

Edward B. Silberstein, M.D.

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2897 '98 DEC -7 19:52

November 2, 1998

Jane Axelrad, Esq.  
Associate Director for Policy  
Center for Drug Evaluation and Research  
Food and Drug Administration  
1451 Rockville Pike, Room 6027  
Rockville, Maryland 20852

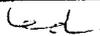
Dear Jane:

It was a pleasure working with you and your group October 27. The open and honest interchange, with each member of the group trying to reach the best possible clarification and understanding of the written material we worked on, was most gratifying.

I have authored two papers on adverse reactions to radiopharmaceuticals: one for non-PET drugs, for which a reprint is enclosed; the other, for PET drugs, which will appear in the November or December Journal of Nuclear Medicine. I have enclosed a preprint of this latter article. As you can see, these drugs have a risk which is roughly 0.1% that of contrast media. Therefore it is difficult for us to deal with Guidance documents which relate to contrast media as well as radiopharmaceuticals when the safety thresholds are so very different.

You and your group have put a new face on the Food and Drug Administration CDER for us, and I very much appreciate your effort.

Sincerely,



Edward B. Silberstein, M.D.  
Eugene L. and Sue R. Saenger Professor  
of Radiological Sciences

cc: Frank Barletta  
Elizabeth Falentino, Esq.  
Jerome Halprein  
Keith Johnson

EBS/rs

98D-0266

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Silberstein, Edward B., Janet Ryan and the Pharmacopeia Committee of the Society of Nuclear Medicine, 'Prevalence of Adverse Reactions in Nuclear Medicine,' *Journal of Nuclear Medicine*, Vol. 37, No. 1, January 1996, pp. 185-192.

Silberstein, Edward B., 'Prevalence of Adverse Reactions in Nuclear Medicine, Erratum' *Journal of Nuclear Medicine*, Vol. 37, No. 6, June 1996, pp. 1064-1067.

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December 8, 1997

Dear Dr. Silberstein,

Thank you very much for your letter of October 16 concerning the safety of PET radiopharmaceuticals in humans.

I read your data which were presented at the Society of Nuclear Medicine Annual Meeting in San Antonio with the greatest interest. I should be very pleased when you could send me the manuscript about this data, when finished, of course under the highest confidentiality.

With kind regards,



Dr. Hans H. van Rooy



Improving Healthcare and Chemistry

## Telefax

Nuclear Medicine, Petten  
Regulatory Affairs

Dr. H.H. van Rooij  
Ass. Director Regulatory Affairs

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To : Dr. E.B. Silberstein  
Company : University of Cincinnati Medical Center  
Fax Number : 1-513-558-7690  
Date : October 7, 1997  
C.C. :

Number of Pages (including cover sheet): 1

- For your information
- Please respond
- Urgent
- Confidential

### Comments:

Dear Dr. Silberstein,

Referring to our telephone call, regarding the human safety of PET radiopharmaceuticals in particular the Fludeoxyglucose F18 product, I would like to propose the following:

1. My request is that you prepare a report, based on the draft for publication.
2. This report should contain a separate section containing a critical evaluation, which gives regard and which bears in mind the following attitudes of authorities:
  - there is always a big risk, unless the evidence contradicts this;
  - clinical investigators are somewhat loose in addressing safety issues if, as in this case, the product seems so interesting.
3. I would prefer to receive your signed report in the beginning of November. The fee is \$ 2000.

I am very pleased to work with you on this matter giving your contacts with Dr. B. Wolfangel and here in Petten with Dr. G. Ensing.

I would appreciate if you keep this information confidential. We will use your report only for regulatory purposes.

With kind regards,

Dr. H.H. van Rooij  
Ass. Director Regulatory Affairs

If the contents of this Telefax is illegible, or pages are missing, please contact:  
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October 16, 1997

To: H.H. VanRooij, Ph.D.

From: Edward B. Silberstein, M.D.

