5

Pediatric PET Research Regulations

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Good intentions are necessary, but not sufficient, to conduct pediatric positron emission tomography (PET) research. This chapter provides direction to guide the process of conducting PET research in children.

Code of Federal Regulations (CFR)

When the executive rule-making voice of the government speaks, it does so officially through the Code of Federal Regulations (1). These are not the laws, per se, but rather the nitty gritty rules necessary to carry out the laws that are made by Congress. For example, Congress may pass a law to provide for a safe drug supply; the executive branch (e.g., the Food and Drug Administration, FDA) carries out the intent of the law and writes the rules (e.g., "Intravenous products shall be sterile and pyrogen-free").

Reading 21 CFR (Title 21 of the CFR, where the FDA rules are located) is about as exciting as reading the telephone book or the Internal Revenue Service regulations for preparing tax returns (until you come to that one paragraph that appears to justify your objective), but it is necessary. The judicial system interprets the regulations and may enforce compliance. Each agency of the executive branch of the government or each specific purpose for a set of regulations has a particular location. Title 10, for example, is where one finds radiation safety and safe use of radiopharmaceutical use in humans. Table 5.1 provides an example of several other locations within the CFR that may be of interest to the reader (3). In addition to the CFR, the various agencies issue letters, guidelines, interpretations, descriptions of courses, comments, request for comments, etc., in an effort to communicate with the public and research investigators, among others. And, like cement, the rules become more solidified with time. Occasionally, the book is opened for a rewrite, providing a glimpse into the "mind" of the government. One such opportunity appeared on November 16, 2004, in an open meeting at the FDA headquarters in which an update of the Radioactive Drug Research Committee (RDRC) regulations was being

Table 5.1. Some additional examples of codified federal policy

07 CFR Part 1C	**Department of Agriculture**
10 CFR Part 35	**Human Use of Radiopharmaceuticals**
10 CFR Part 745	**Department of Energy**
15 CFR Part 27	**Department of Commerce**
16 CFR Part 1028	**Consumer Product Safety Commission**
21 CFR Part 361.1	**Radiopharmaceutical Use in Humans**
40 CFR Part 26	**Environmental Protection Agency**
45 CFR Part 46	**Public Welfare, Protection of Human Subjects**
45 CFR Part 690	**National Science Foundation**

Note: There are source documents, regulations, amendments to regulations, Web sites, parts, subparts, preliminary documents for review, rewrites, updates, clarifications, and numerous other forms of communication.
Source: Data from ref. 2.

considered (4). The regulations will be examined shortly, particularly as they relate to PET research in children. Table 5.2 provides a resource list to facilitate communication (4,5,14).

Pathways Allowed by the Federal Regulatory System

There are three major routes to conduct research that are allowed by the federal regulatory system: (1) an investigational new drug (IND) application, (2) a physician-sponsored IND, and (3) the RDRC mechanism (6–8,15–21).

The full IND approach is the one taken by drug manufacturers who intend to obtain FDA approval to market a pharmaceutical to the general public, usually for commercial purposes. The manufacturer conducts physical, chemical, and biologic studies in vitro and then in animals prior to studies in humans (clinical trials, phases I, II, III described below), followed by postmarketing studies (phase IV), post–new drug approval. The pharmaceutical house has sufficient talent, expertise, and staff in its regulatory and medical departments to know how to proceed on its own.

A second pathway is the physician-sponsored IND, which usually involves studies with more than 30 subjects, can be conducted at one or multiple sites, and can involve agents that are new entities, new routes of administration, new dosage forms for existing or new drugs, new populations (including children) or disease states, new indications, etc. The physician or other qualified investigator (with a physician as co-investigator) is usually medical center or hospital based and will be required to fill out FDA forms 1571, 1572, and 1573 among possibly others. This process of how to compile, assemble, complete and submit the physician-sponsored IND has been reviewed broadly and in detail elsewhere (15).

