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May 11, 2005

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 Food and Drug Administration
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RE: Docket No 2004N-0432; Radioactive Drugs for Certain Research Uses

This statement was prepared as a joint response from the investigators in the Pediatric Research Pharmacology Units (PPRU) Network to the above referenced FDA notice. Three quarters of all medications marketed today do not carry Food and Drug Administration (FDA) approved labeling for use in neonates, infants, children and adolescents. Only five of the 80 drugs most frequently used in newborns and infants are labeled for pediatric use. The FDA has recently made regulatory changes to facilitate labeling of drugs for pediatric use. Recent legislative changes in the FDA Modernization Act (FDAMA) provide strong incentives to conduct studies of drugs in children. In addition, the FDA 1998 Pediatric rule requires that drugs with a health benefit for children be studied in children as well as adults. The National Institute of Child Health and Human Development (NICHD) established and funded the PPRU network to establish a platform for pediatric clinical trials in response to the critical need for pharmacological studies in children.

We believe that the use of positron emission tomography (PET) with specifically designed radiopharmaceuticals for the study of pediatric disorders has led to important treatments for children and holds great promise in future applications, particularly in the development of drugs for specific use in children. The regulatory environment for conducting the initial studies necessary for the development of specific PET tracers for pediatric use is currently in a state of flux and could potentially shift in a direction that would make it much more difficult to advance this technology in the future. *We are providing input to prevent future installation of unnecessary regulatory impediments to pediatric research with radiopharmaceuticals.*

There are currently two FDA-sanctioned avenues whereby initial evaluation of potential PET tracers are allowed using human subjects (including pediatric subjects): 1) approval by a local Radioactive Drug Research Committee (RDRC) as described in 21 CFR 361.1, and 2) approval by the FDA directly via an Investigational New Drug (IND) application as described in 21 CFR 312. The RDRC route has facilitated the development of many PET (and SPECT) tracers since its establishment in 1975 because the requirements and

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documentation necessary using this mechanism for tracer development studies are much less rigorous than those required by an IND. The RDRC is primarily concerned with the preparation of the tracer, quality control procedures to assure its purity, and the calculated radiation doses to individual organs and to the subject overall that result from the administration of a given radiolabelled tracer candidate.

The first issue we would like to address is the radiation dose limit for pediatric subjects. The radiation dose limit for adult research subjects, as defined in the current regulations, allow, for the most part, the administration of candidate PET tracers in radioactive quantities sufficient for the generation of good quality PET scan data. The current regulatory radiation dose limits set for subjects under 18 years of age (at 1/10 the adult levels), however, are well below those allowable for accepted clinical PET scans and often restrict the allowed tracer dose to such an extent that the quality of the PET scan data may be compromised. We feel that these current levels are unrealistically low. Furthermore, since these regulations provide the only radiation dose limits in the FDA regulations, these dose limits have been regarded as benchmarks to assess risk by Institutional Review Boards (IRB). Thus, we propose that dose limits be raised to allow testing of radiopharmaceutical drugs at clinically relevant doses in children. Otherwise, clinical studies using radiopharmaceuticals in children, such as clinical studies currently conducted with FDG, will necessarily be based upon adult studies.

Specifically with regard to pediatric subjects, the FDA asks the following questions:

Does 361.1 provide adequate safeguards for pediatric subjects during the course of a research project intended to obtain basic information about a radioactive drug, or should these studies only be conducted under an IND?

We believe that 361.1 provides adequate safeguards for children. This is because as a condition for RDRC approval, a particular study must also be approved by an IRB which evaluates broader issues of study design, subject risks, etc. including those federal regulations which specifically address the use of pediatric subjects in research (21 CFR 50 Subpart D and 45 CFR 46 Subpart D). Additionally, a study involving pediatric subjects must receive input from a pediatrician designated as a consultant to an RDRC prior to approval. Furthermore, we would suggest that the scope of this regulation be expanded to allow more initial PET radiopharmaceutical developmental studies for both children and adults. The IND mechanism, which was designed to provide safeguards for first human use of therapeutic agents, requests excessive data for this indication. For PET radiopharmaceuticals, there is little need for the pharmacological and toxicological data necessary for therapeutic agents, since PET scanning involves the administration of a single dose of the radiopharmaceutical in tracer quantities which, by definition, indicates no pharmacological effect. These tracer doses range from 1,000 to 1,000,000 fold lower doses than therapeutic doses.

