

STATEMENT BY

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INTRODUCTION

Good morning, Mr. Chairman and Members of the Subcommittee. I am Dr. Steven Gutman, Director of the Office of *In Vitro* Diagnostic Device Evaluation and Safety in the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA or the Agency). I am pleased to speak today about FDA's role in regulating medical devices and to provide information regarding the Adaltis Labotech device.

REGULATORY BACKGROUND

FDA is responsible for protecting the public health by assuring the safety and effectiveness of drugs, biological products, food, cosmetics, medical devices, and products that emit radiation. We do this by keeping abreast of public health issues, developing regulations that further protect the American people, and enforcing the regulations and the statutes that govern these products.

This hearing specifically touches on FDA's medical device regulatory authorities. As defined by Federal law, the term "device" covers several thousand health products, ranging from simple articles such as tongue depressors and heating pads, to cutting-edge and complex devices such as pacemakers, lasers, and imaging technologies. The definition of device specifically includes articles intended for use in the diagnosis of disease or other conditions as well as *in vitro* reagents. Therefore, among the broad menu of device products that FDA regulates are commercialized

analytical tests and laboratory equipment intended for use in clinical laboratories. FDA refers to these as *in vitro* diagnostic devices (IVDs).

The Medical Device Amendments of 1976 amended the Federal Food, Drug, and Cosmetic Act to give FDA specific authority to regulate the safety and effectiveness of medical devices. Using a risk-based classification framework, FDA places every medical device into one of three “classes” depending on the degree of regulatory control needed to provide reasonable assurance of safety and effectiveness of the device for its intended use. Devices posing the lowest risk, such as bandages, are placed in Class I and are subject to general controls. These general controls include manufacturing establishment registration, Quality System Requirements for manufacturing, provisions regarding adulteration and misbranding, record keeping, and reporting of adverse events. FDA refers to these adverse event reports as Medical Device Reports (MDRs).

If general controls alone do not reasonably ensure the safety and effectiveness of a device, but FDA can identify an additional measure or measures that would provide that assurance, the Agency places that type of device into Class II. Class II devices are subject to special controls. Examples of Class II devices include instruments for measuring glucose or hemoglobin. Class II devices generally pose higher risks than Class I devices. They are subject to the general controls that also apply to Class I devices, plus one or more of a wide range of special controls that the Agency may designate. These special controls may include guidance documents, performance standards, post-market surveillance, patient registries, and/or labeling, which, taken together with the general controls, are sufficient to provide a reasonable assurance of safety and effectiveness of the device.

When FDA cannot be assured that the combination of general controls and special controls is sufficient to reasonably ensure safety and effectiveness of a medical device, FDA will place the device into Class III, which are subject to premarket approval. Examples of Class III devices include new tests for diagnosis of cancer or serious infectious diseases such as SARS. Pre-market Approval (PMA) requires manufacturers to submit an application, which is subject to careful scientific review by FDA to provide reasonable assurance of the safety and effectiveness of the device. FDA approval of a PMA application is necessary before a manufacturer may market a Class III device. Once approved for marketing, Class III devices also remain subject to the general controls already described.

As I already mentioned, one of the general controls that is applicable to all classes of devices is adverse event reporting. Under FDA regulations, manufacturers and importers of devices are required to report deaths and serious injuries to FDA that their device may have caused or contributed to, as well as certain malfunctions (“near misses,” which are malfunctions of a type that is likely to cause or contribute to a death or serious injury). User facilities are required to report device-related deaths to FDA, and to report device-related serious injuries to manufacturers. (If the manufacturer is unknown, they should report the serious injuries to FDA). Of course, FDA encourages anyone with knowledge of a device-related problem -- even a less serious one -- to report it to us, through our MedWatch system.

FDA has developed special databases to ensure simplified and standardized reporting of adverse post-market events to the Agency and currently has regulatory staff with specific expertise in IVDs monitoring reports for these products. The Agency uses MDRs to help provide signals of

device problems so it can determine whether follow-up is necessary. If FDA does follow-up and discovers a problem with a device, there is a broad menu of actions that can be taken depending on the nature and severity of that problem. These include issuing public health information to alert users on how to avoid the problem; requiring corrective actions such as recalls, repairs and notifications; and taking various actions to stop further distribution of the affected devices until the problems are corrected.

