



NEWS

Plan to attend the AMDM 32nd Annual Meeting and the 510(k)/OIVD Workshop

The 32nd AMDM annual meeting (April 21-22, 2005) and the 510(k)/OIVD Workshop (April 19-20) are both fast approaching. Meeting brochures have been mailed to all of you who receive this newsletter. If you misplaced your copy, the meeting program and registration information are available on the AMDM website (www.amdm.org). These two events are a tremendous value, both in terms of the low registration fees and the information one receives. Both of these meetings are largely attended and the post meeting attendee reviews indicate the usefulness of the material presented.

We look forward to seeing you there.

AMDM Officers and Directors

<i>President</i>	Patricia B. Shrader Vice President, Corporate Regulatory Affairs Becton Dickinson & Company
<i>Vice President</i>	Wole Edwin Vice President, QARA/Public Affairs bioMerieux, Inc.
<i>Secretary</i>	Robert Tomaselli Director, Regulatory Affairs Veridex, L.L.C.
<i>Treasurer</i>	Leif Olsen Regulatory Affairs Specialist Hogan & Hartson, L.L.P.
<i>Directors</i>	Christopher Bentsen, Manager, Regulatory Affairs, Quality & Clinical, Bio-Rad Laboratories Cathy Craft, Director, Regulatory Affairs, Dade Behring Joe McMullen, Associate Director, Regulatory Affairs, Gen-Probe, Inc. Karen Richards, Senior Director, Regulatory Affairs, Chiron Corporation, Blood Testing Div. Judi Smith, Principal, Sienna Partners

Division of Bioresearch Monitoring – General Information

Origin

The Food and Drug Administration's (FDA) bioresearch monitoring program was established in 1977 by a task force which included representatives from the drug, biologics, medical device, veterinary medicine, and food areas. The need for such a program was evident in a survey of the conduct of studies involving FDA-regulated products by the FDA field inspection operation between 1972 and 1974. Following a review of the inspectional findings, the Congress mandated that FDA develop and implement an agency-wide program.

The bioresearch monitoring program at CDRH was expanded in June 1992. In May 1993 the Bioresearch Monitoring Branch became the Division of Bioresearch Monitoring in the reorganization of the Office of Compliance. The Division monitors sponsors, institutional review boards, clinical investigators, and nonclinical laboratories involved in the testing of investigational devices.

Program Objectives

The objectives of the bioresearch monitoring program are twofold: (i) to ensure the quality and integrity of data and information submitted in support of investigational and marketing clearance applications or submissions [IDEs, PMAs, and 510(k)s]; and (ii) to ensure that human subjects taking part in investigations are protected from undue hazard or risk. The Division is also charged with the implementation of the FDA's Application Integrity Policy (AIP) for medical devices and radiological health products.

The program objectives are achieved by several means which are discussed in the program functions and inspection program sections below.

(continued on page 2)

President Bush Nominates Dr. Lester Crawford to be FDA Commissioner

As Acting Commissioner of the FDA, the nation's principal consumer protection agency, Dr. Crawford ensures the safety and protection of the public's health.

Previously, Dr. Crawford was Chair of the Department of Physiology-Pharmacology at the University of Georgia, Administrator of the Food Safety and Inspection Service (USDA) and Deputy Commissioner of FDA. From 1997-2002, he was Director of the Center for Food and Nutrition Policy at Georgetown University and at Virginia Tech, where it moved in 2001.

Dr. Crawford has played major roles in mandatory nutrition labeling, the formation of the World Trade Organization and the control of chemical and microbiological contaminants of food. He has been an advisor to the World Health Organization of the United Nations for much of his career.

Dr. Crawford is a Member of the National Academy of Sciences Institute of Medicine. He is a Fellow of the Royal Society of Medicine (UK) and a Fellow of the International Society of Food Science and Technology. In 1984, he was inducted into the French Academy of Veterinary Medicine. In 1991, he received the Wooldridge Award, the British Veterinary Association's highest award.

Dr. Crawford received his Doctor of Veterinary Medicine (DVM) from Auburn University, his PhD in pharmacology from the University of Georgia, and his Honorary Doctorate (MDV) from Budapest University.

