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## **ABSTRACT**

In the 1980s, the FDA allowed a more liberal interpretation of 21 CFR Part 361 and RDRCs were allowed to approve “first in man” studies of certain radioactive drugs administered in tracer quantities. This interpretation reduced costs and simultaneously facilitated radiotracer development leading to more rapid clinical introduction of diagnostic radiopharmaceuticals. RDRC approval was based on (1) the fact that the drugs were administered in tracer doses and, in tracer doses, the amount of the drug would almost certainly be too low to cause a pharmacological effect and/or (2) the tracer was chemically very similar to a drug that had been shown to be safe in man. If the RDRC approved studies showed that the tracer had promising characteristics, the investigator applied for an IND.

Toxicity studies are required for an IND but, in fact, if the tracer under investigation is labeled with Tc-99m, it is impossible to perform toxicity studies because one cannot obtain enough Tc-99m or Tc-99 to even synthesize a milligram of a Tc-99 or Tc-99m based drug. Tc-99m has too short a half life and even if a Tc-99-ligand complex could be obtained in sufficient quantities, animal studies would be prohibited because there would be no effective way to dispose of the animal carcass (Tc-99 is a beta emitter with a half life of 210,000 years).

Toxicity studies are typically performed using the ligand, the Tc-ligand complex and kit or formulation components. In the dose escalation toxicity studies, the dose of the ligand is escalated but, by necessity, the dose of the Tc-ligand complex remains relatively constant. It is important to note that the ligand and the Tc-ligand complex have different chemical structures, usually a different charge and undoubtedly different biodistributions. Evaluation of ligand toxicity is relevant for kit formulation when a mg of the ligand may be administered with the Tc-ligand complex but it is not relevant for research studies when the ligand is separated from the Tc-ligand complex and only the Tc-ligand complex is administered. All Tc-complexes, even those which have INDs, have been administered to humans without dose escalation toxicity studies being performed to evaluate the Tc-ligand complex.

Since dose escalation toxicity studies are impossible to perform with Tc-ligand complexes, I would like first to request the FDA to give RDRCs the authority to allow “first in man” studies with Tc-99m complexes which, because of physical constraints,

will have to be administered in tracer doses. The investigator would be required to demonstrate that the Tc-ligand complex has been separated from the ligand and that only the Tc-ligand complex would be administered. Second, I would like to request that the RDRCs also be given authority to approve "first in man" studies when the radiopharmaceutical will be administered in tracer quantities (less than 1 nanogram/kg) and has a structure similar to an agent that has been shown to be safe in man. Such a policy would improve patient care by more rapidly bringing new diagnostic agents from the laboratory to the clinical arena and, at the same time, would reduce medical costs.