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EDITORIAL

The New Food and Drug Administration Center for Devices and Radiological Health Engineering and Physics Laboratory and Methods for Testing Software That Controls Infusion Pumps

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Introduction

On June 15, 2007 the U.S. General Services Administration (GSA), in partnership with the U.S. Department of Health and Human Services' Food and Drug Administration (FDA), dedicated the Center for Devices and Radiological Health (CDRH) Engineering and Physics Laboratory (also known as Building 62) at the FDA's new campus at the White Oak Federal Research Center outside Washington, DC in suburban Maryland (**Figure 1**). This is the fifth building at the campus to be opened, following dedication of the Life Sciences Laboratory (2003), Office Building 21 (2005, Office Building 22), and the Central Shared Use Building (2006). As editor of *Journal of Diabetes Science and Technology*, I was invited to the dedication, but because of a schedule conflict, I could not attend. Instead, I visited this new building the following month and received a private tour of the building.

Figure 1. Entrance to the FDA White Oak campus.

Recent History of the FDA

The White Oak campus was originally established in 1944 as the Naval Ordnance Laboratory. Its mission was to conduct research on military guns and explosives. Later, the mission was expanded to include research involving torpedoes, mines, and projectiles. The Navy's White Oak facility was closed in 1997 and turned over to the GSA for the purpose of developing a new campus for the FDA.

FDA's current operations in the greater Washington area have been scattered among dozens of leased buildings throughout suburban Maryland. The White Oak campus will eventually replace all these existing fragmented facilities with new laboratories, office buildings, and support facilities. The last part of the White Oak

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consolidation is presently scheduled to be ready for occupancy in 2010. The new FDA campus will include 14 interconnected buildings with a total of 2.33 million square feet of space and is being built in phases as Congress approves funds. The complex will support FDA's Center for Devices and Radiological Health, Center for Drug Evaluation and Research, Center for Biological Evaluation and Research, Office of Regulatory Affairs, and offices for the Center for Veterinary Medicine and Office of the Commissioner. The campus' historic main building, which is visible from New Hampshire Avenue, with its stately entrance and brick façade, will eventually house the Office of the Commissioner and the Office of Regulatory Affairs and will be the gateway to the campus.

The consolidation project is intended to create the required modern facilities for the FDA to best perform its mission and respond to the needs of the United States for medical product review, approval, and supply needs. This facility is intended to help attract and retain excellent scientists by providing them with a state-of-the-art facility for carrying out top-quality analyses to protect our nation's health. Such a plan is especially critical as the nation faces new challenges in ensuring that FDA-regulated products are not used as vehicles for terrorism.

CDRH Engineering and Physics Laboratory

The five-level 145,000 square foot CDRH Engineering and Physics Laboratory will house approximately 160 CDRH employees, and also has short-term space for 30 or so students and research collaborators. This building will consolidate the engineering and physics research components of the CDRH (**Figures 2** and **3**).

The high-tech laboratories within that building will evaluate electromagnetic and medical devices, as well as radiological instruments and consumer appliances that generate ionizing or nonionizing radiation. Specialists in engineering, physics, mechanics, imaging, and materials science will conduct research at the facility. The facility contains electromagnet shielding, numerous vibration isolation slabs for electron microscopy (**Figure 4**), deionized and degasified water, laser devices, and a high bay ground floor that houses an anechoic chamber and other shielded test chambers for electromagnetic interference and radio frequency research. The building utilizes several energy-efficient systems for heating and cooling. "We expect that this will be an asset that is unique in the research world," according to Charles Warr, Associate Director for Laboratories of the Office of Science and Engineering Laboratories at CDRH.

Figure 2. FDA Engineering and Physics Laboratory, facing east.

Figure 3. FDA Engineering and Physics Laboratory, facing north.

Figure 4. Electron microscope on a vibration isolation slab in Building 62.