He has been married since 1963 to Catherine Walker of Birmingham, Alabama. They have two daughters, Leigh and Mary, and four grandchildren.

Statement by Mike Leavitt, Secretary of Health and Human Services, Regarding the Nomination of Dr. Lester Crawford to be FDA Commissioner

Dr. Lester Crawford is an outstanding choice for Commissioner of the Food and Drug Administration (FDA). For nearly a century, FDA has earned the public's trust in protecting the food and medicine we give our families. To millions of people, the FDA brand is a seal of quality and safety that is based on the best science in the world, and I look forward to working with Dr. Crawford to build on that trust in the 21st century.

Dr. Crawford has dedicated his career to advancing the nation's public health and will lead the way as we

enter a new era of individualized medicine and rapidly developing science. With Dr. Crawford's leadership, FDA will provide the world's safest drugs and empower citizens with the tools they need to make informed choices about their health.

Bioresearch Monitoring (continued from page 1)

Program Functions

The Division of Bioresearch Monitoring's (DBM) operations are directed toward several program areas. These include (1) audits of clinical data contained in PMA and some 510(k) submissions, ordinarily prior to approval; (2) audits of IDE sponsor submissions; (3) inspections of non-clinical laboratories that perform medical device-related safety testing; (4) inspections of Institutional Review Boards that monitor investigational device studies; (5) enforcement of the prohibition against commercialization of investigational devices; (6) providing education, training and guidance to regulated industry and (7) implementation of the FDA's Application Integrity Policy (AIP). Descriptions of

(continued on page 3)



**AMDM NEWS is published
for members of the
Association of Medical
Diagnostics Manufacturers.**

For membership information, or
for address changes, write:

Association of Medical Diagnostics Manufacturers

555 13th Street, N.S., Suite 700

Washington, DC 20004-1109

or call **(202) 637-6837**

www.amdm.org

Copyright 1989, AMDM

Glossary

A glossary of terms that are used to describe in vitro diagnostic products including lab tests and home-use tests.

Accuracy

- A measure of closeness of agreement between a test result and an accepted reference value.

EXAMPLE: If you have a standardized reference material at a known value (such as 180 mg/dl of cholesterol), accuracy measures how close the result of the test you are using will get to the known value. You may have a test that is very precise yet very inaccurate, which would be the case if your device measures 180 mg/dl of cholesterol reproducibly as 240 mg/dl.

Analyte

- The part of the sample that the test is designed to find or measure.

EXAMPLE: A home pregnancy test measures human chorionic gonadotropin (hCG) in urine. The analyte is hCG.

Approved Test

- A test that has been approved by FDA, based on the manufacturer's data showing that it is safe and effective for its intended use.

For a new type of test, or for a test that presents higher risk to the patient, the manufacturer performs studies to show that the test does what it claims to do and does not present any unreasonable risk. The manufacturer submits the results in a "premarket approval application" that FDA reviews. If FDA approves the application, the manufacturer can begin selling the test.

Cleared Test

- A test that has been cleared by FDA, based on the manufacturer's data showing that it is similar to other tests that are already being sold.

(continued on page 4)

Bioresearch Monitoring *(continued from page 2)*

some of these activities are summarized below:

- PMA data audits are conducted through comprehensive on-site inspections by FDA field office staff. Source data generated and collected by clinical investigators are compared with the data and information submitted by the sponsor to FDA in support of such applications. These audits help to ensure the quality and integrity of the information used by the FDA to render safety and effectiveness decisions. Additionally, FDA field staff review the appropriate records to ensure protection of the rights and welfare of the clinical research subjects participating in these studies. Where clinical data exists in 510(k) submissions, assignments may be issued requesting audits of that data.
- When indicated, inspections of clinical investigators participating in IDE studies are conducted.
- Good Laboratory Practice (GLP) inspections are undertaken to investigate compliance with regulations promulgated under 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies. Compliance with these regulations is intended to ensure the quality and integrity of safety data obtained from animal studies submitted to FDA.
- Surveillance information received from district offices, the public, the industry, and other sources related to commercialization or promotion of investigational devices is reviewed. If the advertisements or articles deviate from the requirements set forth in 21 CFR 812.7 (Prohibition of promotion and other practices), the Division follows up by means of a letter to the promoter or a request for inspection of the responsible party.
- Implementation of the FDA's Application Integrity Policy involves investigations of sponsors that are suspected of submitting false or misleading data to the FDA. It also includes the review, evaluation, and monitoring of validity assessments required to be completed by sponsors found guilty of fraudulent activities.

