INTERNATIONAL MEDICAL DEVICE REGULATORY

# MONITOR

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## Industry: No Justification For MDD Recast

A European Commission proposal to overhaul the legal framework underpinning the Medical Device Directives (MDD) is premature and lacks "any evidence-based justification," according to a joint position paper by seven medical device associations.

The paper cites a 2003 commission report that concluded the existing legal framework was stable and sound, as well as the 2007 MDD amendments, which incorporated minor changes into the legislation (*IMDRM*, October 2007). Those go into effect in March 2010, and the industry groups say time is needed to implement and evaluate those changes.

Among the provisions in the revised MDD are new clinical trial requirements, enhanced notified body involvement in dossier evaluation for Class II devices and launch of a European device database by March 2010.

After identifying several problems with the revised MDD, the commission launched a public consultation in June aimed at simplifying and strengthening the legal framework for device regulation (*IMDRM*, June). EU member states have until Dec. 21 to transpose the revised MDD into national law.

The commission said the three main directives — MDD, Active Implantable Medical Device Directive (AIMDD) and In Vitro Device Directive (IVDD) — and six implementing directives resulted in a fragmented regulatory system that would become even more disparate when transposed into national law.

Industry counters that the proposed recast would consolidate — not simplify — device regulation and says lumping the IVDD with the AIMDD and MDD ignores major differences in the IVDD format.

Moreover, any further revisions to the MDD should be aligned with the Global Harmonization Task Force's (GHTF) global regulatory model. "Harmonisation with the GHTF Model would have a number [of] advantages especially when all founding members adopt the GHTF model," the position paper says.

The groups also dispute the need for a centralized medical device agency, saying existing mechanisms for classification, premarket approval and postmarket surveillance are adequate to assure the safety of highest-risk devices. They call for strengthening and harmonizing the accreditation

process and supervision of notified bodies, adding that these activities can be achieved under the current framework.

"The trade associations believe that the existing framework, in the spirit of the GHTF principles, is working well and contributes to patients' timely access to safe and innovative medical technology," the groups say. "Reopening regulatory discussion at this point threatens the future competitiveness of our industry which comprises both multinational companies" and small and medium-size enterprises.

The seven associations that contributed to the position paper are COCIR (radiological and electromedical equipment), the European Diagnostic Manufacturers Association, the European Hearing Instrument Manufacturers Association, the Federation of the European Dental Industry, and Eucomed and Eurom VI (both medical technology associations). Together, they represent 95 percent of Europe's device market.

In separate comments, Eucomed urges the commission to reconsider any revamp of the device regulations' legal framework, saying the existing system has protected the public without creating an undue burden on industry. "One of the things to be celebrated is that the European Medical Device Directives introduced not only a harmonized regulatory regime, but a new international paradigm for device regulation … a system that has strongly influenced regulation in other countries to the benefit of Europe," Eucomed says.

The position paper is available at www.emea.europa.eu/Inspections/docs/43043807en.pdf. — Meg Bryant

## Dental Amalgam Exonerated By Expert Panel

The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks has concluded that dental amalgam is safe for use in patients and that its overall risks and benefits are no greater than those of alternative restorative materials.

Nonetheless, the use of mercury-containing dental amalgam is likely to continue to decline as newer tooth-colored and adhesive alternatives — such as composite resins, glass ionomer cements, ceramics and gold alloys — become more popular, the committee says.

A reduction in the use of mercury "would be beneficial both for the decrease in indirect human exposure and environmental considerations," the committee says in a recent report, *The Safety of Dental Amalgam and Alternative Dental Restoration Materials for Patients and Users*.

The commission adopted a proposal in 2005 for a communitywide strategy aimed at reducing mercury levels in the environment and human exposure. Part of that plan called for evaluating the use of dental amalgam and the need for additional regulatory measures.

The committee's review found no scientific evidence of adverse systemic effects or systemic disease associated with the use of dental amalgam. In addition, the report says amalgam restorations tend to last longer and are less costly than alternatives, which have a higher incidence of secondary caries.

Patients are at greatest risk of exposure to mercury during replacement or removal of amalgam fillings, the report notes. Therefore, it advises against removing clinically effective amalgam restorations unless the patient has an allergic reaction.

The use of some alternative materials has been linked to cytotoxic and mutagenic effects, as well as allergies in patients and dental personnel. "Far less information is available concerning exposure, toxicity and clinical outcomes for alternative materials," the report says.