If we assume that 361.1 provides adequate safeguards for pediatric subjects during such studies, given our present knowledge about radiation and its effects, can we conclude that the current dose limits for pediatric subjects do not pose a significant risk? If not what dose limits would be appropriate to ensure no significant risk for pediatric subjects? Should there be different dose limits for different pediatric age groups?

The current dose limits do not pose a significant risk to pediatric subjects. However, the current dose limits do restrict the applicability of certain radiopharmaceuticals in children due

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to overly restrictive dose limits. For example, the current dose limits set by RDRC regulations would not allow testing in children with clinically-accepted doses of the most clinically used PET tracer (2-deoxy-2-[¹⁸F]fluoro-D-glucose or FDG), which would give a radiation dose of 3-5 rem to bladder depending on the size of the child (the RDRC regulations allow no more than 0.5 rem). The primary issue in setting radiation dose limits in these pediatric studies is what is the maximum acceptable dosimetry (both individual organ and whole body or effective dose) that will allow sufficient radioactivity to be administered to the subject in order to obtain meaningful, good quality data (i.e. sufficient count rate, good target/nontarget signals with relatively low noise) from the proposed PET scan. Assuming that the best, most sensitive technology is used, the current maximum permissible levels (1/10 the adult limits of 3 rem whole body/gonads and 5 rem any other organ) for pediatric subjects often does not allow the administration of enough of the radiotracer necessary to give quality data.

The method for establishing the radiation dose limit and calculating the dose of radioactivity in the current 21 CFR 361.1 regulations is now obsolete. The International Commission of Radiological Protection and the National Council on Radiation Protection and Measurements has adopted the effective dose method (E, the sum of the equivalent doses in all the tissues and organs of the body, factoring in susceptibility of specific tissues and organs to radiation effects) for designating the radiation dose. The effective dose for a clinical adult FDG PET scan is approximately 10 mSv, and this dose conveys a lifetime cancer mortality risk of 0.0005 (data from presentation by Dr. Orhan Suleiman, FDA Senior Science Policy Advisor, at FDA public meeting on November 16, 2004). The dose to an adult-size adolescent would be the same as for an adult, whereas for a 5 year old given a typical 2.6 mCi FDG dose, the effective dose is 5.6 mSv. Given that the lifetime risk of dying from cancer of 23.66 for males and 19.99 for females (SEER Cancer Statistics Review 1975-2001), this additional risk of 0.0005 is minimal, and this type of risk should not be used as a justification for effectively excluding children from the medical benefit of powerful technologies using radiopharmaceuticals.

There seem to be conflicting signals from the FDA with regard to children as research subjects. On the one hand, several recent initiatives [FDAMA and Pediatric Rule (1997, 1998), Best Pharmaceuticals for Children Act (2002), Pediatric Research Equity Act (2003)] encourage, and indeed require, use of a pediatric population in drug development studies, particularly if those studies involve diseases or conditions unique to this population. On the other hand, with respect to the FDA input on the use of pediatric studies under RDRC regulations, guidance from the FDA suggests that the primary concern is the potential risks to individual subjects from the radiation and other procedures associated with these studies. In the view of the FDA Office of Pediatric Therapeutics as articulated by Dr. Sara Goldkind at the November 16, 2004 public meeting, the best way to minimize these risks is to require that any research involving the administration of radioactive compounds to pediatric subjects (including studies that are currently allowed under Federal RDRC regulations) be conducted via the IND process.

