

A Monthly Alert to Regulations
Affecting the Medical Device
and Diagnostic Industries

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India, Brazil, South Africa Agree To Boost IP Rights

Intellectual property (IP) rights must be strengthened to ensure access to effective, appropriate and affordable medical technologies and pharmaceuticals, health ministers from India, Brazil and South Africa said at a recent meeting.

The health ministers, gathered for a meeting of the India-Brazil-South Africa (IBSA) Trilateral alliance, renewed their commitment to improve cooperation in health and medicine by pooling the individual experiences and capabilities of the three countries.

South African Health Minister Manto Tshabalala-Msimang called Brazil a leader in IP rights, adding that IBSA would benefit from Brazil's guidance in navigating through the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, set out by the World Health Organization. Brazil's strategy on IP rights includes compulsory licensing and resistance to the agenda promoted by the World Intellectual Property Organization, which seeks to impose IP standards on developing countries that exceed those stipulated by the World Trade Organization's agreement on Trade-Related Aspects of Intellectual Property Rights.

"It will therefore be very important for us as IBSA partners to move together cooperatively at all international forums on this matter if we are to make any headway in our battles to protect innovation and knowledge from our countries and continents, which are usually vulnerable to exploitation," Tshabalala-Msimang said at the meeting.

The countries also agreed to strengthen cooperation on public health laboratories, health surveillance, traditional medicines and registration of devices and drugs. The alliance was formed in 2003 to enhance economic cooperation. — Meg Bryant

India Tells Device Firms To License Products Now

Manufacturers and importers that have not obtained licenses for medical devices targeted in October 2005 for mandatory licensing must do so now or face a penalty, according to a recent notice by the Drug Controller General of India (DCGI).

Industry has had more than two years to license catheters, bone cements, heart valves, intraocular lenses, orthopedic implants, cardiac

stents, drug-eluting stents, in vitro cannulae, scalp vein sets and internal prosthetic replacements. Continuing to manufacture devices in the 10 specified categories without a license is “unlawful and would attract penalty” under the country’s drug laws, DCGI Surinder Singh says in the notice.

The 2005 regulation listed the 10 types of devices as drugs under the provisions of India’s Drugs & Cosmetics Act of 1940, requiring them to be licensed for manufacture, import, sale and distribution.

India’s Central Drugs Standard Control Organization (CDSCO) outlined the requirements for imported devices in a March 1, 2006, guideline and gave companies 60 days to register their products and apply for an import license. That deadline was extended to June 29, 2006, after industry complained it did not have sufficient time to provide the necessary documents on origin, approval and sale of the devices. That August, CDSCO provided additional information to clarify issues raised by affected businesses (*IMDRM, August 2006*).

Applications for license are to be made through the state drug control authority in whose jurisdiction the manufacturer is located, the new notice says. They then will be forwarded to the DCGI for approval. — Meg Bryant

ASEAN Reveals More Details Of Regional Device Directive

Plans for an Association of Southeast Asian Nations (ASEAN) medical device directive (AMDD) could bring tighter regulation and harmonization to the region’s device market.

The proposed 18-article directive would cover a broad scope of activities — from registration and placement of devices on the market to conformity assessment and creation of a postmarket alert system (*IMDRM, May*).

Manufacturers and others dealing in devices would be required to register with the national regulatory authorities in whose markets they do business and to provide a comprehensive package of technical documents on their products.

Other key features of the proposed AMDD include:

- Definition and scope of the device;
- Essential requirements for safety and performance;
- Classification of medical devices;
- Reference to standards;
- Labeling;
- Product claims;
- Clinical investigations;
- Institutional arrangements;
- Safeguard clauses;
- Confidentiality;

- Special cases; and
- Implementation.

According to an outline of the first draft, prepared by Singapore’s Health Sciences Authority (HSA), conformity assessments will cover quality management systems, technical documentation, postmarket surveillance, declaration of conformity and registration of devicemakers and their products. A reference to ISO 13485, which lays out quality management systems requirements for medical devices, will be included in the directive, the HSA said.

The AMDD also will require clinical trials to comply with principles of the Helsinki Declaration “to prevent ASEAN from being a ground for unethical clinical investigations,” the HSA said.

The ASEAN Consultative Committee on Standards and Quality Medical Device Product Working Group agreed to adopt the ASEAN harmonized in vitro diagnostic (IVD) device classification scheme and include it as an annex to the AMDD. The four-class scheme stems from the seven risk-based classification rules for IVDs set out by the Global Harmonization Task Force (*IMDRM, August*).