Part of the problem in assessing the risk of alternative restorative materials is that they are regulated as Class IIa medical devices, which means the manufacturer does not have to include a design dossier with the full chemical specification of the product. As a result, it is difficult to establish the general safety of these materials, the report says, adding that "caution should be exercised before new variations are introduced into the market."

The scientific committee recommends telling patients of the relative risks and benefits of both dental amalgam and various alternatives so they can make informed decisions about their care.

The report is available at ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_016.pdf.

In a separate report, the Scientific Committee on Health and Environment Risks (SCHER) says the mercury associated with the use of dental amalgams accounts for a small fraction of the total mercury released into the environment.

SCHER attempted to quantify the risk of inorganic releases from dental amalgams for top predators and concluded it was not possible to do so. "Nevertheless, the development of probabilistic risk estimations offer[s] alternatives, and the possibility of conducting sensitivity analysis should be investigated," it says.

The panel also found the available information too limited to conduct a proper comparative assessment of amalgam alternatives. The SCHER report can be found at ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_089.pdf. — Meg Bryant

## ECHA Manual to Facilitate REACH Preregistrations

After receiving numerous inadequate or incomplete preregistrations, the European Chemicals Agency (ECHA) has published a how-to manual on preparing a technical dossier for registrations and product- and process-oriented research and development (PPORD) notifications.

The agency received more than 140 PPORD notifications as of June 18 and sent 100 notices to companies concerning the completeness of their submissions. In nearly two-thirds of those cases, ECHA had to request additional information. As of June 13, 1,427 companies had attempted to preregister a total of 7,360 chemical substances. Of those, roughly 2 percent lacked the required substance identity information, ECHA says.

The agency is responsible for carrying out the 2006 REACH (registration, evaluation, authorization and restriction of chemicals) legislation, which replaced 40 laws with a single EU-wide system (*IMDRM*, July 2007). REACH covers all EU-made and imported chemicals in quantities of one ton or more per year.

ECHA began accepting preregistrations June 1. Companies that preregister by Dec. 1 will have from November 2010 through May 2018 to fully register their products, depending on the quantities of chemicals involved and their hazard classification. Firms that do not meet the Dec. 1 deadline will be barred from manufacturing or importing their chemicals until they are fully registered by the agency.

*Data Submission Manual 5: How to Complete a Technical Dossier for Registrations and PPORD Notifications* provides guidance on preparing submissions according to the temporary procedures described in the REACH-IT section of ECHA's website.

The majority of problems with technical dossiers relate to incomplete information on the identity and composition of a substance, the agency says. Other common errors involve incomplete analytical information and omission of contact details.

"By using this new manual, companies can have more certainty that their dossiers pass the completeness check at the first submission," the agency says.

More than 98 percent of the preregistrations received thus far use either European Inventory of Existing Chemical Substances or Chemical Abstracts Service identifiers, according to ECHA. It urges companies that preregister by chemical or other names to use internationally recognized nomenclature such as International Union of Pure and Applied Chemistry names. It also recommends using English names.

The manual is available at www.echa.europa.eu/doc/reachit/compl_tech_dossier_manual_20080701.pdf. — Meg Bryant

## China Touts Improvements in Postmarket Monitoring of Medical Devices

The Chinese government has reinforced its efforts to establish a nationwide system for monitoring medical device-related adverse events, the State Food and Drug Administration (SFDA) says.

As of December 2006, 31 provinces, autonomous regions and municipalities had set up provincial institutions to monitor and evaluate adverse events. Their activities led to revocation of registration certificates for polyacrylamide, reregistration of dialysis powder and the recall of extracorporeal circulation circuits, the agency says in a white paper it recently released.

The paper, "Status Quo of Drug Supervision in China," provides an overview of the current Chinese market for medical devices, pharmaceuticals and traditional medicines and recent improvements in regulatory oversight. Available in English on the SFDA website, the report is an effort to reassure foreign companies and regulatory authorities that the SFDA is running a tight ship following the rash of safety issues it confronted a year ago. The document also suggests an increasing transparency in how the SFDA conducts business.

The agency says a technical testing system has begun to take shape at both the national and provincial levels for device regulation. Ten national centers are responsible for registration-related testing of domestic Class III devices and imported devices. They also conduct sample quality tests of Chinese-made medical devices.