A third pathway is the RDRC approach. Using this mechanism, the FDA delegates authority to a local committee to approve research studies (usually up to 30 patients, although the number can be higher under certain circumstances, for example, if FDA form 2915 is completed). The composition of the membership of that committee has FDA prior approval. Authority is given by this committee to investigators to conduct only phase I and phase II clinical trials, meeting very

strict and specific criteria (see below). Under no circumstances are the results from such studies to be used to make clinical decisions for any of the participants in the study until the study is completed and the data are analyzed. In theory, the findings are investigational and remain unproven at this point. It is possible that approved clinical methods used to validate the research finding may be clinically helpful or of benefit to a study participant. For example, the findings from a computed tomography (CT) scan used to study the metabolism and distribution of a new diagnostic radiopharmaceutical such as a radiolabeled monoclonal antibody that was designed to locate a tumor, may find their way to the patient's or subject's medical record, but not information provided by the radiolabeled monoclonal antibody. This RDRC

Table 5.2. Selected reference sites and sources relative to pediatric PET research

Food and Drug Administration (December, 2004)	
Main telephone number	**1-888-INFO-FDA**
E-mail	**http://www.FDA.gov**
Drug information telephone number	**1-301-827-4570**
Pediatric Drug Development (PDD)	**1-301-594-PEDS (7337)**
E-mail	**Pdit@cder.FDA.gov**
Division of Drug Imaging and Radiopharmaceutical Drug Products (DMIRPD)	**DMIRPD, RDRC Drug Program**
E-mail	**http://www.FDA.gov/cder/regulatory/RDRC/default.htm.**
Radioactive Drug Research Program	
Address	**Food and Drug Administration Center for Drug Evaluation and Research Division of Medical Imaging and Radiopharmaceutical Drug Products HFD-160 Parklawn Building, Room 18R-45 5600 Fishers Lane Rockville, MD 20852 Attention: RDRC Team**
Director	**George Mills, MD**
Senior manager	**Capt. Richard Fejka, USPHS, RPh, BCNP**
Clinical trials	
Government	**http://www.Clinicaltrials.gov**
United Healthcare Foundation	**http://www.Unitedhealth-carefoundation.org/emb.html**
Books	
Kowalsky RJ, Falen SW. *Radiopharmaceuticals in Nuclear Pharmacy*, 2nd ed. Available from the American Pharmaceutical and Nuclear Medicine Association, Washington, D.C. http://www.pharmacist.com/store/cfm	
Clinical evidence by the evidence-based update on more than 1000 medical conditions including clinical trials. British Medical Journal. Free of charge to healthcare professionals. http://www.unitedhealthcarefoundation.org/Emb.html	
Legislative Information Gateway to the Congressional Record and Congressional Committee Information. http://thomas.loc.gov	

Source: Data from refs. 4–13.

approach to conduct PET research in children is the one on which we concentrate in this chapter (6–8,16–18,21).

The Clinical Trial Process

The clinical trial is a biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective (17,18). Trials of an experimental drug, device, treatment, or intervention may proceed through four distinct phases. Sometimes more than one phase can be conducted at the same time. The actual number of subjects studied in each phase may depend in part on the incidence or prevalence of the disease state or condition being investigated.

Phase I

This phase entails testing in a small group of people (e.g., 20 to 80 subjects) to determine efficacy and evaluate safety (e.g., determine a safe dosage range) and identify side effects. A typical phase I trial of a new drug agent frequently involves relatively high risk to a small number of participants. The investigator and occasionally others have the only relevant knowledge regarding the treatment because these are the first human uses. The study investigator may be required to perform continuous monitoring on participant safety with frequent reporting to institute and center staff with oversight responsibility.

Phase II

This phase entails a study of a larger group of people (several hundred) to determine the efficacy and further evaluate safety. A typical phase II study follows phase I studies, and there is more information regarding risks, benefits, and monitoring procedures. However, more participants are involved, and the disease process confounds the toxicity and outcomes. An institute or center may require monitoring similar to that of a phase I trial or may supplement that level of monitoring with individuals with expertise relevant to the study who might assist in interpreting the data to ensure patient safety (17,18).

Phase III

This phase entails a study to determine the efficacy in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions, to monitor adverse effects, and to collect information to allow safe use. The definition includes pharmacologic, nonpharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community-based trials and other population-based trials are also included. A phase III trial frequently compares a new

treatment to a standard treatment or to no treatment, and treatment allocation may be randomly assigned and the data masked. These studies frequently involve a large number of participants followed for longer periods of treatment exposure. Although short-term risk is usually slight, one must consider the long-term effects of a study agent or achievement of significant safety or efficacy differences between the control and the study groups for the masked study. An institute or center may require a data safety monitoring board (DSMB) to perform monitoring functions. This DSMB would be composed of experts relevant to the study and would regularly assess the trial and offer recommendations to the institute or center concerning its continuation.

