World Molecular Imaging Society

www.wmis.org

The World Molecular Imaging Society is an international scientific educational organization dedicated to the understanding of biology and medicine through multimodal in vivo imaging of cellular and molecular events involved in normal and pathologic processes and utilization of quantitative molecular imaging in patient care.

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Dear Drs. Fejka and Krefting,

We are sending this letter on behalf of the World Molecular Imaging Society (WMIS), which is the largest world organization of physicians and scientists in the field of molecular imaging, including positron emission tomography. Many of the WMIS investigators in the USA are actively involved in the development of new molecular imaging agents and approaches for better understanding of the biological basis of disease, for early diagnosis, as well as for selection and monitoring of individualized therapies. As described below, we respectfully request that the FDA modify the current RDRC guidelines to permit an alternative assessment of human safety for new tracers.

For many years the Radiation Drug Research Committee (RDRC) has been a very important mechanism in academia for initial physiological and pharmacological investigations of new PET imaging probes in humans. Therefore, the WMIS considers the RDRC a key mechanism for these early investigations for the most promising PET radiopharmaceuticals before IND applications are initiated.

Sections 21 CFR 361.1(b)(2) and (d)(1)(i) of the RDRC require that the dose to be administered must be known not to cause any clinically detectable pharmacological

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effect and in the most recent (August 2010) FDA guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM163892.pdf) your office that this information should be obtained by previous administration to humans.

We are concerned that that without modification the guidance's restricted interpretation of the RDRC would lead to several unintended consequences for PET radiopharmaceutical development. First it would require all academic institutions to perform very expensive (in the order of two hundred thousand dollars) toxicological tests in animals for IND applications for new PET imaging probes. A new PET imaging probe may be discarded with a few experiments in humans because of undesirable pharmacokinetic properties, which could be easily and safely investigated under the RDRC mechanism. Physicians and investigators in the field are always concerned about their research subjects, most specially when studying new PET probes, which has always been done with an excellent record of human safety.

As an alternative approach to obtain information about any possible pharmacological activity of new PET probes, we strongly recommend that FDA consider two additional methodologies: (A) With the tracer amounts used with PET (e.g., typical masses injected are in the sub-microgram range/70 Kg person) the probability of pharmacological activity is non-existent (no case has been described in 40 years of a PET probe having pharmacological activity at the doses administered); and (B) to verify the point under (A), animal studies can be established at X100 mass doses prior to protocol approval, similar to FDA requirements for INDs.

On behalf of the molecular imaging community and the many patients, who would greatly benefit from the use of new imaging probes, we respectfully request that the FDA current RDRC guidelines and interpretation be modified permitting the proposed alternative assessment of human safety for these tracers. We would be happy to provide expert input and work closely with the FDA on this matter.

With best regards,

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