

In recent years, there have been significant advances in molecular imaging technology. Much of this advance has been in the field of diagnostic imaging with the use of CT and MRI contrast agents as well as nuclear medicine SPECT and PET agents that utilize molecular imaging principles. While some of these radiopharmaceutical molecular agents are considered “drugs” in the sense that their development could fall under RDRC guidelines, many are considered “biologic” agents, and do not currently fall under RDRC regulations. Biologics regulated by the CBER include:

- ☞ Monoclonal antibodies for in-vivo use
- ☞ Proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, or microorganisms, and recombinant versions of these products
- ☞ Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response)
- ☞ Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo 1
- ☞ Cellular products, including products composed of human, bacterial or animal cells (such as pancreatic islet cells for transplantation), or from physical parts of those cells (such as whole cells, cell fragments, or other components intended for use as preventative or therapeutic vaccines)
- ☞ Vaccines (products intended to induce or increase an antigen specific immune response for prophylactic or therapeutic immunization, regardless of the composition or method of manufacture)
- ☞ Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests
- ☞ Antitoxins, antivenins, and venoms
- ☞ Blood, blood components, plasma derived products (for example, albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives, (for example clotting factors), blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations including radiolabeled or conjugated forms, and certain fibrinolytics such as plasma-derived plasmin, and red cell reagents

In recent discussions with the FDA, it was made clear that the RDRC cannot approve biologics because of the potential for a physiological response, despite the fact that 21 CFR 310.3(n) specifies that a "radioactive drug" includes a "radioactive biological product" as defined in section 21 CFR 600.3(ee), which in turn specifies "a biological product which is labeled with a radionuclide."

According to the CDER, “Monoclonal antibodies (MoAb) are not appropriate for study under the RDRC auspices because by their very nature, MoAb's are capable of eliciting a

biological response (by reacting with the antigen they can fix complement, are capable of inducing an immune response, etc.) and as such one could expect a pharmacologic effect/reaction to occur although maybe not outwardly measurable. Although a radioactive biological may be included in the definition of a drug according to 21 CFR 310.3(n), our concern here is not the definition of what may be studied, but that there is a potential for a pharmacologic effect to be elicited [so that] to approve the protocol as appropriate under the RDRC mechanism [RDRC members must] be assured that the dose administered will not produce a pharmacologic effect in the subject.”

In general, only small quantities of any agents are used for biodistribution studies under RDRC, typically ranging from microgram to milligram quantities. For biologics, the quantity is often greater, but still lower than typically given for therapeutic administration (in which a biological response is desired). For example, Rituximab (Rituxan) given for treatment of non-Hodgkins lymphoma is dosed using 375 mg/m^2 or approximately 650 mg per dose for an average size adult. A typical course consists of four doses given over a period of four weeks. We have proposed biodistribution studies under RDRC guidelines using as little as 1 mg antibody, but have been denied due to the reasons cited above.

As with any drug, there is a risk of side effects or allergic reactions. I would argue that the FDA should not consider a side effect or potential allergy as a biological response. While it may be somewhat more likely for allergic reactions to occur with biologics in comparison to other drugs, those effects can be mediated in clinical research protocols by using standard administration of acetaminophen and an antihistamine.

Because of this position taken by the FDA, it is necessary to file an IND for investigation of all biologic agents. Considering the rapid pace of research into biologic agents, I believe that the IND process will hinder development of these agents into new radiopharmaceuticals and molecular imaging probes. Despite a compendium of thousands of antibodies used in research laboratories, we have seen only a few new biologics approved for nuclear medicine imaging and therapy in the past five years. Of these, even fewer are FDA approved for routine diagnostic and therapeutic use today.

I would propose that the FDA consider a mechanism to give authority to the RDRC to approve biologics for use in clinical research studies.