

A Memoir of Pediatric Nuclear Medicine: Part II: Challenges in the Development of a Subspecialty

By the 1960s and 1970s it was clear that nuclear medicine techniques showed promise in a number of applications. What was not immediately clear was how these techniques should be applied in children. Perhaps the most basic tenet of all pediatric practice is that children are not merely miniature adults, with diagnoses and treatments titrated down by metrics of size and weight. This was especially true in nuclear medicine, where the potential effects of radioisotopes added a separate dimension to concerns about specialized approaches in children.

Pediatric nuclear medicine faced a number of challenges in its developing years. First was the obstacle of critical mass: only a few practitioners specialized in the area, and no professional organization or meeting venues focused solely on their concerns. This difficulty was compounded by deeply ingrained public misconceptions about radiation and its effects and by a complex and sometimes frustrating system of regulatory requirements and constraints. At the request of Conrad Nagle, editor of Newsline, I have prepared this look back at some of the efforts from this period in which I was directly involved.

The Pediatric Nuclear Medicine Club

With the increasing use of radioisotopes in children in the mid 1960s, pediatric nuclear medicine practitioners

naturally gathered at larger professional meetings to discuss common problems and exchange experiences. As pediatric nuclear medicine practice increased, it became obvious that these communications could be better accomplished through a more formalized organization. With support from individuals such as S. Ted Treves, MD, at the Boston Children's Hospital and David Gilday, MD, at the Hospital for Sick Children in Toronto, Ontario, I organized the first meeting of pediatric nuclear medicine practitioners at the 1974 Annual Meeting of the SNM in San Diego, CA. I posted homemade signs (Fig. 1) around the meeting hall, with the goal of developing a pediatric interest group within the SNM. The leadership of the society expressed their concern to me that our special interest group meeting was being convened to create another society that would be in competition with the SNM, a prospect that the founders of the club did not envision then or later. Approximately 40 individuals attended the initial meeting, including physicians, technologists, physicists, nurses, pharmacists, and industry representatives. The goals for the pediatric club were established. I was chosen to serve as the spokesperson for the group, and Sue Weiss, CNMT, was elected secretary.

Several ambitious goals were proposed at this meeting, including a formal request for recognition of a pediatric nuclear medicine group by the SNM. A major objective was to petition the SNM for a formal representative on the program committee and for a specific time slot on the scientific program for a pediatric nuclear medicine category at the annual meeting. Several technologist members of the club, including Weiss, Royal Davis, CNMT, and Elizabeth Kilburn, RTNM, also succeeded in securing a pediatric track for the technologist section programs at the SNM annual meetings. Another initial goal was to pool data and information for the purposes of peer-reviewed publication by the membership. The club members agreed to cooperate and coordinate research studies and to conduct conjoint phase III safety and efficacy studies to obtain U.S. Food and Drug Administration (FDA) approval for various radiopharmaceuticals in children. Another goal was to promote the use of nuclear medicine in other pediatric subspecialty organizations and to referring pediatricians.

At the 1975 Annual Meeting of the SNM in Philadelphia, PA, the interest group was formally named the Pediatric



James J. Conway, MD

From the Newsline Editor:

This is the second in a 3-part series from James J. Conway, MD, a distinguished pioneer in pediatric nuclear medicine and past president of the SNM. In the first part of the series (J Nucl Med. 2006;47:N12–N20), he recalled the individuals and early advances that contributed to the introduction of pediatric applications into the mainstream of nuclear medicine practice. In this installment, he looks at the establishment and evolution of the Pediatric Nuclear Club within the SNM and at the challenges faced by the subspecialty in its formative years. In the final installment, he will provide a fascinating and highly personal memoir of his own experiences as a researcher, clinician, and educator.

Conrad Nagle, MD

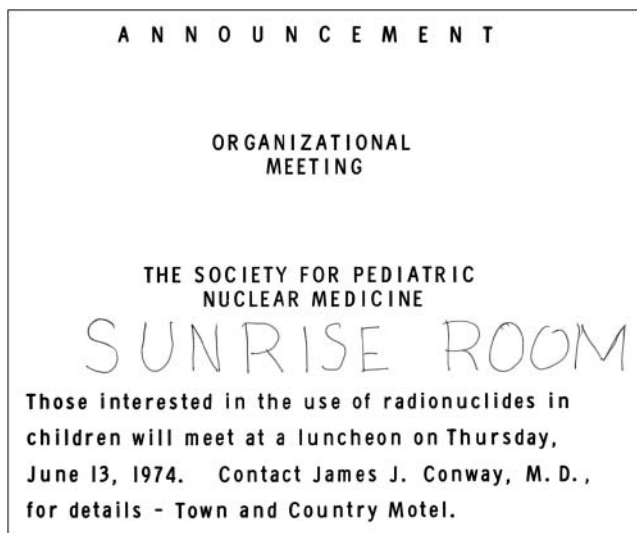


FIGURE 1. Sign used at the 1974 Annual Meeting of the SNM in San Diego, CA, to invite SNM members to the organizational luncheon of what would become the Pediatric Nuclear Medicine Club.

