# New Internal Radiation Dose and Modeling Software; FDA Approves Commercial MIRDOSE Successor

Michael Stabin, PhD, Assistant Professor of Radiology and Radiological Sciences, and colleagues at Vanderbilt University received FDA exemption (premarket notification, 510K) on June 15 for the production and distribution of software containing personal computer code designed to update the now outmoded but still much sought after MIRDOSE3.1. Called OLINDA/EXM (for Organ Level INternal Dose Assessment/EXponential Modeling), the software was developed over the course of several years as a direct result of difficulties in MIRDOSE distribution and increasing incompatibility with upgraded systems. "We are pleased to finally be able to offer this software, which extends beyond the limits of previous dose calculation software and adds new and useful features," said Stabin. "And we're particularly proud to have worked so successfully with the FDA, which was very responsive and helpful throughout the process."

## Background

The primary purpose of the original MIRDOSE software was to perform calculations needed to obtain dose estimates for the various organs of the body once the kinetics of a radiopharmaceutical agent were established. The code's other purpose was to help standardize dose calculations in the user community through the use of recognized models and techniques for dosimetry. The MIRDOSE code series, which appeared in the mid-1980s, was designed primarily to relieve the tedium of performing repetitive manual dose calculations by hand using lookup tables. With these codes, basic dose calculations could be made in seconds instead of hours. MIRDOSE1 was used only in-house at the Radiation Internal Dose Information Center (RIDIC; Oak Ridge, TN), where it was developed. The program was limited in its applications and could be run on only one type of computer. MIRDOSE2 was released in 1987 for IBM-compatible computers and included about 60 radionuclides and 6 anthropomorphic phantoms representing both children and adults (the Cristy–Eckerman series). MIRDOSE2 was widely distributed and used in the nuclear medicine community. MIRDOSE3 was released in 1994 and included more than 200 radionuclides and 10 phantoms (including a series representing the pregnant and nonpregnant woman). Version 3 also included a model for calculating self-dose to small, unit-density spheres (such as tumors) and an improved and more detailed bone and marrow model developed by Keith Eckerman, PhD, of Oak Ridge National Laboratory (ORNL). RIDIC distributed the software free of charge.

As reported in Newsline *(J Nucl Med.* 2000; 41[6]: 13N–19N), inquiries by the FDA in 2000 led to suspension of RIDIC distribution of MIRDOSE3. The reason for this elective action was the FDA's concern about whether such software should be classified as treatment planning devices that would require premarket notification and other regulatory compliance. RIDIC has since lost its funding support, and the MIRDOSE software has been unavailable except through copies circulated informally among physicists and nuclear medicine physicians. Even these copies have proven problematic, because the last MIRDOSE edition does not work with operating systems later than Windows 98.

"It has been clear since RIDIC stopped distributing MIRDOSE that the nuclear medicine community needs and wants a tool like this," said Stabin. One measure is the number of individuals who contact the SNM annually hoping to purchase a copy of MIRDOSE. "There's a tremendous amount of interest in dosimetry in general today, as many new compounds, mostly therapeutic agents, are under investigation," said Stabin. As a partial response to this interest, in 2002 he led an international group of radiation specialists in launching a Web site with a broad spectrum of useful information. The RADAR (RAdiation Dose Assessment Resource) site (www.doseinfo-radar. com) has as its stated goals "putting together various resources in the field, integrating them into a single system, and making them available to a wide audience as quickly and efficiently as possible." In the 2 years since the site debuted, Stabin has received frequent positive feedback from around the world, particularly from individuals interested in learning more about performing dosimetry calculations. "And, of course, we're asked frequently about the availability of MIRDOSE," he said. "Although MIRDOSE is no longer available, we're proud to be able to offer our updated alterative."