Member countries will hold national public consultations on the draft AMDD beginning in November and running through next April 30. The Medical Device Product Working Group hopes to finalize the directive by 2010. — Meg Bryant

US Guidance Helps Small Firms Apply for Reduced User Fees

Small businesses that want to save money on fiscal 2009 medical device user fees, which become effective Oct. 1, can get some help from a guidance published recently by the U.S. Food and Drug Administration (FDA).

Small businesses may qualify for discounted rates of most 2009 user fees. To qualify as a small business, a manufacturer must have gross receipts or sales of no more than \$100 million for the most recent tax year. If it has gross sales or receipts of no more than \$30 million, a firm may qualify for a fee waiver for its first premarket approval application (PMA) or report.

Proof of qualification should be submitted to the FDA 60 days before the fee application is sent, the agency says. Businesses that qualified for the small business discount in fiscal 2008 must re-qualify for 2009. Current small business status will expire Sept. 20.

Under the Medical Device User Fee and Modernization Act (MDUFMA), the fee rates for various submissions are set according to percentages of the standard fees for a PMA, a product development protocol or a biological licensing application, according to an agency notice. The standard fee for a PMA in fiscal 2009 will be \$200,725.

The registration fee for manufacturers, single-use device reproducers and specification developers will be \$1,851; this fee is not reduced for small businesses.

Other 2009 fees — for standard and small businesses, respectively — are:

- Panel-track supplement — \$150,544 and \$37,636;
- 180-day supplement — \$30,109 and \$7,527;
- Real-time supplement — \$14,051 and \$3,513;
- 510(k) submission — \$3,693 and \$1,847;
- 30-day notice — \$3,212 and \$1,606;
- 513(g) request for classification information — \$2,710 and \$1,355; and
- Annual fee for periodic reporting on a Class III device — \$7,025 and \$1,756.

To avoid a delay in the review of their applications, manufacturers should pay user fees before or at the time of submission. Small businesses must be qualified as such before paying a reduced small business fee, the agency says.

The new guidance supersedes the version released last year.

The FDA's notice on fiscal 2009 device user fees is available at edocket.access.gpo.gov/2008/pdf/E8-17739.pdf. The fiscal 2009 "Medical Device User Fee Small Business Qualification and Certification" guidance can be seen at www.fda.gov/cdrh/mdufma/guidance/2009.pdf. — Renee Frojo

NICE Sets Conditions for Using Drug-Eluting Stents

The UK's National Institute for Health and Clinical Excellence (NICE) is sticking with its recommendation that drug-eluting stents (DESs) be restricted to patients with coronary artery disease who would be at a high risk of future interventions if a conventional bare-metal stent (BMS) were used instead.

The recommendation applies when the artery to be treated is less than 3 mm in diameter or the affected section of the artery is longer than 15 mm, according to a final guidance NICE recently re-released. Cost also factors into the decision to use DESs: The price difference between a DES and BMS can be no more than \$600.

NICE first issued the guidance in February. Stentmaker Cordis appealed it in March, arguing that the agency was trying to fix or control the price of the stents or establish procurement policy for the UK's National Health Service (NHS). The company cited evidence that DESs are cost-effective at price premiums up to roughly \$800–\$900 more than the cost of BMSs, and said this should be reflected in the guidance.

NICE reissued the final guidance following its denial of Cordis' appeal in late July.

The maximum price difference between DESs and conventional BMSs permitted in the guidance is available at some UK hospitals and achievable throughout the NHS, according to Andrew Dillon, chief executive of NICE.

"This decision to recommend the use of drug-eluting stents will ensure that, despite their higher cost, they will continue to be an important treatment option for patients" who need them, Dillon said.

Coronary heart disease claimed 117,500 lives in the UK in 2002 and accounts for 9.7 percent of all disability-adjusted life years lost across Europe, the guidance says.

According to the British Cardiovascular Intervention Society, the use of stents to repair damaged arteries rose from 80 percent to 94 percent between 1999 and 2005, the guidance notes. By 2005, 62 percent of all stents used in the UK were DESs.