Phase IV

This phase entails studies done after the intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use. The controversy that appeared in the lay media in December 2004 as well as in medical publications (22) concerning adverse events associated with Vioxx and Celebrex is an example of a postmarketing discovery following new drug approval.

Radioactive Drug Research Committee Update Meeting and Transition

After more than a quarter of a century, it became obvious that technologic progress and events had surpassed the intent of the original 1975 FDA, RDRC regulations (6–8,16). During the current transition period (June 2005) and until the updated RDRC regulations are finalized, the 1997 FDA Modernization Act (FDAMA) provides a mechanism for the uninterrupted production of PET radiopharmaceutical by specifying that they should meet United States Pharmacopoeia (USP) monograph standards (23,24). An example of a PET radiopharmaceutical coming through that process was ^{18}F-fluorodeoxyglucose (FDG) injection, which received a new drug approval in less than 6 months after submission on August 5, 2004 (25).

RDRC Update Issues

Six issues or areas of concern, proposed by the FDA/RDRC, were placed on the agenda for discussion (4,5):

1. Pharmacologic issues
2. Radiation dose limits for adult subjects
3. Assurance of safety for pediatric subjects
4. Quality and purity
5. Exclusion of pregnant women
6. RDRC membership

As this chapter is being written, participants at the open meeting and other interested parties and organizations are submitting written comments for the record and for consideration regarding the updated regulations. Who could have predicted in 1975 how to best conduct research or manufacture pharmaceuticals (including radiopharmaceuticals), given the advent of monoclonal antibodies, cloning, stem cells, gene therapy, biologic response modifiers, and the growth of PET and other imaging modalities?

Vulnerable Populations

There are four populations addressed specifically in Title 45 part 46 of the Code of Federal Regulations, which deals with public welfare protection of human subjects (2,19–21):

Subpart A: Human subjects, research subjects, and volunteers as controls or normals
Subpart B: Additional protections for pregnant women, human fetuses, and neonates
Subpart C: Additional protections pertaining to biomedical and behavioral research in prisoners
Subpart D: Additional protections for children as subjects in research (21).

Assurance of Safety for Pediatric Subjects

Currently 21 CFR 361.1 (that FDA section of the code that deals with radiopharmaceutical research in humans) allows the study of radioactive drugs in subjects less than 18 years of age without an IND application, if the following conditions are met:

1. The study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, is without significant risk, and is supported with review by qualified consultants to the RDRC.
2. The radiation dose does not exceed 10% of the adult radiation dose as specified in 21 CFR 361.1 (b)(i) and, as with adult subjects, the following additional requirements are met:
3. The study is approved by an institutional review board (IRB) that conforms to the requirements of 21 CFR part 56.
4. Informed consent of the subject's legal representative is obtained in accordance with 21 CFR part 50.
5. The study is approved by the RDRC, which assures all other requirements of 21 CFR 361.1 are met (5,16).

Alternatively, when a study is conducted under an IND (as compared to a RDRC) in accordance with part 312 (21 CFR part 312), the sponsor must submit to the FDA the study protocol, protocol changes and information amendments, pharmacology/toxicology and chemistry information, and information regarding prior human experience with the same or similar drugs (see 21 CFR 312.22, 312.33, 312.30 and 312.31). Additionally, 21 CFR 32 requires that sponsors (of the IND) promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor by any source, foreign

or domestic. This includes information derived from any clinical or epidemiologic experience, reports in the scientific literature and unpublished scientific papers, as well as reports from foreign regulatory authorities. 21 CFR part 32 also requires that sponsors submit IND safety reports to the FDA (4,5).

Pediatric Concerns Considered for Update

Does 21 CFR 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 be conducted only under an IND?

If we assume that 21 CFR 361.1 provides adequate safeguards for pediatric studies during such studies, given our present knowledge about radiation and its effects, can we conclude that the current dose limits would be appropriate to ensure no significant risk for pediatric participants? Should there be different dose limits for different pediatric groups (5)? At present, it is estimated that only about half of the RDRCs in conjunction with their IRBs consider approval of radioactive drug research in children. The operative phrase appears to be minimal risk.