Software Usage Testing

One laboratory that stood out during our tour was that of Brian Fitzgerald and Paul Jones. They are developing systems to assess the performance of medical software, such as that which controls insulin infusion pumps and which would eventually control an artificial pancreas (**Figure 5**). Device software is becoming increasingly complex and regulators need effective methods for assuring that the software is safe and reliable.

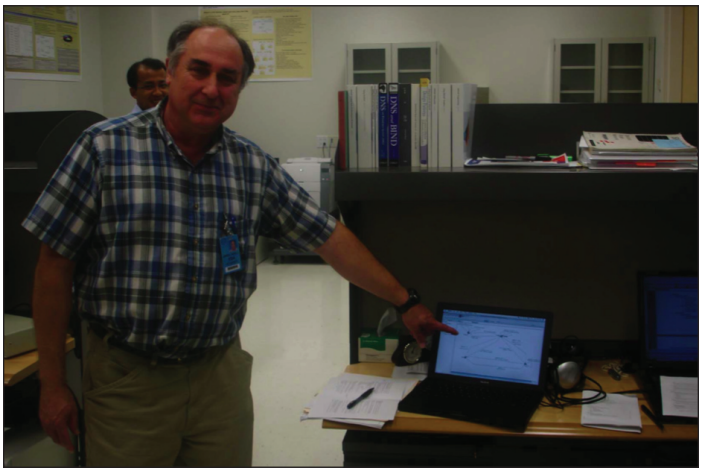

Figure 5. Paul Jones, in his laboratory, demonstrating a system for evaluating medical software.

Performing premarket analysis of software is difficult because of the complexity of the software. This complexity, often represented by tens of thousands, if not millions of lines of code, frequently contains subtle and latent errors. These errors can result in device failures. Traditionally establishing the cause of a failure as a consequence of software requires one of three difficult approaches. The analysis can include exhaustive testing of all the combinations of software instructions, which may require months, years, or even be impossible for complex devices. The analysis can use a modeling-based approach that relies on having detailed information and knowledge about a device design; a prohibitive effort at present. Finally, the analysis can entail a review of the source code in its entirety, which, given the extreme complexity of many current medical devices, can be an impossibly difficult task for a regulator or third party without a background in developing software for that manufacturer.[1]

As an alternative to these strategies, Fitzgerald, Jones, and colleagues at the FDA CDRH Office of Science and Engineering Laboratory (OSEL) are developing safety models to facilitate premarket review of software. A software safety model characterizes safety properties of the device being used in the intended environment. This formal method-based approach utilizes development of an open system safety model that individual manufacturers can contribute to. Such a model incorporates a set of usage and safety requirements that can be defined, analyzed, and verified with the help of automated model checking tools. Manufacturers can extend this safety model in their development process to incorporate product-specific features.

Using this type of model, FDA scientists can derive test case sequences for a device. Each test case is a set of user inputs and system events. Using these test cases, regulators can record all the distinct paths or test sequences and their corresponding outcomes. The set of outcomes, referred to as a test suite, can be made publicly available to any device manufacturer. A test suite can include (1) test cases demonstrating safety properties that must always be satisfied, (2) optional test cases that correspond to best practices that are desirable but not mandatory, and (3) error conditions that must never occur.

When the manufacturer is developing a device, its software can be tested against the test suite to verify their implementation of the safety model. Discrepancies between expected outcomes per the test suite and observed outcomes per the actual product being tested represent failures of compliance. If the test results are in agreement, then the product can be claimed to be in compliance with the established safety criteria.

The benefits of testing with safety models are (1) assurance that a minimum level of product safety has been attained; (2) fewer errors by manufacturers who might attempt to construct their own models; (3) simplified postmarket and forensic analysis of products, comparing outcomes of safety analyses established in the premarket review with such analyses in the postmarket state; and (4) fewer product recalls and regulatory actions.

The research group at OSEL is currently developing an infusion pump usage model that will be suitable for testing software that controls an insulin infusion device. The model consists of (1) a user interface, (2) a usage/safety module, (3) a pump module, and (4) a patient module.