Re: Safety of PET radiopharmaceuticals in humans

Positron emitters were discovered in 1928 and the positron camera was introduced in 1963. Almost 35 years later positron emission tomography is defining an important role in the evaluation of cardiac metabolism and blood flow, central nervous system disease and neoplasia. Most PET radiotracers are small molecules which are analogues of common metabolites. It is crucial to the utilization of PET radiopharmaceuticals to determine definitively the safety of this class of radiopharmaceuticals. Among the potential for safety problems of these radiotracers is the fact that they frequently require on site synthesis from multiple agents. There is considerable difficulty in performing sterility and pyrogenicity tests preinjection because of the short half lives of most PET radiopharmaceuticals. A study of the safety of PET radiopharmaceuticals was therefore undertaken by the Pharmacopeia Committee of the Society of Nuclear Medicine.

22 leading PET facilities across the United States volunteered to collaborate. An adverse drug reaction was defined as any response to the radiotracer, which was noxious and unintended, occurring in man at doses used for diagnosis or therapy of disease or for modification of physiologic function. A form was developed and mailed to each PET facility for monthly prospective reporting of adverse reactions both to positron emitting radiotracers and to interventional drugs used with PET which had caused serious side effects leading to hospitalization or death. Not to be reported on this form were reactions from overdoses (this is a misadministration); vasovagal responses; or injury from poor injection technique. A retrospective study was also performed at each contributing center.

The criteria for categorizing adverse reactions developed by the Pharmacopeia Committee has been published (Silberstein, E.B. and Ryan, J., Prevalence of adverse reactions in Nuclear Medicine, J Nucl Med, 1996;37:185-192, with Table 4 reprinted as an Erratum in J Nucl Med, 1996;37:1064-1067). Four categories of causality were carefully defined in an attempt to relate any adverse reactions to the injected radiotracers: "not related"; "conditional, unlikely, or remote"; "possible"; and "probable". Details of the definitions appear in the publication noted above.

In the retrospective review performed at each institution of PET procedures performed prior to the initiation of the prospective study (begun in April, 1994) 33,925 patients were found to have been imaged, with no adverse reactions. Employing a specially designed form, a 30 month prospective study was then done. Each of the 22 centers provided a monthly report form describing any adverse reactions seen. This required each center to ascertain that the patient had no problems related to the injection for 24 hours following the administration of the radiotracer.

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In this prospective study 42,458 procedures were performed and again no adverse reactions were found. During the prospective study 2,737 pharmacologic interventions were performed, with no serious adverse reactions leading to hospitalization or death.

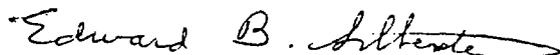
Thus, combining the retrospective and prospective studies, there were no adverse reactions from 76,383 PET radiotracer doses. Employing 95% confidence limits (required with a zero numerator) the probability of an adverse reaction from a PET radiotracer would be, at most,  $7.1/10^5$  doses from the prospective study, or, combining the retrospective and prospective studies, the chance of an adverse reaction is at most (95% confidence limits)  $3.9/10^5$  doses.

The safety of these radiotracers is related: to the nature of the drug administered, which is generally a metabolite of a naturally occurring chemical in the body; to administration of these tracers in microgram amounts; to binding of radiotracers to receptors at far lower concentrations than receptor-binding drugs with pharmacologic actions; and to the success of standardized synthetic techniques in yielding uniformly sterile and pyrogen free radiotracers.

These data were presented at the Society of Nuclear Medicine Annual Meeting in San Antonio, Texas on June 4, 1997 and appear in abstract form in J Nucl Med 1997; 38:112P.

A manuscript about this data is in preparation at this time.

With warm regards,



Edward B. Silberstein, M.D.  
Professor of Internal Medicine and Radiology

EBS/rs

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December 18, 1997

Dr. Hans H. Vanrooy  
Mallinckrodt Medical B.V.  
Westerduinweg 3  
P.O. Box 3  
NL-1755 ZG Petten  
The Netherlands

Dear Dr. Vanrooy:

From your telephone call of December 15 I must assume that the data which I sent to you was inadequate for your purposes. This data, with 95% confidence limits for a zero numerator, accompanied by our criteria for assessing causality is being fleshed out now, and a preprint should be available in January. Best regards.

Sincerely,



Edward B. Silberstein, M.D.  
Professor of Internal Medicine and Radiology

EBS/rs