Nuclear Medicine Club of the SNM. The club has met at every SNM annual meeting since and regularly presented pediatric scientific papers followed by a business meeting and a member's miscellany of interesting cases. From the beginning, many international members have participated in the club's activities.

In 1975, I suggested that one of the definitive educational goals for the club could be the publication of a bibliography of pertinent pediatric nuclear medicine literature. At the time, literature searches were often laborious and difficult. It was proposed that the discipline was sufficiently new that such an undertaking would not present a formidable task for the fledgling group. Volunteer compilers were accepted from those in attendance, and categories of interest were assigned. The volunteers and their assigned topics included Kilburn, for pediatric nuclear medicine technology; Gilday, for the central nervous system; Henry Wellman, MD, for the thyroid; Treves, for cardiac applications; Phil O. Alderson, MD, for lung studies; myself for genitourinary applications; Jerold M. Lowenstein, MD, for radioimmunoassay; Massoud Majd, MD, for skeletal imaging; Hirsch Handmaker, MD, for liver, abdomen, and spleen; Robert G. Brown, MSc, for radiopharmaceuticals; and Eugene L. Saenger, MD, and Michael J. Gelfand, MD, for radiobiology and dosimetry. The result was the compilation of a bibliography of 1,659 references pertinent to pediatric nuclear medicine from more than 2,500 contributors. The Pediatric Nuclear Medicine Club's *A Bibliography of Pediatric Nuclear Medicine Literature* was published in 1976 by Searle Radiographics, Inc. and distributed free to nuclear medicine practitioners (1). It should be remembered that the sophistication of the Internet and a computerized Index of Medical Literature for medical reference searches were undreamed of at this time. The compilation

of this specialized bibliography on pediatric nuclear medicine simplified research for many authors by providing a well-codified means of access to historical and other pertinent references in the literature.

In 1990, membership in the Pediatric Nuclear Medicine Club had grown to more than 100. According to the bylaws of the SNM, a minimum of 100 members was necessary for recognition of the club as an SNM council. I recommended that the club petition for SNM council status at the 1990 meeting. Although several members feared that we would lose the sense of purpose and fellowship generated at yearly meetings, the group voted to seek council status. The petition for recognition was submitted to the SNM Board of Trustees, and council status was granted on June 10, 1991.

In June, 1992, the Society of Pediatric Radiology (SPR) conducted a survey. Of 65 pediatric radiology facilities in the United States, only 36 responded to the survey. Of these, only 11 had 50% full-time equivalent pediatric nuclear medicine practitioners (2). Of additional interest, a significant number of pediatric nuclear medicine practitioners, both then and now, have not joined the SNM. At least 250 individuals participate in Gelfand's pediatric nuclear medicine e-mail community (3), yet the SNM Council on Pediatric Imaging currently has only 120 official members. Gelfand's list server has been a major link for communication and interaction of practitioners, especially in the intervals between meetings, and he should be lauded for bringing this freely available site to fruition.

Important functions of the SNM Pediatric Council have been representation on the SNM Board of Trustees and later in the House of Delegates. Perhaps more important has been representation on the program committee for the annual meetings. Members have served as reviewers for pediatric articles for *The Journal of Nuclear Medicine (JNM)* and the *Journal of Nuclear Medicine Technology (JNMT)* as well as for many other journals. Pediatric Council members have had professional and social get-togethers at the annual meetings of the SNM and of the European Association of Nuclear Medicine. At the meetings of the World Federation of Nuclear Medicine and Biology, we have had well attended pediatric nuclear medicine tracks and even "College Bowl" challenges in Toronto, Ontario; Sydney, Australia; and Berlin, Germany. The 120 members of the Pediatric Imaging Council of the SNM today include technologists, basic scientists, radiopharmacists, nurses, industry members, and nuclear medicine physicians from the United States and around the world.