The user interface consists of all possible buttons and screens available to the user. The core usage model encompasses common features of all types of infusion pumps (such as alarms, the volume of fluid delivered, the amount of fluid remaining in the reservoir, and the level of patient

interaction) and wrappers, which are extensions to the core containing specific features of each type of pump. The core model can be represented by unique configurations, composed of specific combinations of wither-or states, such as on or off, dormant or active, and alarm sounding or not sounding. The pump module represents the syringe, tubing system, reservoir, and drug boluses and includes special events such as interruptions of flow and disconnections. The patient module is usually passive, but the patient can trigger a bolus dose of insulin or change a basal rate. The current model does not allow for monitoring physiological changes that the patient would experience in the event of hypoglycemia.

The usage model is designed to incorporate various pump configurations, inputs, alarms for extreme states, and probabilities for each possible transition from the current state. Currently, the usage model describes 292 unique pump configurations and 3500 transitions.

To date, approximately 39,000 test-case sequences have been used to test an OSEL patient-controlled analgesic infusion pump model. The testing uncovered 46 errors, 5 of which were safety-critical errors that were potentially able to cause hazardous situations. The other 41 were errors of lesser severity, but of potential severity to adversely affect the performance of the pump.[2]

Postmarket Analysis

A thorough premarket analysis should minimize the need for postmarket analysis of software. Errors can be introduced into software following premarket analysis through bug fixes and evolutionary maintenance (changes). In these cases, the marketed software will be different than what was reviewed in the premarket analysis, and the modified software could cause a safety-related error. Postmarket product review would be needed following such an error in order to determine the reason for the error and to stipulate corrective action.

To evaluate postmarket software-related failures, OSEL is currently researching various static analysis tools, one of which is program slicing. Program slicing focuses on parts of a product's code that might contain an error. Any statement or transition that has no effect on a particular point of interest in the code is deleted. The code responsible for the failure then stands out. The code is reanalyzed with the usage model until the error is identified and corrected. In some cases, if the product had passed the premarket usage test, then the usage model would have to be updated to account for the software error and generate a new test suite.

An alternate approach to program slicing for identifying postmarket software errors is to combine slicing analysis with model abstraction. In this approach, the program is disassembled so that the critical individual software instructions can be identified. The program is then converted into an abstract model. This model can be used to test the validity of the program. Whereas slicing provides a top-down model of program comprehension by breaking a program up into static slices, model abstraction provides bottom-up program comprehension, starting with individual commands and building up to an abstract program that essentially resembles the original program in question. Tools based on both of these techniques are currently being developed and refined by OSEL for postmarket software analysis L.

Future of Software Testing

The application of usage modeling, which is currently under development in the new FDA CDRH Engineering and Physics Laboratory, enables reviewers of medical software products to assess software performance more quickly and effectively. Analysis of software is becoming increasingly important to the FDA in its premarket reviews and, when necessary, its postmarket reviews. The tools for software analysis that the FDA is developing will be of great importance in regulating closed loop insulin delivery systems that are currently being developed.

The mission of the FDA OSEL is to develop reliable standardized test methods for CDRH and industry use; perform anticipatory scientific investigations on emerging technologies and introduce new technology into the regulatory process as appropriate; provide highly technical consulting services to CDRH; contribute laboratory data to national and international standards used in CDRH decision making; provide scientific and technical training for CDRH staff members; and maintain laboratory collaborations and relationships with scientific researchers in academia and other Federal laboratories, as well as to coordinate and oversee CDRH's activities that support the development of national and international standards. The new FDA Engineering and Physics Laboratory will greatly assist OSEL in those tasks.

References:

1. Jetley R, Iyer SP, Jones PL. A formal methods approach to medical device review. Computer. 2006;39:61-7.
2. Jetley R, Iyer SP, Jones PL, Spees W. A formal approach to premarket review for medical device software. Proceedings of the 30th Annual International Computer Software and Applications Conference; 2006. p. 169-77.