## Innovations on a Trusted Model

The MIRDOSE software had phantom libraries that permitted calculation of radionuclide doses for individuals of different ages and sizes and for women at different stages of pregnancy. The program, however, did not include libraries of doses for nuclear medicine radiopharmaceuticals. The user needed to calculate the input data

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### About the MIRD Committee

The SNM MIRD Committee is tasked with (a) developing and compiling methods for calculating internal radiation dosimetry of distributed radionuclides in humans, compiling and disseminating supporting data needed to implement such methods, and studying dose response for normal organs and tumors to internal emitters; (b) compiling and disseminating data regarding internal dosimetry, absorbed fractions, and dosimetric models; (c) and holding regular meetings to monitor progress of task groups, receive updates on research in the field, and monitor and plan projected publications. In addition to regularly publishing pamphlets and reports on various internal dosimetry topics, the MIRD committee also sponsors regular sessions at the SNM, including continuing education offerings.

Members of the current MIRD Committee include: Evelyn E. Watson, Chair; Stephen R. Thomas, PhD, vice-chair; Henry D. Royal, MD, Board Liaison; and members Wesley E. Bolch, PhD, Aaron B. Brill, MD, PhD, Darrell R. Fisher, PhD, Ruby Meredith, MD, PhD, George Sgouros, PhD, Jeffry A. Siegel, PhD, Michael G. Stabin, PhD, and Barry W. Wessels, PhD.

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that described the biokinetics of a given radiopharmaceutical, from his or her own animal or human data or perhaps from data found in the literature. Standardized kinetic models were intentionally not included in the code, because kinetics for radiopharmaceuticals change often as new information becomes available and as models change and improve. "MIRDOSE was simply a tool that permitted the calculation of radiation dose estimates using the MIRD technique once the kinetic model was defined by the user," said Stabin.

In addition to compatibility with current operating systems, OLINDA/EXM offers a number of new and innovative features. The software contains all new code (the code was rewritten from scratch in a new language), several new organ models, and a module called EXM (written by RADAR colleagues at CDE, Inc.) that fits kinetic data to specified functions. OLINDA/EXM also permits adjustment of standard phantom organ masses to patient-specific organ masses (measured by techniques such as PET, SPECT, CT, or MRI). Just as with MIRDOSE, OLINDA/EXM users will enter results of kinetic models into the code, which uses them with models of the human body that have been established in the literature to calculate estimates of the radiation dose to organs in the body, as well as effective dose quantities. The dose factors used in OLINDA can also be found on the RADAR Web site. The technical bases for these data appeared in the journal *Health Physics* (2003;85:294–310). The EXM portion of the new code allows users to perform kinetic analyses, fitting sums of exponentials to data gathered in animal or human studies.

The software and supporting documentation were carefully formulated to address all of the concerns expressed by the FDA 4 years ago. Although the vast majority of the applications of this code are theoretical applications involving diagnostic applications of radiopharmaceuticals, current interests in radiopharmaceutical development clearly suggest the use of such standardized codes in therapeutic applications, retrospectively or otherwise. "The FDA, I think, recognized the importance of this software to the user community," said Stabin. "Once we provided them the appropriate information, they were extremely helpful in delivering critical reviews and advice that helped us navigate the 510K process, and, in the end, this rigorous review process considerably improved our end product." He emphasized that the end result is "not MIRDOSE 4—although we hoped to build on the past successes of MIRDOSE, this is an entirely new product that is more flexible and accessible and linked to a wide range of support data and on-line resources." To learn more about the OLINDA/EXM software, visit the software page on the RADAR Web site (www.doseinfo-radar.com/RADARSoft.html).

The RADAR group is currently working to bring together international physicians and physicists to formulate more standardized tools and methods that can be delivered to practitioners who need them to obtain and analyze dosimetry information. "I just returned from a stimulating time at the European Association of Nuclear Medicine Congress, where it was clear that physicians worldwide want to do good dosimetry for their patients and in their research," said Stabin. "We just have to find ways to make it practical and accessible." The RADAR group is currently working with this international group to organize and disseminate standardized methods, tools, and training materials for internal dose calculations.