Another 30 centers at the provincial level are responsible for sample testing devices within their jurisdictions and for registration testing of certain medical devices, the report says. Rounding out the evaluation system are nine academic-based testing organizations and 22 device standardization technical committees.

"The Chinese government attaches great importance to the formulation of administrative regulations concerning medical devices," the report says. Since 2000, when medical device legislation took effect, the SFDA has issued regulations on device registration, classification, standards, clinical trials, good manufacturing practice, evaluation of quality systems of manufacturers, provisions for indications, advertising and labeling and packaging, the report says. The agency also has developed 155 national and 531 industry standards relating to quality of medical devices.

According to the report, China produces more than 3,000 types of medical devices and holds significant market shares in digital X-ray, MRI, ultrasound and CT products. By the end of last year, it had 12,591 registered device manufacturers.

"China can manufacture medium-sized medical equipment for export and is moving toward the world's top rankings

in respect of research into techniques for wearable device[s], biomedical materials and tissue engineering," the report says.

The white paper is available at eng.sfda.gov.cn/cmsweb/webportal/W43879541/A64028182.html. — Meg Bryant

**To view the full text of this document, click here.**

## 'Street Smarts' Key to Doing Business in Asia

U.S. device firms choosing Asian distributors must be more "street smart" than when they work in Europe because of cultural and regulatory differences, an expert says.

For starters, devicemakers must get their regulatory staff more involved in the company's search, so they can analyze the distributor's regulatory department, Ames Gross, president of Pacific Bridge Medical, said.

Asia has seen an emergence of private distribution companies that usually are not well funded. Many lack expertise in selling Western products, Gross said, speaking at the Medical Device Manufacturers Association's annual meeting. Few large-scale, private nationwide medical product distributors are available in China, for instance, so it is necessary to put together several private regional groups there.

The search for a Chinese distributor must be slow and methodical, Gross said, and should involve "no marketing — just 'here are the products.'"

While bribery has long been associated with doing business in China, it is not as big a part of the culture anymore. Gross noted a former head of the Chinese Food and Drug Administration was terminated and executed for bribery.

India, like China, is plagued by a fragmented distributor network, so firms likely will need more than one distributor to cover the country, Gross said. Research is key to dealing with infrastructure issues in India, which has more problems in this area than China and Japan, he added.

Since many Indian distributors are unable to handle regulatory issues such as device registration, Gross advised devicemakers to consider distributors who deal in other imported products.

Finding a Japanese distributor takes longer than in other Asian countries, according to Gross. This is because relationships, which are crucial in Japan, may take several years to develop, so firms must move slowly and build trust.

This means tuning into Japanese culture, which is more formal. "You have to wear a suit," he said, and set up meetings six weeks in advance.

Firms also must separate their Japanese and non-Japanese businesses. For example, doctors in China will not respond well to Japanese distributors, Gross said, adding that other countries may have similar issues.

He noted that although medical device registration in Japan still is difficult, Japanese doctors and dentists can import unregistered devices for personal use. However, all the marketing for unregistered products needs to take place outside of Japan, including the use of non-Japanese websites. If it is done in a legitimate manner, this kind of importation will not hurt a company's future chances for registration, he said.

Although the path to Japanese registration is improving, reimbursement levels are coming down in an attempt to reach Western levels, so devicemakers will have to be smarter to succeed there, Gross said. — April Astor

## UK Issues Guidances to Improve Vigilance Of Heart, Glucose Devices

To ensure medical devices are as safe as possible, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued two new vigilance guidances — one on CE Marked artificial heart valves and the other on devices that measure blood glucose at the point of care or in the home.

"Guidance on the Medical Devices Vigilance System for CE Marked Artificial Heart Valves" will help manufacturers comply with Medical Devices 93/42/EEC and should be used in conjunction with the European Commission's "Guidelines on a Medical Devices Vigilance System" and the MHRA's Directives Bulletin 3 — "Guidance on the Operation of the EU Vigilance System in the UK."

It provides information on what should be reported, which adverse events do not need to be reported and when valve reoperations must be reported.

Examples of reportable incidents include:

- Housing ring or stent failure;
- Separation of sewing cuff from housing or stent;
- Valve replacement due to severe hemolysis;
- Transient ischemic attack or cerebrovascular accident;
- Valve thrombus in the absence of a clotting disorder;
- Leaflet or occluder fracture or escape;
- Structural deterioration;
- Tissue failure within seven years of implant, under certain circumstances;
- Accessories or instrument failure;
- User error resulting in death or serious injury;
- Abnormal degree of pannus overgrowth; and
- Paravalvular leak.