It appears that we are in danger of repeating our history of neglecting medical research in children in the name of protecting them from potential harm. The experience in drug therapy of newborns and children has taught us a great and valuable lesson, that excluding newborns and children from requisite drug evaluation and doing no studies in these populations for their assumed "protection" can result in therapeutic tragedies and needless (or preventable) deaths. Examples such as the chloramphenicol gray baby syndrome, kernicterus due to sulfa drugs, and many others are part of the historical record. By setting overly restrictive radiation limits for children, we will greatly diminish their access to PET and SPECT as tools to study their unique

health problems. A rational and careful use of these advanced technologies in newborns and children appears justified based on the well-known data on pharmaco-therapeutic tragedies in these vulnerable populations who have historically been excluded from the initial stages of drug development.

There are many devastating pediatric disorders that are either life threatening or hold high risk for life long disability in which PET technology holds a promise for a better understanding the biological underpinnings and thereby enabling new treatments. This is best illustrated by the important contribution of PET to the treatment of epilepsy resistant to conventional antiepileptic drug therapy. By using new imaging approaches in children, the brain region responsible for the epilepsy can be more accurately identified and surgically removed. This results not only in cessation of seizures but also improved cognitive development. Without PET research, children with infantile spasms would not have been discovered to be operable, and it would be extremely difficult to pinpoint the epileptic tuber amidst the multiple tubers in patients with tuberous sclerosis complex. The concept of intervening early during brain development is an important one for many neurodevelopmental disorders. Early intervention based on increased understanding of brain dysfunction may provide new approaches to treatment of disorders involving delay in cognitive development such as autism, for whom current treatment offers little hope for attainment of independence in adulthood.

The PPRU Network has approved, as a protocol in the network competitive renewal application, a study using PET technology to our youngest children—those in the immediate neonatal period. This study aims to address apnea in the newborn by understanding differences in receptor function involved in the control of breathing during brainstem development. It is clear that this is a worthwhile endeavor, but can we expose these premature infants to radioactivity? In fact, these premature infants are already being exposed to numerous radiological tests as part of their intensive clinical care. The dose of a PET scan under the current regulations is only a fraction of the radiation dose typically received by the preterm infant who often requires repeated chest x-rays or CT scans for lung disease, repeated abdominal x-rays or CT scans for necrotizing enterocolitis, and CT scans for intracranial hemorrhage.

Under the current regulations, children have not benefited to the same extent as adults from advances in PET technology for oncology and cardiology. Also limited has been the application of PET and SPECT in children to address psychiatric disease and substance abuse, which are often first manifested during childhood and adolescence. Functional imaging of radiolabeled tracers currently offers the only method to assess how altered development leads to these chronic and disabling disorders. It is clear in our estimation that the risk of the radioactive dose in comparison to the risks associated with these life-changing disorders is a reasonable one.

However, a basic premise for the design of a scientific study is to compare experimental results from the designated population to those of an aged-matched normal control group. Should we expose completely normal children to radiation doses that will raise their risk of dying of cancer from 23.66% to 23.6605%? Additional risks of the procedure, in particular sedation, in younger children must also be considered. We propose that the risk to children over the age of 8-10 years, in which sedation is not necessary, is minimal to the individual child. Further, we propose screening of healthy children to identify and exclude those children who have had a large past medical exposure to radiation and strong family history of cancer. In the future, risk

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may be further minimized by prescreening for genes (such as mutations in DNA repairs enzymes) that may put certain individuals at higher risk. In order to minimize risk to the population as whole, we suggest the adoption of uniform acquisition protocols, and that normal control data collected be put into a national database for use by multiple investigators. Strategies for establishing normal values in young children may come from the development of technology to allow a larger field of view and smaller aperture so that dynamic imaging of normal organs can be acquired during the same scanning period as the target organ.

As advocates of children's well being, it is our duty to protect children not only from the minimal risk of low doses of radiation, but also to develop strategies which allow children to safely benefit from tools that hold promise for increased understanding and treatment of their unique diseases.

Sincerely,

A handwritten signature in black ink that reads "Cheston M. Berlin, Jr., M.D." The signature is written in a cursive style with a large, stylized initial 'C'.

Cheston M. Berlin, Jr., M.D.
University Professor of Pediatrics
Chair
Pediatric Pharmacology Research Unit Network