Protections for Children Involved as Subjects of PET Research

There are three basic areas of concern in using children as PET research subjects: (1) conformity with IRB requirements, (2) radiation dosimetry of not more than 10% of the adult dose and in conformity with ALARA (as low as reasonably achievable) considerations, and (3) special considerations relevant to vulnerable populations (2,5,16,21). Under certain circumstances, the secretary of the Department of Health and Human Services (HHS) may waive some or all of the requirements of these regulations for research of this type (2,21).

Some Additional Protections Addressed in 45 CFR Part 46, Subpart D

To whom do the requirements to carry out the regulations apply?

To whom do the requirements apply as subjects, and who may give assent and grant permission for the children?

What are the IRB responsibilities related to children?

What protections are appropriate for research not involving greater than minimal risk?

What protections are appropriate for research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects?

What protections should be required for research involving greater than minimal risk and no prospect of direct benefit to individual subjects but likely to yield generalizable knowledge about the disorder or condition?

What protections should be required for research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children?

What is the requirement for permission by parents or guardians and for assent by children?

What protections should be required and who grants permission for children who are wards of the State? (21).

RDRC Specific Responsibilities Abstracted from the CFR

This section is taken directly from the minutes of the University of Pittsburgh Medical Center (UPMC) RDRC and Human Use Subcommittee (HUSC), Radiation Safety Committee, Dennis Swanson, M.S., Chairman (26).

In taking this action, the RDRC considered and assured that each of the following criteria were met:

1. The research study is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology or biochemistry. The research study is not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes.
2. The research study involves the use of a radioactive drug(s), which will be prepared in accordance with a RDRC-approved drug master file or HUSC/RDRC Form 1002. The drug master file of HUSC/RDRC Form 1002 documents:
    a. that the amount of active ingredient or combination of active ingredient shall not cause any clinically detectable pharmacologic effect in humans as known based on pharmacologic dose calculations derived from data available published or other valid human studies;
    b. absorbed dose calculations based on the MIRD formalism and biologic distribution data available from the published literature or from other valid studies;
    c. that an acceptable method will be used to radioassay the drug prior to its use;
    d. that adequate and appropriate instrumentation will be utilized for the detection and measurement of the specific radionuclide;
    e. that the radioactive drug meets appropriate chemical, pharmaceutical, and radionuclidic standards of identity, strength, quality, and purity as determined by suitable testing procedures;
    f. that, for parenteral use, the radioactive drug is prepared in a sterile and pyrogen free form; and
    g. that the package and labeling of the radioactive drug is in compliance with the requirements of 21 CFR 361.1 and NRC (if applicable) and Commonwealth of Pennsylvania regulations regarding radioactive drugs.
3. For this specific research protocol:
    a. Scientific knowledge and benefit is likely to result from this study;
        — The proposed research is based on sound rationale derived from the published literature or other valid studies.
        — The proposed research is of sound design.

b. The radiation dose is sufficient and no greater than necessary to obtain valid data.
   — In consideration of available radioactive drugs, the radioactive drug used in the study has the combination of half-life, type of radiation, radiation energy, metabolism, and chemical properties that results in the lowest radiation dosimetry as needed to obtain the necessary information.
   — For adult subjects: the projected radiation dose to the whole body effective dose equivalent (EDE), active blood-forming organs, lens of eye, and gonads does not exceed 3 rem (single study) or 5 rem (annual and total dose), and the projected radiation dose to any other organ does not exceed 5 rem (single study) or 15 rem (annual and total dose).
   — For subjects under the age of 18 (if applicable), the projected radiation dose does not exceed 10% of the adult limits.
   — The projected radiation dose commitments address expected radionuclidic contaminants and x-ray and other radiation-emitting procedures performed as part of the research study.
c. The projected number of subjects is sufficient and no greater than necessary for the purpose of the study as supported by a statistical or other valid justification;
d. The proposed population is appropriate to the purpose of the study; and
   — The involvement of subjects less than 18 years of age, if applicable, is justified as (1) presenting a unique opportunity to gain information not currently available; and (2) necessitating the use of such subjects. The scientific review of research involving subjects less than 18 years of age is supported by qualified pediatric consultants to the RDRC.
   — Pregnancy testing, to confirm absence of pregnancy prior to administration of the radioactive drug(s), is performed on female subjects of childbearing potential.
e. The investigators are qualified by training and experience to conduct the proposed research study.
   — The research study involves, as a listed co-investigator, a physician "authorized user" recognized by the Radiation Safety Committee, University of Pittsburgh, as qualified to oversee the preparation, handling and use of the radioactive drug (26).