Manufacturers should evaluate each of these incidents on a case-by-case basis to determine reportability and ensure compliance with reporting requirements, the guidance says.

Elective valve replacement due to a field safety corrective action need not be reported unless subsequent examination reveals a problem that could cause death or serious injury, the guidance says. Reoperations triggered by local or systemic changes in the patient's health should be reported because they may relate to the artificial valve.

"Guidance on the In Vitro Diagnostic Medical Devices System for Devices for the Measurement of Blood Glucose in the Point of Care Testing and Home Environment" provides similar reporting information. Adverse events related to a malfunction or deterioration of the device or its systematic recall must be reported. Examples include display issues, performance problems, user error, incidents of unknown origin, inadequate labeling and use instructions, and faulty design and manufacturing.

"The manufacturer's investigation should include, as appropriate, an analysis of the manufacturing records, a postmarket surveillance review, stability studies, analysis of the returned meter and of the returned strips, use of control solutions on retained strips and retained meters, and a presentation of the results," the draft says.

Firms need to have procedures in place for handling situations in which neither the blood glucose monitor nor blood glucose meter test strip is returned, the guidance says.

Information in the manufacturer's final vigilance report should include results of any clinical evaluation in which the patient's condition may have contributed to the adverse event; a final assessment, including what triggered the incident and follow-up plans; and corrective actions taken.

Comments on both guidances are due Aug. 31.The guidance on artificial heart valves is available at www.mhra.gov.uk/Publications/Regulatoryguidance/Devices/Otherdevicesregulatoryguidance/CON020786. The document on blood glucose measuring devices can be accessed at www.mhra.gov.uk/Publications/Regulatoryguidance/Devices/Otherdevicesregulatoryguidance/CON020785. — Meg Bryant

## MHRA Launches Public Consultation on ATMPs

The Medicines and Healthcare products Regulatory Agency (MHRA) wants industry input on the UK's proposed exemption plan for advanced therapy medicinal products (ATMP) that are prepared on a case-by-case basis and used in a hospital according to a prescription for a specific patient.

The European Council adopted its regulation of new medical products based on genes, cells and tissues May 31, 2007, following approval by the European Parliament (*IMDRM*, May 2007). The ATMP regulation, which takes effect Dec. 30, lays the groundwork for a single, harmonized regulatory framework for those products in the EU.

Under the UK's exemption scheme, traceability, quality and pharmacovigilance of ATMPs must be equal to those requirements authorized under the centralized procedure. The MHRA says the hospital exemption proposals concerning those issues, as well as patient information and ethics, also should apply to ATMPs prepared as "specials." Specials are national arrangements set up under a derogation in Article 5.1 of Directive 2001/83/EC.

The UK proposal would require reporting of adverse events but not periodic safety update reports as they would be hard to conduct on products manufactured on a nonroutine basis, the MHRA says in a consultation released last month.

The agency would retain the right to request a risk management plan for an ATMP. "Initial consideration of the need for such a plan would be instigated at the point that a manufacturer's license is sought to operate under the exemption and would reflect the nature of the proposed activity," the MHRA says.

The agency proposes that the manufacturer would be responsible for traceability of ATMPs under the hospital exemption. When the manufacturer is not the hospital, defined responsibilities for the hospital administering the product should be in place, the MHRA says.

Firms seeking a license to manufacture ATMPs would be encouraged to consult with the MHRA to ensure they apply under the appropriate scheme.

The MHRA also suggests amending the advertising provisions relating to "specials" to permit circulation of price lists but not advertisements of specific products. The change is in line with proposed requirements for advertising under the UK's hospital exemption for ATMPs.

The consultation on ATMPs can be accessed at www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON020714. — Meg Bryant

## Expert: U.S. FDA Adopts 'Tough Cop' Stance on MDR Enforcement

Failure to comply with medical device report (MDR) regulations has created an atmosphere of distrust between the U.S. Food and Drug Administration (FDA) and some companies, leading the agency to crack down on enforcement of MDRs, an expert says.

Since the beginning of the year, warning letters relating to MDRs have constituted 42 percent of all letters issued by the FDA to device companies. This is a jump of 9 percent over the number issued for the same period last year, Pamela Furman Forrest, partner at King & Spalding, said at an FDAnews audioconference.