Combating Radiation Hysteria

The growing subspecialty had much to overcome, both in the culture and in dealing with sometimes contradictory and constraining regulatory efforts. Radiation hysteria was a pervasive force in the 1960s and 1970s. Much of the public's perception of "radiation risk" was rooted in the after-effects of the Hiroshima and Nagasaki bombings and was supplemented by the widely publicized risk data that emerged gradually during the 1960s. These data were derived primarily from

exposures resulting from massive and instantaneous single exposures, often associated with early deaths. Soon the longer-term effects from lesser exposures began to manifest themselves as a variety of cancers and chronic illnesses. It was natural for these findings to have a significant effect on the public's perception of risk from medical imaging and therapeutic procedures employing radiation.

Other long-term radiation risk data had been made public earlier with the poisoning of radium dial painters, overexposures in radiotherapy (especially in pediatric applications), and in contrast agents, such as thorotrast, found to have deleterious effects. Much of the published data on radiation risks was being determined from these most egregious incidents of overexposure and then extrapolated to estimates of risk from clinical radioisotope studies.

Various "theoretical risks" were being determined by scientific bodies, such as the International Commission on Radiological Protection (ICRP) and the National Commission on Radiological Protection (NCRP). Those organizations conceptualized and debated different models of risk that could be extrapolated from a threshold level to a no-threshold level. The concept of radiation risk was being developed and modified with each release of data and estimated known exposures. These open debates confused the public and provided fodder for the antiradiation activists.

Compounding the problem, self-proclaimed radiation risk "experts" (often with axes to grind) devised their own data interpretations, sometimes for promotion of their publications. These individuals were spotlighted in the national radio and television media. One "scientist expert" proclaimed on the *Phil Donahue Show* that a single unit of radiation, the rad, delivered to the brain would result in 1 out of 200 children developing brain cancer within his or her lifetime. This telecast reached more than 25 million viewers throughout the world. Such proclamations had serious detrimental effects on the public's perception of radiation risk. After this show aired, a distraught mother called me about her son, who had recently undergone a brain scintigram. I spent several hours with the mother, attempting to dispel her fears that she had approved a study that had "a very high chance" of causing her son's death. I protested to Donahue's staff that the presentation on his show of the risks of radiation to children was highly exaggerated and created fears in many parents that might prevent them from allowing their children to undergo necessary radiologic and nuclear medicine studies or treatments. A number of months later, Donahue invited me to present my side of the story on his show. Fortunately, I had been trained previously in television presentations at the Home Box Office studios in New York City, through an American College of Nuclear Physicians (ACNP)-sponsored program of media training for its leadership. I believe that I succeeded in dispelling a great many public fears about radiation risks while on the Donahue show. I placed radiation risk and benefits from radiologic and nuclear medicine procedures into a proper perspective,

emphasizing the real risks from disease processes. I was selected subsequently to participate on Committee 3, the medical committee, of the ICRP, where I am proud to have contributed to the development of 2 important radiation protection documents for the patient (4) and for the worker in radiology and nuclear medicine (5).

Some popular mythologies about radiation are particularly persistent. In film after film, exposure to radiation created giant mutations or resurrected unlikely prehistoric behemoths. More than 30 popular comic book and cartoon characters, including Spiderman, the Hulk, the Beast, and even Captain America, owed their special powers to inadvertent exposure to radiation. It was ingrained in many of us as children that radiation is a dangerous and (perhaps more important) *evil* force (6).

All of these revelations, real or unreal, served to impede the general acceptance of the use of radioisotopes in children, despite the fact that many nuclear medicine studies delivered lower absorbed radiation doses than comparable radiographic studies. At the same time, as a profession, we also came to know that radiation has a greater effect upon children and so we adopted the principles of the ICRP, the NCRP, and the Nuclear Regulatory Commission (NRC) to administer absorbed radiation doses that are "as low as reasonably achievable" to provide a satisfactory study.

Meeting the Challenge of Government Regulation

Perhaps the greatest impediment to the growth of pediatric nuclear medicine encountered in the early years was government regulation in all its forms. Regulations arose from the many national and local government agencies and from the "self-imposed regulations" that originated in medical organizations. At the government level there were at least 20 national organizations that included the NRC, FDA, DOE, DOT, FTC, BRH, EPA, APA, CRS, and the JCAHO—an alphabet soup of regulatory bodies that do not need spelling out for most readers of this journal. Similar bodies at the state and local level have included the IDNS, EPA, CBH, and RSC. For everyone practicing nuclear medicine, the submission of complex applications and reporting forms, along with frequent and often unannounced inspections, became a way of life. At our institution, we finally had to insist that no more than 1 agency could inspect on any single day, because the inspectors sometimes bumped into one another and disrupted clinical work.