Illustrative Examples that Have Come to the UPMC-RDRC Requiring Directed Change, Correction, or Reconsideration

1. Not including the gallium-68 rod transmission scan to calibrate the PET scanner as part of the radiation dosimetry.
2. Submitting a phase III clinical trial to the RDRC.

3. Submitting an appropriate research protocol and informed consent for a study using ^{18}F-FDG to the IRB, but not the RDRC.

4. Inappropriate expression of radiation dose and risk to the patient in the informed consent. The UPMC has adopted a uniform radiation risk statement model which it recommends be used in both the consent and protocol, although other statements are also acceptable, for example, "Participation in this research study involves exposure to radiation from the two PET transmission scans, the one 12 mCi (a unit of radioactivity dosage) injection of [15-O] water, one 15-mCi dose of [11-C]WAY, and one 10-mCi injection of [11-C]raclopride. The amount of radiation exposure you will receive from these procedures is equivalent to a whole-body radiation dose of 0.47 rem (a unit of radiation exposure). This is less than 10% of the annual whole-body radiation exposure (5 rem) permitted to radiation workers by federal regulations. There is no minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cell abnormalities) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this study is considered to be low and similar to other everyday risks" (26).

5. While using magnetic resonance imaging (MRI) for co-registration with PET, performing the PET scan before MRI. A certain number of MRI subjects will be eliminated or withdrawn due to claustrophobia. If this is the case, then they have been exposed to the radiation dose unnecessarily.

6. A patient has a pregnancy test at a screening session 1 month prior to a research PET scan. The pregnancy test is due to the research nature of the PET scan. The pregnancy test should be conducted as close as possible to the time that the PET scan is scheduled; within 48 hours of PET.

7. A patient has a pacemaker and is going to have an MRI prior to a PET study. If there is a question of metal or metal fragment being attracted by the magnets, then an x-ray may be required. The x-ray is required as part of the research and thus should be included as part of the dosimetry table and consent.

8. A new drug that has been tested in thousands of mice to treat memory loss is to be trace radiolabeled and administered to humans as part of a multicenter trial of 50 patients at each site. Because the drug has never been given to a human (lack of a pharmacologic effect cannot be substantiated), and is a multicenter study with over 30 patients, it is best conducted under an IND. Even for a radiopharmaceutical, the mass of the administered radiolabeled compound currently must be quantified.

9. A physician wants to test a brachytherapy unit on his patients who have a tumor different from the one for which the FDA gave initial approval. There are 10 patients and he is comparing two types of seeds in two different cell types. This should not be submitted to the RDRC, but should be reviewed by the Human Use Subcommittee. The holder of the IND is a manufacturer of a radiation device.

10. A study comes before the RDRC that is so complicated that the members of the committee don't believe it can be carried out without losing data. The project is sent back for reconsideration because if the

data cannot be analyzed in a meaningful way, then subjects will have been exposed unnecessarily.

