

Statement submitted October 24, 2004.

My name is Walter Wolf, PhD, Distinguished Professor of Pharmaceutical Sciences, and Director, Pharmacokinetic Imaging Program, University of Southern California. I am also the Chair, since its inception, of RDRC #36, and I was Director of the Radiopharmacy Program at USC from 1968 through 1995, when the scope of the Radiopharmacy Program was expanded to Pharmacokinetic Imaging.

I wish to submit the following comments on the information that was released by CDER on 10/5/04 by e-mail entitled: FDA public meeting: RDRC Program, and which contained as an attachment a document entitled: RDRC_public_meeting_Objectives&Questions.9-04.doc. This document will be referred here as "RDRC.doc A". And to the notice that appeared in the Federal Register/Vol. 69, No. 192/Tuesday, October 5, 2004/ Proposed Rules, pages 59569-59572. The purpose of the meeting are to discuss a number of issues that propose to discuss possible changes in the scope and authority of the Radioactive Drug Research Committees, (RDRC's), which were established pursuant to 21CFR 361.1.

1. My first concern is one of terminology. Both 21 CFR 361.1 and RDRC.doc A uses the wording of "pharmacological effect", when what is really meant (or should be meant) is "therapeutic or toxicological effect". Biodistribution, which is the primary reason for the use of any radiopharmaceutical, is a pharmacological effect. Alfred Goodman-Gilman, in the introduction to the 10th. Edition of Goodman and Gilman's, "The Pharmacological Basis of Therapeutics" (McGraw Hill, New York, 2001) states that the way Pharmacology was defined in the first edition in 1941 as "the knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate and excretion, and therapeutic uses of drugs" has remained virtually unchanged since. And Title 21 (US Pure Food and Drug Act) defines a drug in USC 21.9.II.321(g)(1) as "Articles intended for the cure, mitigation, diagnosis or treatment of disease in man or other animals".

Hence, I am formally recommending that the wording "pharmacological effect" be replaced by "therapeutic or toxicological effect" in any revision of 21CFR 361.1.

2. The main concern I have, however, is with the fact that there is no clear understanding of what is the liability of the members of the RDRC's. I had raised that question in February of 2004, and on 2/20/04 I had written to the FDA, attn. Dr. Orhan Suleiman:

What is our liability coverage as an FDA committee?

When we talked [earlier today] we discussed whether we were an FDA committee operating locally, or whether we were an institutional committee approved by the FDA.

My reading of 21CFR361.1 is that we are an FDA committee, and function for and in behalf of the FDA.

The first part of 21CFR361.1(b) reads: ...

(b) The conditions under which use of radioactive drugs for research are considered safe and effective are:

(1) Approval by Radioactive Drug Research Committee. A Radioactive Drug Research Committee, composed and approved by the Food and Drug Administration in accordance with paragraph (c) of this section,

There is no provision that I can read in either section (b) or (c) that suggests that the RDRC is anything but an FDA committee, rather than an institutional committee approved by the FDA.

Indeed, in section (c)(1) it states:

.... A Radioactive Drug Research Committee shall be either associated with a medical institution operated for care of patients and with sufficient scientific expertise to allow for selection of committee members from its faculty

My reading of this section is that the association is intended to allow for the availability of faculty with the appropriate expertise. And in all my years as Chairman of RDRC#36, whenever we proposed a new member, we submitted his/her CV to the FDA, and at no time were we asked to indicate any institutional approval or involvement in such appointments.

On 2/20/04 Dr. Orhan Suleiman advised me that “We are formally raising the question with our FDA lawyers, which unfortunately will take some time”. Last time I inquired, a few weeks ago, I was advised that there was still no response from the FDA lawyers.

The reason this question becomes even more important at this time is that the identification of toxic effects of compounds that have not been tested extensively before in animals and humans is not trivial, and there may be a potentially significant liability when administering a compound whose toxicity is not fully known to a human being. Who has the liability for any adverse effects, and what is the protection afforded to members of the RDRC for potential claims of damages (whether justified or not)?

Inasmuch as the RDRC’s are FDA committees, what is the liability protection provided by the FDA to the members of the RDRC?

3. In section 1A of RDRC.doc A it asks what amount of a physiological compound (as opposed to a drug) can be given to an individual before one can observe any undesirable (e.g., toxicological) effects. Provisions must be made to stratify this answer in terms of the pathophysiology of the individual undergoing the study, including problems arising because of genomic variability and under more extreme circumstances, inborn errors of metabolism.
4. As a minor point, the issue of what is a “child” and what is an “adult” needs to be clearly spelled out. RDRC.doc A considers, as I have done in the past, that persons under 18 are children and over 18 are adults. Yet I was specifically taken to task by an NIH study section on the basis that NIH regulations (grants2.nih.gov/grants/peer/tree_glossary.pdf, 2002) states that: “For purposes of this policy, a child is an individual under the age of 21 years”. The FDA and the NIH need to work out this difference in definition. Otherwise, it will continue creating problems for RDRC’s and IRB’s.