Effective voluntary self-regulation arose from the creation of hospital institutional review boards and Radioactive Drug Research Committees. The ACNP and the American College of Radiology also provided self-regulation guidelines. In addition, the American Academy of Pediatrics issued its recommendations for the use of drugs in children (7). The U.S. Department of Health, Education, and Welfare (today Health and Human Services) issued its own regulations in *General Considerations for the Clinical Evaluation of Drugs in Infants and Children* (8). Both of

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these documents imposed restrictions on the use of non-FDA-approved drugs in children. At the time, none of the commercially available radiopharmaceuticals had undergone clinical testing in children or secured FDA approval for these applications. However, we could still prescribe radiopharmaceutical drugs on an individual basis.

The most serious impediments to the growth of pediatric nuclear medicine came from the NRC and the FDA, although many of the other agencies influenced the direction of research and practice. A classic example of a regulatory impediment was the approval of ^{99m}Tc -pertechnetate for radionuclide cystography. In the late 1960s, Donald Blaufox, MD, and I, working independently and unknown to each other, were developing a gamma camera technique to study vesicoureteral reflux in children (9–10). C.C. Winter, MD, had successfully documented vesicoureteral reflux in children using radioisotopes and a scintillation probe detector in 1965 (11). Our first radionuclide cystogram at the Children's Memorial Hospital (CMH) in Chicago, IL, was performed in January 1970. We performed some 70 studies in the following year on a \$3,000 research grant from the general research program at CMH. Table 1 summarizes the long regulatory scenario that ensued. In short, 15 years would pass before final FDA and NRC approval would allow practitioners to instill 1 mCi of ^{99m}Tc -pertechnetate into the bladder of a child.

An especially aggravating role in this process was played by the NRC. In spite of the 1980 FDA approval of ^{99m}Tc -pertechnetate for radionuclide cystography, some NRC inspectors, attempting to protect the public from unnecessary radiation, cited practitioners for performing radionuclide cystography by a route of administration not

described in the FDA package insert. Thus, although we had gained approval for the routine use of ^{99m}Tc -pertechnetate in children, the interpretation by NRC inspectors was that it was not approved for administration into the bladder—or any other orifice for that matter. The result was that practitioners were forced to use x-ray cystography, which delivered significantly higher absorbed radiation doses to children.

This regulatory impediment required the filing of a New Drug Application (NDA) supplement for the instillation of ^{99m}Tc -pertechnetate into the bladder for radionuclide cystography. I persuaded Joe Goldstein of Medi-Physics Corporation and H.C. McCleary, Jr., Andrew Bass, H. Maroon, and Michael Swiatocha of E.R. Squibb and Sons to conduct limited phase III clinical trials with instillation of ^{99m}Tc -pertechnetate into the bladder and to submit supplements for their NDA-approved radiopharmaceuticals to satisfy the NRC's interpretation of the route of administration rule. Letty Lutzker, MD, and I conducted the limited phase III clinical trials and filed all of the necessary paperwork with the FDA. This goal was finally met in 1985—15 years after the first radionuclide cystography with a gamma camera was performed. I remain convinced that without constant badgering by members of the FDA Radiopharmaceutical Drugs Advisory Committee (RDAC) and its chairs Ralph Robinson, MD, and Barry Siegel, MD, that ^{99m}Tc -pertechnetate might still not be fully approved for radionuclide cystography.

Another example from the early regulatory difficulties makes it easier to understand the frustration experienced by early practitioners of pediatric nuclear medicine. The U.S. Atomic Energy Commission (AEC; precursor to the NRC) had assumed control of radioisotopes for medical purposes

TABLE 1
Innovation to Approval: Regulatory Saga of ^{99m}Tc -Pertechnetate in Pediatric Radionuclide Cystography

Action	Date
First radionuclide cystogram at Children's Medical Hospital	January 1970
First presentation of 100 cases at a professional meeting	September 1971
First scientific publication	August 1972
Rejection by FDA for placement on "Well Established List"	February 1975
Petition for a Medi-Physics NDA* supplement	July 1975
100 cases collected at 4 pediatric centers to prove safety and efficacy	April–June 1976
Squibb NDA supplement submission	January 1977
Medi-Physics data filed	June 1978
Squibb data filed	March 1979
Medi-Physics inquiry	May 1979
FDA Medi-Physics approval	December 1980
NRC restricts "route of administration"	April 1982
FDA Squibb approval	August 1982
Additional clinical trials for "route of administration"	1983–1984
NRC acceptance of the "route of administration"	1985