References

1. Fostering a culture of compliance. National Institutes of Health education and outreach seminar. Pittsburgh, July 15, 2004.
2. Administering and overseeing clinical research. Title 45 Public welfare. Part 46 Protection of human subjects. Revised November 13, 2001. Effective December 13, 2001. Subpart A—Federal policy for the protection of human subjects. Basic DHHS policy for the protection of human research subjects. In: Fostering a Culture of Compliance. National Institutes of Health education and outreach seminar. Pittsburgh, PA, July 15, 2004. http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm.
3. Fostering a culture of compliance. National Institutes of Health education and outreach seminar. Code of Federal Regulations. The common rule (Federal Regulations). Pittsburgh, PA, July 15, 2004. http://ohrp.osophs.dhhs.gov/ human subjects/guidance/45cfr46.htm.
4. Notice of public meeting—radioactive drugs for certain research uses. Radioactive Drug Research Committee (RDRC) program. Rockville, MD, November 16,2004. http://www.fda.gov/cder/regulatory/RDRC/default.htm.
5. Agenda of public meeting—radioactive drugs for certain research uses. Radioactive Drug Research Committee (RDRC) program minutes. Rockville, MD, November 16, 2004. http://www.fda.gov/cder/meeting/clinicalresearch/default.htm.
6. Positron emission tomography (PET) related documents. http://www.fda.gov/cder/regulatory/PET/default.htm.
7. What information does the RDRC review? Radioactive Drug Research Committee (RDRC) program. http://www.fda.gov/cder/regulatory/RDRC/review.htm.
8. What are the responsibilities of the RDRC? Radioactive drug research committee (RDRC) program. http://www.fda.gov/cder/regulatory/RDRC/Responsibilities.htm.
9. http://grants.nih.gov/grants/guide/notice-files/not98–084.html.
10. Having trouble keeping up with clinical trials? APhA-AAPM news you can use 4(2), October 28, 2004. http://www.pharmacist.com. Info-center@apha.org.
11. Kowalsky RJ, Falen SW. Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 2nd ed. Washington, DC: APhA, 2004. http://www.Pharmacist.com/store.cfm.
12. Clinical evidence to help support the clinician's skillful use of scientifically valid and evidence based information. http://Unitedhealth carefoundation.org.ebm.html.
13. How do I find and track bills? Health Physics News 2005;33(1):3. http://www.hps.org.
14. FDA meeting to focus on radioactive drugs for basic research. APhA-AAPM electronic newsletter. http://www.apha.net.org.
15. Levine G, Abel N. Considerations in the assembly and submission of the physician sponsored investigational new drug application. In: Hladik WB, Saha GB, Study KT, eds. Essentials of Nuclear Medicine Science. Baltimore: Williams & Wilkins, 1987:357–386.

16. Pediatric drug development. http://www.fda.gov/cder/pediatrics/index.htm.
17. NIH grants-general information glossary (NIH-grants policy statement, revised 12/01/03. In: Fostering a Culture of Compliance. National Institutes of Health education and outreach seminar. Pittsburgh, PA, July 15, 2004:6–15. http://www.grants.nih.gov/grants/terms_.htm.
18. NIH guide: NIH policy for data and safety monitoring, release date June 10, 1998. In: Fostering a Culture of Compliance. National Institutes of Health education and outreach seminar. Pittsburgh, PA, July 15, 2004. http://grants.nih.gov/grants/guide/notice-files/not98–084.html.
19. Administering and overseeing clinical research. Title 45 Public welfare. Part 46 Protection of human subjects. Revised November 13,2001. Effective December 13, 2001. Subpart B—additional protections for pregnant women, human fetuses and neonates involved in research. In: Fostering a Culture of Compliance. National Institutes of Health education and outreach seminar. Pittsburgh, PA, July 15, 2004. http://ohrp.osophs.dhhs.gov./humansubjects/guidance/45cfr46.htm.
20. Administering and overseeing clinical research. Title 45 Public welfare. Part 46 Protection of human subjects. Revised November 13, 2001. Effective December 13, 2001. Subpart C—additional protections pertaining to biomedical and behavioral research involving prisoners as subjects in research. In: Fostering a Culture of Compliance. National Institutes of Health education and outreach seminar. Pittsburgh, PA. July 15, 2004. http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm.
21. Administering and overseeing clinical research. Title 45 Public welfare. Part 46 Protection of human subjects. Revised November 13, 2001. Effective December 13, 2001. Subpart D—additional DHHS protections for children involved as subjects in research. In: Fostering a Culture of Compliance. National Institutes of Health education and outreach seminar. Pittsburgh, PA, July 15, 2004. http://ohrp.sosphs.dhhs.gov/humansubjects/guidance/45cfr46.htm.
22. COX-2 inhibitors under scrutiny in wake of Rofecoxib withdrawal. APhA Drug Info Line 2004;1–2.
23. Food and Drug Administration Modernization Act of 1997. Title 21. Section 121. Positron emission tomography. http://www.fda.gov/cder/regulatory/Pet/petlaw.html.
24. Radiopharmaceuticals for positron emission tomography-compounding. Chapter 823. US Pharmacopeia 20/National Formulary 25, 2002.
25. Update—new fludeoxyglucose F-18 injection PET drug approved in less than 6 months. http://fda.gov/cder/regulatory/pet/Fludeoxyglucose.htm.
26. Swanson DP. Radioactive drug research committee/human use subcommittee meeting minutes. University of Pittsburgh. Pittsburgh, PA, November 17, 2004.