” (besides the fact that different doses are used by different patients to obtain the same therapeutic effect, i.e., control of symptoms and signs of fat malabsorption) should not be required.

##### **Lines 248-250**

***“At a minimum, because cystic fibrosis is primarily a pediatric disease, the efficacy studies in the NDA should include clinical studies in pediatric patients with cystic fibrosis.”***

Since pediatric studies always pose more complex ethical and organizational problems than studies in adults, it would be advisable do define an acceptable age range for the “pediatric” population. In fact, the ethical consideration related to and the feasibility of some study designs may be greatly influenced by the age of the patients involved.

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

##### **Lines 204-207**

***“The bioactivity and/or bioavailability of the active ingredients should be determined at the site of action (gastrointestinal tract). The lipase, amylase, and protease activities should be determined from aspirates from the stomach and duodenum. The data should be obtained under fasting conditions as well as after a standard meal stimulation”***

The placement of a gastric or a duodenal tube causes clinical and ethical problems in children with CF and is not without risks, in our opinion, even in adult patients with CF. These patients, in fact, are especially prone to serious and even life-threatening respiratory tract infections, thus enhancing the potential danger of any invasive manoeuvre involving the airways. More importantly, the results of stomach and duodenum aspiration trials performed in healthy volunteers and/or chronic pancreatitis patients are not necessarily relevant to CF patients. There are in fact several published papers confirming that the gastrointestinal environment in CF patients differs significantly from the environment of normal subjects, including prolonged transit time and/or lower postprandial pH. It is therefore our opinion that the aspirates trials in normal subjects as outlined in the draft guidance would not provide clinically relevant information pertaining to CF patients. Furthermore, since pancreatic enzymes are in practice given during a meal, the behaviour of a formulation of pancreatin under fasting condition is not relevant from the clinical point of view.

Based on the above consideration that the aspirates trials in normal adults and children not only could pose serious ethical and safety questions but also not likely to provide any clinically useful

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and/or relevant information regarding the performance of the drug product in CF patients, we strongly recommend that Lines 204-207 be deleted.

**Comments on the FDA News announcement (P04-48) of April 27, 2004 and the “Questions & Answers on Exocrine Pancreatic Insufficiency Drug Products” section of the FDA announcement on the FDA website**

In these two documents, FDA suggested that the recommended requirements for an NDA product described in the Guidance (such as viral clearance step in the drug substance manufacturing process and analytical characterization of the Drug Substance and the Drug Product) should not impact the cost of the product. We do not agree with this comment for the following reasons:

1. it is clear that there will be additional analytical testing required for the characterization of both the Drug Substance and the Drug Product. Just the additional testing alone, not to mention the associated analytical development costs, will increase the cost of the product;
2. if manufacturing process modifications are required for viral clearance/deactivation as suggested in the guidance, there will be major additional expenses related to production costs (e.g. additional labor and equipment time, additional purification steps);
3. to improve the drug product stability and to reduce overfill at the minimum needed level, more protective and expensive packaging materials may be required.

Due to the new regulatory requirements recommended in the draft guidance, Drug Substance and Drug Product manufacturers will likely incur significant increases in manufacturing costs associated with the future production of PEPs.