*New Drug Approval status

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after World War II. Radiopharmaceuticals were exempted from the requirements of the Food, Drug, and Cosmetics Act of 1962, because they were under the control of the AEC. The FDA took back responsibility for some radiopharmaceuticals in 1965 by placing the most commonly used radioisotopes, such as ^{131}I , on the "Well Established List." The FDA accepted data from the literature as support for the safety and efficacy of certain commonly used radiopharmaceuticals and to secure approval for routine clinical use. However, the FDA determined that pediatric indications for these same radiopharmaceuticals had not been "documented in the literature" and thus were not accepted in the approval process for the well-established list. As a consequence, the so-called "orphan clause" was included on all package inserts (12). The orphan clause stated that the radiopharmaceutical had not been proven safe and effective for clinical use in children. A practitioner who used the radiopharmaceutical in a child did so on an individual prescription basis (as is the right of a licensed physician). The practitioner thus accepted any risks that might be associated with the nonapproved drug. The result was an understandable reluctance in some institutions to apply even the most common nuclear medicine techniques in children, despite clear evidence of the effectiveness of these techniques in diagnosis and treatment.

In an effort to remove the orphan clause from package inserts, I persuaded volunteers from the Pediatric Nuclear Medicine Club to conduct limited clinical trials and submit additional supporting data from the literature to document the safety and efficacy of the more common radiopharmaceuticals for specific pediatric indications. Pediatric nuclear medicine practitioners who expended considerable time and effort with me on this endeavor included Treves, Handmaker, Gelfand, Lutzker, Judith Ellen Ho, MD, Howard Ted Harcke, Jr., MD, Sidney Heyman, MD, Diane Duszynski, MD, and George Sfakianakis, MD. Of course, none of the work could have been accomplished without the technological assistance of pediatric nuclear medicine technologists, such as Weiss at CMH, Davis at Boston Children's Hospital, and many others.

A number of individuals in the radiopharmaceutical industry provided significant resources and service for this pediatric indications project. They included Edward Holmes, Sam Barker, James Finn, Linda Drachman, and Len Sloomaker. Without the tremendous amount of effort and paperwork in submitting the class action petitions, the orphan clause might still be included in all of our common radiopharmaceutical package inserts. In all instances, the cost of these limited controlled phase III clinical trials was borne by the volunteer individuals and their institutions.

In the early 1980s, members of the SNM and the ACNP again answered the call to document substantial evidence of safety and efficacy for "unusual" radionuclide procedures in children and adults based upon literature data. I served as the chair and organizer of an ad hoc group of volunteers to develop class action petitions that were submitted with the

encouragement of the FDA for their medical review as testimony of the safety and efficacy for these new indications and routes of administration. Among the individuals who worked on the "new indications" projects were Leon Malmud, MD, and myself for oral $^{99\text{m}}\text{Tc}$ -sulfur colloid for gastroesophageal reflux; Wellman, Aslam Siddiqui, MD, and Bruce Mock for intrathecal $^{99\text{m}}\text{Tc}$ radiopharmaceuticals for radionuclide cisternography; Ed Suprenant, MD, and Michael Hayes, MD, for $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentaacetic acid lung aerosol; Tapan Chaudhuri, MD, for radionuclide dacrocystography; Jim Woolfenden, MD, and Dennis Patton, MD, for cutaneous blood flow measurements with intradermal injection of ^{133}Xe ; and Gregory Gergans, MD, for lymphoscintigraphy. Other individuals who worked on projects included Alderson and Barbara Y. Croft, MD. Many physicists at the participating institutions provided absorbed dosimetry calculations for the package inserts. Sue Flint of the New England Nuclear Corporation volunteered her company's bibliographic resources for the members of the ad hoc committee.

Because of the rapidly increasing use of radiopharmaceuticals in children, the FDA appointed pediatric nuclear medicine practitioners to the RDAC to address the use of nonapproved radiopharmaceutical drugs in children. I was appointed to the committee in 1976 and served until 1985. Gilday and Treves were among other early members. Through the use of limited prospective phase III clinical trials at a number of institutions, retrospective reviews of the literature, and the cooperation of manufacturers, $^{99\text{m}}\text{Tc}$ -pertechnetate and many other radiopharmaceuticals were finally approved for use in children. Another pediatric project initiated by the RDAC that assisted the FDA in the drug approval process was the determination of pediatric absorbed dosimetry calculations under the guidance of Treves as subcommittee chair. These volunteer efforts resulted in additional FDA approvals for a number of commonly used radiopharmaceuticals in children.