The regulations enforced by the bioresearch monitoring program for medical devices are found in four sections of the CFR:

[21 CFR 812 - Investigational Device Exemptions](#)

(continued on page 4)

Glossary (continued from page 3)

For a test that is similar to others already on the market and that is considered to have low risk to the user, manufacturers submit information to show that the test performs similarly to the other tests. The manufacturer submits the results in a "premarket notification" that FDA reviews. If FDA determines that the test is substantially equivalent to another test, the manufacturer can begin selling the test.

Exempt Test

- A test that is considered to have such low risk to the patient that FDA does not require manufacturers to submit any premarket approval application or notification.

False Negative

- A test result that incorrectly says the analyte, disease, or condition is not present when it actually is present. False negatives can be due to human error, test error, or substances in the sample that interfere with the test.

EXAMPLE: A woman who is pregnant receives a test result saying that she is not pregnant.

False Positive

- A test result that incorrectly says the analyte, disease, or condition is present when it is actually not present. False positives can be due to human error, test error, or substances in the sample that interfere with the test.

EXAMPLE: A woman who is not pregnant woman receives a test result saying she is pregnant.

Indications for Use

- A description of why a patient would use a certain test.

Intended Use

- A description of what the manufacturer intended to measure with a certain test.

(continued on page 6)

Bioresearch Monitoring (continued from page 3)

21 CFR 50 - Protection of Human Subjects

21 CFR 56 - Institutional Review Boards

21 CFR 58 - Good Laboratory Practice for Nonclinical Laboratory Studies

Inspection Programs

FDA's inspection programs include two types of assignments: routine inspections and directed inspections (sometimes termed "for cause"). The routine assignments include inspections of clinical investigators, sponsors, IRBs, or nonclinical laboratories that are randomly selected for coverage under one of four compliance programs. These assignments are issued to monitor adherence to FDA regulations.

A directed inspection is requested when some specific problem has been identified within one or all entities of the program. The problem may be observed during the review of sponsor submissions related to ongoing IDE investigations or following evaluation of clinical data submitted in a PMA or 510(k) application. Verbal or written complaints from patients, physicians, or competitors may also result in a directed inspection. Inspections issued for PMA data audits also fall into this category.

Deviations revealed during inspections are presented in writing and discussed with the responsible individual at the close of the inspection. Once an inspection has been completed, an establishment inspection report (EIR) is prepared and submitted by the district office. This report is then reviewed and classified by the Division of Bioresearch Monitoring.

Classifications assigned to inspections indicate whether or not the establishment is operating in compliance with the regulations. The classification scheme used by FDA is as follows:

NAI - No Action Indicated

VAI - Voluntary Action Indicated

OAI - Official Action Indicated

Depending upon the assigned classification, the Division may issue an untitled letter or warning letter based upon the severity of the deviations. These letters are intended to communicate the FDA's position on a matter, but do not commit the FDA to take further enforcement action. They are issued for the purpose of achieving voluntary compliance with the expectation that a majority of firms and individuals will comply with the regulations and implement

(continued on page 5)

Bioresearch Monitoring (continued from page 4)

corrective actions to prevent recurrence of the deviations.

When deviations are flagrant or significantly impact the quality and/or integrity of the research data, various actions have been used by the Division to achieve compliance in the bioresearch monitoring program area. Data audits have resulted in the Division's recommendation to invoke the Application Integrity Policy against the sponsor or reject clinical research data used to support a PMA. Data audits for 510(k)s that disclosed improprieties have led the sponsor to withdraw submissions. Monitoring efforts of IDE studies have led to the Division's recommendation for withdrawal of IDEs. Inspections of violative IRBs have resulted in administrative sanctions that suspend the institution's authority to approve new studies and/or add new subjects to existing studies.