Out of the 19 warning letters dealing with MDRs issued from Jan. 1 through July 8:

- 12 were issued because of a failure to develop, maintain and implement written MDR procedures;
- 10 were for failures to submit an MDR within 30 days of receiving or becoming aware of an adverse event or refusal to provide required information; and
- Three were for failure to investigate and evaluate the cause of an adverse event.

Common pitfalls included incidents in which companies overlooked seemingly minor complaints, failed to document all steps of a complaint investigation and did not train personnel to report information within the allotted time period.

"As a result, the FDA resorts to micromanaging companies that it becomes frustrated with," Forrest said. "FDA has a very conservative view of MDR requirements."

She said a worst-case scenario involved TMJ Implants, which was cited in July 2007 for failure to file 17 MDRs. When the company told the FDA it was "misinterpreting" the MDRs, the agency responded by fining the corporation and two executives a total of $630,000 — claiming the company was not investigating the complaints thoroughly enough to determine if they were reportable.

To avoid noncompliance, Forrest advised manufacturers to establish effective MDR procedures that incorporate FDA regulations and address full identification and timely communication of any possible adverse events, including minor malfunctions. They then should thoroughly log complaints into a database to be carefully screened.

"What gets often overlooked are malfunction events that are potentially harmful," Forrest said. "These often get short shrifted and come back to haunt a company."

Manufacturers should assume a particular malfunction will recur, as required by the regulation, rather than assessing the likelihood that it will recur, she advised.

Miscalculated internal timelines and attention to reporting deadlines are the second most common pitfall, Forrest said. According to the FDA, manufacturers are considered to have become aware of a reportable event when any employee becomes aware of it — not when the complaint reaches the regulatory department for analysis. Everyone in the company can become sensitive in the routing of complaint information if companies make it a priority to comprehensively train relevant personnel, she said.

She also suggested manufacturers stay on the FDA's good side by making good-faith efforts to obtain MDR information. More than one request for information should be made in writing, and all attempts to retrieve information about a complaint should be documented.

As it stands, manufacturers have 30 days to submit individual MDRs for a device that may have caused or contributed to a serious injury or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The FDA is implementing changes that are part of the FDA Amendments Act of 2007 that will require 30-day individual MDRs for malfunction of Class II, Class III and other devices as determined by the agency. Malfunctions for other devices, such as most Class I and many Class II devices, will require quarterly submission of MDRs in a summary form.
— Renee Frojo

## GHTF Publishes Final Guidance On IVD Classifications

The Global Harmonization Task Force's (GHTF) Study Group 1 has released its final guidance on classification of in vitro diagnostic (IVD) medical devices.

The final version contains some minor additions but no substantive changes from the draft published in May 2007 (*IMDRM*, June 2007). It recommends a four-tiered, risk-based classification system specific to IVD devices. When more than one classification rule applies to an IVD device, the product is to be classified at the highest risk indicated.

Section 6.0, "Recommendations and Factors Influencing IVD Medical Device Classification," includes two new points concerning stand-alone control materials:

- Stand-alone control materials with quantitative or qualitative assigned values intended for one specific analyte or multiple analytes should be placed in the same class as the IVD reagent(s); and
- Stand-alone control materials with no assigned values intended for use with multiple or single analytes should not be placed in the same class as the IVD reagent(s).

The guidance also expands the types of IVD devices intended for use in blood grouping or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissues or organs intended for transfusion or transplantation that would fall into Class D, the highest risk. The list includes ABO system [A (ABO1), B (ABO2), AB (ABO3)], rhesus system [RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e)], Kell system [Kell (K)], Kidd system [JK1 (Jka), JK2 (Jkb)] and Duffy system [FY1 (Fya), FY2 (Fyb)] determinations. All other IVD devices intended for those uses would be classified as Class C — high individual risk or moderate public health risk.

The two subsets, Class C or D, for blood grouping devices are based on the "nature of the blood group antigen the IVD medical device is designed to detect, and its importance in a transfusion setting," the guidance says.

Other changes include the addition of prenatal screening tests for congenital disorders and clarification on how to classify self-administered tests. IVD devices intended for blood gases and blood glucose determinations should be classified as Class C. However, classification of other self-tests is to be determined using a set of seven classification rules provided in the guidance.