A Note on Industry Partners

I would be remiss in not acknowledging the role of industry in the development of pediatric nuclear medicine. In the very early years, the Nuclear-Chicago Corporation sponsored free symposia in numerous cities both in the United States and abroad. Academicians and other practitioners were invited to present lectures about their developing pediatric practice. These 1-day symposia were well attended by those eager to learn about techniques and tailored approaches.

In the ensuing years, numerous manufacturers, including the Picker Corporation, Mallinckrodt Inc., General Electric Corporation, Medi-Physics, and Syncor, sponsored educational programs both locally and at SNM annual meetings. The instrument manufacturers were especially helpful in modifying their equipment to conform to the imaging needs of small children. Pediatric practitioners were

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faced with the challenge of imaging children who might weigh 1 pound or 250 pounds, and ingenuity was often needed. Our hospital carpenters manufactured a wooden table with a cutout that fit the camera's collimator. We were then able to place the infant or small child directly on the collimator for better resolution.

The pharmaceutical manufacturers played a major role in the development of indications for pediatric use for many of the commonly used radiopharmaceuticals. Although the FDA encouraged manufacturers to sponsor phase III clinical trials in children, the high cost of such trials was a burden that some radiopharmaceutical manufacturers could not assume, considering the relatively low volume of such agents sold for pediatric applications. However, the need for data led to the formation of fruitful investigative partnerships between industry and pediatric nuclear medicine specialists, with many of these relationships lasting now for decades.

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reforming the clinical trial process—both trial design and trial conduct—would dramatically improve the efficiency of product development, which means getting products to patients faster at less cost.”

Several of the projects should be of particular interest to the nuclear medicine/molecular imaging community. Project 12, Drug Targets as Critical Path Tools: Cancer Therapies, describes development of diagnostic tests that “may prove to be useful markers to predict responsiveness to therapy” and “would make development of targeted cancer therapies more effective and efficient.” Project 26, Imaging in Cancer, specifies the development of FDG PET as an additional response measure in non-Hodgkins lymphoma. Project 25, Imaging Biomarkers in Neurocognitive Diseases, suggests “functional imaging such as FDG PET as a measure of glucose metabolism, may provide a biomarker to assess earlier, more subtle, changes in the progression of these diseases.” Project 28, Noninvasive Therapy Monitoring, notes “molecular tags that can be located through imaging techniques could dramatically improve product development by enabling sponsors to correlate response with drug availability at the target site and to evaluate the relationship between organ toxicity and drug distribution to that organ.” Other projects call for imaging of inflammation in cardiovascular disease, diagnostic markers for neuropsychiatric conditions, and development of performance standards for imaging displays.

To facilitate completion of these projects in a timely manner, the FDA will bring together partnerships and consortia to accomplish a majority of the projects. The initiative will require a new, cooperative partnership among

the primary research, evaluation, approval, and medical treatment delivery and reimbursement divisions of HHS, including the FDA, National Institutes of Health, Centers for Medicare & Medicaid Services, and Agency for Healthcare Research and Quality. The FDA is currently identifying several priority Critical Path research opportunities. Some of the projects in the list could be undertaken by a single organization, whereas others will require collaborations coordinated and supported by the FDA. For example, a major Critical Path undertaking also announced on March 16, which seeks to develop guidance on the use of standard biomarkers to predict safety in drug development, will be coordinated by the Critical Path Institute and carried out by a newly formed Predictive Safety Testing Partnership including Bristol-Myers Squibb, Johnson & Johnson, Merck, Novartis, and Pfizer. The FDA, although not a member of the partnership, will assist it in an advisory capacity.

“It is important to note that the list released today is meant to spur a continued dialog among industry, academia, patient, and professional groups and government organizations about the research priorities that need to be accomplished in our effort to modernize the medical product development process,” added Woodcock. “We believe it is crucial to build a national infrastructure to support and continually improve the Critical Path Initiative. Therefore, we must reach beyond specific opportunities and build collaborations to work together to encourage continued development of the Critical Path sciences.”

More information about the Critical Path Initiative is available at www.fda.gov/oc/initiatives/criticalpath/.

U.S. Food and Drug Administration