For additional information about the bioresearch monitoring program in CDRH, contact:

Michael E. Marcarelli, Pharm.D., Director
Division of Bioresearch Monitoring (HFZ-310)
Office of Compliance
Center for Devices and Radiological Health
2094 Gaither Road
Rockville, Maryland 20850
Telephone (240) 276-0125

Contacts

For additional information about the Investigational Device Exemption (IDE) Program contact:

Elisa Harvey, D.V.M, Ph.D., Director
Investigational Device Exemption Program
Program Operations Staff
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, Maryland 20850
Telephone (301) 594-1190

CDRH

Foreign Establishment Registration

Background

Since the enactment of the Medical Device Amendments of 1976, foreign firms whose medical devices are imported into the United States have been required to list their devices with the U.S. Food and Drug Administration (FDA). As medical products imported into the United States increased, Congress concluded that FDA needed to obtain additional information about these foreign firms. This resulted in the requirement that these firms register with the FDA.

Congress also saw a need to facilitate communications between FDA and foreign manufacturers. As a result, foreign firms whose products are imported into the United States must provide for a United States agent residing in or with a place of business in the United States.

What is registration and listing?

"Registration" is the process through which the foreign establishment or the "owner/operator" of an establishment that manufactures, assembles, or otherwise processes a device for distribution in the United States provides to FDA information about the facility and its management. Owner/operator means the corporation, subsidiary, affiliated company, partnership, or proprietor

directly responsible for the activities of the establishment that is registering. For general information on registration, go to: [/cdrh/devadvice/341.html#link_1](http://cdrh/devadvice/341.html#link_1)

"Listing" is the process through which the foreign establishment or owner/operator identifies to FDA the types of devices that it distributes or offers for distribution in the United States. For further information on listing, go to: [/cdrh/devadvice/342.html#link_1](http://cdrh/devadvice/342.html#link_1)

How do I obtain forms and instructions?

- Foreign establishments that have already listed their devices but need to register may obtain registration forms and instructions by downloading them directly from [/cdrh/reglistpage.html](http://cdrh/reglistpage.html).
- Send email to our Comment/Feedback form
- You may obtain registration and listing forms, as well as instructions, by calling 800-638-2041, extension 114.
- If you are an international caller the number to dial is 011-1-301-443-6597.
- Also, you may request the forms and instructions by facsimile (FAX) at 301-443-8818 (domestic), or 011-1-301-443-8818 (international).

Glossary (continued from page 4)

In Vitro Diagnostic Test

- A medical test that analyzes body samples, such as blood, urine, stool, or saliva, for specific components or analytes.

Label

- Written material and instructions that accompany the medical test. Labeling includes the writing on the outside of the box as well as instructions packaged with the test.

Over-the-Counter (OTC)

- Products that can be purchased and used by anyone at home. These do not require a doctor's prescription.

If manufacturers intend to sell their test kits over-the-counter, they must demonstrate that untrained users can perform the test and get results.

Package Insert

- Information about the test and/or instructions that come inside the box or package.

Qualitative Test

- Tests that give results in terms of negative or positive.

EXAMPLE: Pregnancy tests, ovulation tests, and drugs of abuse detection tests indicate whether or not the person has the condition.

Quantitative Test

- Tests that give results in terms of numbers.

EXAMPLE: Glucose meters indicate how much glucose is present in the sample.

Screening Test

- An initial or preliminary test. Screening tests do not tell you if you definitely have a disease or condition. Rather, positive results indicate that you may need additional tests or a doctor's evaluation to see if you have a particular disease or condition.

OIVD

FDA Extends Pilot Program for Evaluation of Globally Harmonized Medical Device Premarket Applications Until July 2006 (The STED Initiative)

The Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA), is taking this opportunity to remind device manufacturers of its pilot program for submitting premarket applications (premarket notifications (510(k)s) and premarket approval applications (PMAs)) in a globally harmonized format. FDA initiated this program in June 2003 and will accept submissions in this format until July 2006.