IVD devices that are intended as controls — with the user and not the manufacturer setting the qualitative or quantitative value — would be Class B, or moderate risk.

The guidance, "Principles of In Vitro Diagnostic (IVD) Medical Devices Classification," is available online at www.ghtf.org/documents/sg1/sg1final_n045.pdf.
— Meg Bryant

**To view the full text of this document, click here.**

## U.S. FDA Prodding Industry on One-Stop PMAP Inspections

Devicemakers that were invited to but did not participate in the joint U.S.-Canadian pilot multipurpose audit program (PMAP) are a priority for U.S. Food and Drug Administration (FDA) inspection, according to an agency director.

Under PMAP, firms audited by an accredited FDA inspector satisfy the inspection requirements for Health Canada (*IMDRM*, October 2006). The program is part of the FDA's harmonization efforts for medical devices, which allow one inspection to fulfill regulatory requirements for multiple jurisdictions.

The FDA's Center for Devices and Radiological Health (CDRH) looked at Health Canada's list of planned audits for the next year and matched them up with sites the FDA was going to inspect, Timothy Ulatowski, director of CDRH's Office of Compliance, said. Facilities scheduled for audits by both regulators were requested to participate in PMAP.

"We had a few takers but not enough," Ulatowski said at the FDAnews Medical Device Quality Congress. "We are going to inspect those people who do not take us up on that one audit." The decision is not punishment for manufacturers' lack of participation, Ulatowski added, noting that the companies were considered inspection priorities anyway.

To guide the center's selection criteria for which firms to inspect, the FDA plans to release a draft guidance this month explaining how the agency will interpret International Organization for Standardization (ISO) audits voluntarily submitted by manufacturers, Ulatowski said. Under the FDA Amendments Act, the agency is authorized to use submitted audit reports to help determine its inspections priorities.

"I'm going to be very positive about [ISO audit reports] in regards to who we are going to inspect and so direct our districts," Ulatowski said.

He also discussed a planned guidance on good importer practices. The guidance would advise industry on what the agency expects from importer practices, which may lead to more or less attention "in regards to inspections, … depending on the application of those practices by industry," Ulatowski said.

The use of certifications by importers is under consideration. For example, CDRH will consider whether firms are applying good importer practices in relation to quality system regulations. "We will put up a fence, a certification fence. That's a proposal," Ulatowski said.

In describing the FDA's enforcement process, he advised manufacturers to go beyond specific citations in warning and untitled letters to look at their systems from a global perspective. "Today we'll find one thing here. We may find the same thing at another facility tomorrow. So you want to take a broad look at what we find and identify in warning letters," he advised. Follow-ups to warning letters are a strong indicator a firm will be audited, he added.

The agency also is incorporating economic factors in its assessment of facilities. For example, when firms grow quickly or there is a change in ownership of a facility or company, the FDA considers these factors in determining which firms to inspect. Leveraging data from foreign regulators is another aspect of the agency's site selection process.

Other indicators that a firm will be inspected in the near future are if it has had a Class I recall, if it has domestic facilities that manufacture Class II or Class III devices and if it produces devices that have had trouble in the past, such as infusion pumps or defibrillators.

The FDA conducted 1,362 quality management system inspections in the last fiscal year, including 286 foreign inspections and six accredited-persons inspections, Ulatowski said.

He admitted the FDA has lost medical device expertise in its inspection force and said rebuilding that expertise is "a big ticket item." Although many of the new inspectors the agency has hired are being deployed to food and drug facilities, "there will be additional activity in the device area," he said.

Ulatowski highlighted congressional efforts to appropriate more resources to the FDA. "Legislation dealing with the frequency of inspections, requirements for inspection, fees for inspections — these things are on the table. [These are] very important topics being discussed by Congress and with FDA," he said. — Christopher Hollis

## CDASH Lays Groundwork for Harmonized Clinical Data Exchange

The first version of the Clinical Data Acquisition Standards Harmonization (CDASH) initiative will be available for clinical research by early next month, enabling trial sites to follow incompatible standards used by different sponsors.

CDASH is an initiative of the Clinical Data Interchange Standards Consortium (CDISC), a global nonprofit organization whose goal is to promote IT interoperability. The organization's Study Data Tabulation Model (SDTM), a standard used for regulatory submissions, has been adopted by industry, Bron Kisler, CDISC's director of terminology and strategic alliances, said at the Drug Information Association's annual meeting.