Thus, FDA has a range of authorities that apply to IVDs and other devices. While FDA inspects device manufacturing facilities to assure conformance with these requirements, particularly requirements for good manufacturing practices and adverse event reporting, the responsibility for inspection and oversight of clinical laboratories that use those devices lies with the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

LABOTECH

As the focus of this hearing is the erroneous test results at Maryland General, let me now tell you about the Labotech device used there. The Labotech device is an automated device intended for use in performing controlled chemical reactions that are the basis of a variety of laboratory tests. The system includes a sample identification station, pipets for applying chemicals needed for the test being performed, incubators and washers, and an electronic eye to read chemical results. This device is considered an open system. That means its manufacturer does not specify the tests that may be performed using it, nor does the manufacturer provide instructions for specific test

procedures. Instead, the device performs functions that are useful in running numerous different assays, but for each specific assay the individual laboratory must program the machine with specific test conditions and procedures. Development or modification of these assay procedures is performed subject to regulations developed under CLIA a program administered by CMS.

The Labotech is considered a class I device, and is subject to general controls. Because of the configuration of this device, it must be manufactured under FDA quality system regulations with design controls. These manufacturing requirements are spelled out in FDA regulations (the quality system regulations) and include requirements for a controlled production environment, production by trained personnel, the presence and use of production and process controls, the implementation of a corrective action and preventive action system, and the need for product verification and validation. The product must be also labeled appropriately with adequate directions for use. This device is also subject to adverse event reporting.

FDA first cleared the Labotech device for marketing in 1992. Since the product was cleared, FDA received one MDR in 2004. An employee of Maryland General Hospital was splashed with patient samples due to a falling wash head. This incident was reported by Maryland General Hospital to the company in 2003. Since there was no indication at the time that the employee had contracted any disease or suffered any other serious injury from the incident, the company judged the event to be one that it was not required reporting at that time. Upon learning in 2004 that the employee now alleges that this incident resulted in her contracting hepatitis and HIV, the company filed an adverse medical event report with FDA about this incident. It is believed that approximately 2500 of these devices have been placed in laboratories worldwide and the device

does appear to provide safe and effective results when used appropriately. FDA takes seriously and investigates MDRs reported to the Agency, however, the nature of this MDR does not lead us to believe that this instrument is unsafe.

FDA first became aware of the problems with test results generated at Maryland General Hospital when our press office received an inquiry about the Labotech device, on March 19, 2004. Shortly thereafter, we contacted our colleagues at CMS, and they reported that they believed this was a laboratory problem, not a problem with the Labotech device.

Since that time, FDA has remained in contact with both CMS and the Maryland Department of Health to share information and see what we can do to assist in the ongoing investigation and correction of the problems observed at Maryland General. We do not have enough information at this time to make further statements about device performance at this site.

Despite our preliminary conclusion that the problems at Maryland General stem from the actions of the laboratory, we have undertaken our own investigation to determine whether the problems at Maryland General might indicate a general problem with the Labotech device itself. That assessment is ongoing, but I can share with you some of the steps we have taken and plan to take. Soon after learning of the problems at Maryland General, we scheduled an inspection of the Allentown, Pennsylvania facility of the U.S. distributor of the Labotech, Aldatis US, Inc. The device is manufactured by Aldatis' parent company, Aldatis Italia, S.P.A., an Italian firm. Our U.S. inspection, which was conducted from April 12 through 14, 2004, focused on whether Adaltis U.S. was aware of the problems and took corrective action. No serious problems were identified.

Since this U.S. site is only a distribution center, FDA is also scheduling a full inspection of the manufacturing site in Italy to include an evaluation of the quality systems in place and the complaint files.

As a result of questions raised at a briefing with this Subcommittee's staff on April 29th, we became aware of two adverse reports about the Labotech that appeared in European databases in 1996 and 1999. The 1999 report resulted in a public health notice in the United Kingdom. FDA is still investigating whether these reports should have been submitted to the FDA MDR database and whether they are related to the problems that were reported to FDA in MDRs. There is no evidence that continued problems have been observed in the European Union since the 1999 report, but FDA expects to follow-up on this issue during the planned company inspection in Italy this summer.

FDA has recently started developing mechanisms for working with Europe to monitor post-market device performance as part of initiatives in the area of global harmonization of device regulation. Problems with device performance that have been included in the European Union databases are now being shared with FDA regulatory staff.

FDA has checked for more informal signals of potential problems with the Labotech in addition to our review of the more formal modes of MDR reporting. We searched published literature for reports of problems. That search revealed no problems but did find two reports of successful research using the device. We also observed that the American Society cited the problems at

Maryland General on the listserve run for Microbiology. No other facilities mentioned problems with the device after seeing this report.

CONCLUSION

Mr. Chairman, FDA will continue to advance our mission to protect the public health by staying abreast of this unfortunate situation through continued communication with CMS and the Maryland Department of Health. And, despite preliminary findings that the Labotech device was not the cause of the problems at Maryland General Hospital and appears to continue to be a safe and effective diagnostic device, we will continue to investigate this issue. I am happy to answer any questions you might have.