Under this program, FDA is permitting manufacturers to submit certain 510(k)s and PMAs in a Summary Technical Document (STED) format. The STED format for regulatory submissions is a harmonized submission format developed by the Global Harmonization Task Force (GHTF), a voluntary partnership of government and industry representatives from the United States of America and four other member states. GHTF promotes international harmonization of medical device regulation through the preparation and distribution of guidelines such as the proposed STED format. The STED harmonized submission format is accepted by multiple regulatory authorities worldwide. While the use of the STED format is still in its early stages, it has the long-term potential to standardize the format of regulatory submissions across jurisdictions.

FDA is encouraging medical device manufacturers to participate in the STED pilot program. Manufacturers will benefit from exposure to the STED preparation process, especially those seeking international regulatory approval/clearance for their devices. In addition, greater industry participation in this program will increase FDA's familiarity with STED submissions and will allow FDA to provide constructive feedback to GHTF on the current STED format.

If you would like to submit a premarket applica-

(continued on page 7)

Third Party Review – How to Use This Program

Four Basic Steps

There are four basic steps to using the program.

1. **Check to see if your device is eligible.** Look at the [list of eligible devices](#) for the Accredited Persons Program to see if the FDA classification regulation and product code for your device are listed. Most Class I and Class II devices are eligible—more than 670 types of devices in all. (If you do not know what classification regulation or product code applies to your device, you can search FDA's [Device Classification Database](#). You can also contact an Accredited Person or FDA's Division of Small Manufacturers, International and Consumer Assistance at dsmica@cdrh.fda.gov for additional guidance.)
2. **Determine which Accredited Persons can review your 510(k) and how to contact them.** One method is to access the [list of eligible devices](#) for the Accredited Persons Program, and then to click on the product code for your device. This will display additional information for the product code, including a list of any Accredited Persons that are eligible to review that type of device. Clicking on the name of an Accredited Person will display FDA's list of Accredited Persons, which provides information on contacting the Accredited Person. Another method is to go directly to the list of Accredited Persons. The [list of Accredited Persons](#) shows the devices each organization is accredited to review, and contact information.
3. **Obtain price quotes from one or more Accredited Persons, and contract for a review.** The fee for an Accredited Person's review is determined by agreement between the 510(k) submitter and the Accredited Person, and is paid by the 510(k) submitter directly to the Accredited Person. Before contracting for a review, you should discuss any important factors such as the timeframe for the review.
4. **Submit the 510(k) to the Accredited Person, with a letter authorizing the Accredited Person to discuss the 510(k) with FDA and to forward it to FDA on your behalf.**

CDRH

Find a Predicate Device

Find a Predicate Device Now

In a 510(k) submission, applicants must demonstrate that a new device is substantially equivalent to a legally marketed device. A claim of substantial equivalence does not mean the devices must be identical, but they must have equivalent intended use, design, energy used or delivered, materials, performance, safety, effectiveness, labeling, biocompatibility, standards, and other applicable characteristics.

The device to which equivalence is drawn is known as the **predicate device**.

A predicate device must:

- have been legally marketed prior to May 28, 1976 (preamendments device), or
- be a legally marketed device which has been reclassified from Class III to Class II or I, or
- be a legally marketed device which has been found to be substantially equivalent to such a device through the 510(k) process.

To find a predicate for your medical device, you can search the 510(k) database. The most useful ways to search the database are by using the applicant name, the product name, or the procode for the type of device you are seeking. OIVD

STED Initiative (continued from page 6)

tion in the STED format, please consult FDA's Guidance on the STED pilot program. This can be found on the World Wide Web at <http://www.fda.gov/cdrh/ode/guidance/1347.html>. Additional guidance for STED preparation can be found on the GHTF web site at <http://www.gh tf.org/sg1/sg1-proposed.html>.

For further information and background on FDA's STED pilot program, please contact Harry R. Sauberman, P.E., at (301) 443-8879, ext. 148, or Kenneth J. Cavanaugh, Ph.D., at (301) 443-8517, ext. 170. CDRH



AMDM Events Calendar

April 19–20, 2005

AMDM/FDA 510(k)/OIVD Workshop

Double Tree Hotel • Rockville, Maryland

April 21–22 2005

AMDM 32nd Annual Meeting

Double Tree Hotel • Rockville, Maryland



Association of Medical diagnostics Manufacturers
555 13th Street, N.W., Suite 700
Washington, D.C. 20004-1109