The U.S. Food and Drug Administration (FDA) requests that drug companies use SDTM for esubmissions; that standard will be aligned with CDASH, Kisler added.

After finalizing CDASH Version 1.0, CDISC plans to develop training programs, deliver presentations at industry meetings and seminars, collect feedback, and add and update SDTM domains as needed, he said.

CDASH is intended to resolve what project director Rhonda Facile called "the investigators' plight: a plethora of data formats and conventions, which are inefficient, multiply the potential for error and make data sharing and mining impossible." The goal is a single set of standards for such information as element names, definitions and metadata, starting with safety standards.

CDASH was developed in response to the FDA's Critical Path Opportunity No. 45 as a way to streamline data collection at investigative sites. The first version is available at www.cdisc.org/standards/cdash/cdraft.html.

"In the past few years, FDA has become a standards-based organization," Armando Oliva, deputy director for bioinformatics at the FDA's Office of Critical Path Programs, said at the conference. "There are tremendous benefits for everybody."

For the FDA, the advantages include higher-quality submission specifications and harmonization across divisions and centers. For industry, the advantage is that "everyone can influence the final outcome to make sure it meets business needs," Oliva said.

The agency also supports Health Level 7 standards for structured product labeling, individual case safety reports and regulated product submissions, he noted.

The CDASH initiative started with SDTM and focused on the content of case report forms (CRFs), Paul Bukowiec, director of statistical programming at Millennium Pharmaceuticals, said. Volunteers were asked to collect sample CRFs from their companies and evaluate their similarities and differences. The aim was not to develop actual forms but to create metadata tables to standardize content.

While the FDA does not design or use CRFs, it is interested in seeing them improved because it audits them and uses the data contained in them, Oliva said. For eCRFs, the FDA standard is Adobe PDF files, but these are not ideal because of variability in the way they format information, especially audit trail data. CDISC's Operational Data Model would fit the bill, but it is still in development, Oliva said.

The FDA will continue to support efforts to standardize clinical data, especially esubmissions, Oliva said. Down the road, clinical research could be done through electronic health records, which could contribute to postmarketing safety data, he added.

The agency discusses esubmissions in its Study Data Specification guidelines, which were updated last year and are available at www.fda.gov/CDER/regulatory/ersr/Studydata.pdf. — Martin Gidron

## TGA to Offer Single Reference For Device Guidelines

Medical devicemakers doing business in Australia will soon be able to consult a single reference base for all their regulatory guidance needs — courtesy of the Therapeutic Goods Administration (TGA).

The TGA hopes to complete a consolidated reference document, which will replace existing guidances and information sheets, by the end of the year.

Manufacturers will be able to access each section of the new *Australian Regulatory Guidelines for Medical Devices* (ARGMD) at www.tga.gov.au as it becomes available. The current set of guidelines will remain in place until the ARGMD is complete.

A partial listing from a draft table of contents includes the following sections:

- Introduction and general overview;
- Essential principles of safety and performance;
- Medical device classifications;
- Conformity assessment evidence;
- Conformity assessment procedures;
- Notification of conformity assessment evidence (previously manufacturers' evidence);
- Inclusion of medical devices in the Australian Register of Therapeutic Goods;
- Application audits;
- Suspension and cancellation from the Australian Register of Therapeutic Goods;
- Access to unapproved medical devices in Australia;
- Ongoing monitoring of devices on the market;
- Fees and charges; and
- Offenses and penalties.

The ARGMD also will address custom devices, combination products, reprocessing of single-use devices and active medical devices, and it will include information on international agreements and differences between the Australian and EU regulatory schemes. However, it will not provide specific information on device regulation in other countries, the TGA says.

So far, the TGA has released drafts for the sections on conformity assessment evidence, essential principles of safety and performance, and fees and charges. Comments on the draft ARGMD document, "Classification of Medical Devices," are due by Aug. 22. It can be accessed at www.tga.gov.au/devices/argmd-drclass.pdf. The draft document on fees and charges is available at www.tga.gov.au/devices/argmd-drfees.pdf.

In drafting the documents, the TGA says it has attempted to incorporate direct quotes from the legislation where possible and avoid duplication by providing information only once, relying on links where necessary. Forms and checklists, which will not be part of the ARGMD, will remain available on the TGA website. — Meg Bryant

**To view the full text of these documents, click here.**

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