The growing use of stents in percutaneous coronary intervention has resulted in a number of regulatory actions this year. This past spring, the European Commission issued a draft guideline on clinical testing of coronary stents (*IMDRM, April*). Around the same time, the U.S. Food and Drug Administration released a draft guidance calling for increased testing requirements for DESs (*IMDRM, April*).

In addition to the recommendations on patient criteria and cost, the NICE guidance provides information on specific DESs, the drugs they elute and their individual costs. It also discusses findings from 17 randomized, controlled trials comparing DESs with BMSs. The clinical results showed all types of DESs to be superior to BMSs in reducing the rate of revascularization in target lesions for up to three years, the guidance says.

NICE has developed tools — such as an audit support for monitoring local practice and a costing report and template — to help organizations implement the final guidance.

"Drug-Eluting Stents for the Treatment of Coronary Artery Disease: Part Review of NICE Technology Appraisal Guidance 71" is slated for review in April 2009. The guidance and the tools can be accessed at www.nice.org.uk/TA152. — Meg Bryant

New UK Forum Makes TEPs First Priority

Human tissue-engineered products (TEPs) and their regulatory status will be the initial focus of a UK public-private forum on medical technology when it holds its inaugural meeting Nov. 27.

The Medical Device Technology Forum is an outgrowth of comments received last year on the Medicines and Healthcare products Regulatory Agency's (MHRA) 2007–2012 strategic plan (*IMDRM, June 2007*). Although the plan highlighted rapid development of TEPs as one of several challenges facing the MHRA,

comments on the plan urged the agency to be more proactive in considering the impact of emerging medical technologies.

The MHRA says the forum will:

- Ensure that novel technologies are appropriately monitored and regulated, enhancing patient and user safety while reducing unnecessary delays to marketing approval;
- Increase agency expertise on novel devices; and
- Bring industry, regulators, scientists and users together to ensure a high level of interaction and awareness of new technologies, their potential uses and implications for how they can be most effectively regulated.

Other possible topics for the forum include microspheres, robotic-assisted surgery, noninvasive blood pressure monitoring, device-user testing methodologies, orthopedic implant load restrictions, market entry barriers for urology and stoma-care products, clarification of the MHRA's position on medical software and the introduction of new technologies into the National Health Service trusts.

Following the initial meeting, the forum will convene twice a year, bringing together about 30 scientists, practitioners, industry experts and lay people to discuss a specific topic, the MHRA says.

The agency is seeking proposals for future forum discussions. A 10-person panel will review suggestions and advise on selection of topics and speakers. These should be sent to christopher.britain@mhra.gsi.gov.uk. — Meg Bryant

Patent Office: Final Rule Would Not Be Retroactive

The U.S. Patent and Trademark Office (PTO) will not retroactively apply a final rule affecting patent application procedures if an injunction against the rule is removed.

The U.S. District Court for the Eastern District of Virginia permanently enjoined the rule in April after Triantafyllos Tafas and GlaxoSmithKline (GSK) challenged it. Tafas, an inventor listed on several patents, sued the PTO in August 2007, and GSK filed suit that October. The two cases were consolidated.

The rule would create a presumption that inventions are patentably indistinct if an applicant files multiple submissions to the PTO that include common inventors or overlapping disclosures on the same date or within two months of a previous filing. The rule requires applicants to identify all related patents and applications.

Tafas claims that the rule is “arbitrary, capricious, an abuse of discretion, otherwise not in accordance with law, contrary to plaintiff’s constitutional rights and in excess of the USPTO’s statutory jurisdiction and authority,” according to court documents.

In its decision, the court found the final rule is “substantive in nature and [exceeded] the scope of the USPTO’s rule-making authority.”

The PTO has appealed the case to the U.S. Court of Appeals for the Federal Circuit. If the court lifts the injunction, the new rule would pertain only to applications filed on or after a future effective date, according to a PTO notice.

The notice is available at www.uspto.gov/web/offices/com/sol/notices/73fr45999.pdf. — Elizabeth Jones

Anti-Preemption Bill Gains Steam With Senate Version

To ensure individuals are not prevented by the U.S. Food, Drug and Cosmetic Act (FDCA) from suing devicemakers under state tort laws, two senators have followed the lead of House lawmakers and introduced a Senate counterpart of the Medical Device Safety Act of 2008 (*IMDRM, April*).

Sens. Edward Kennedy (D-Mass.) and Patrick Leahy (D-Vt.) introduced the companion bill to H.R. 6381, which has 62 co-sponsors in the House. The bill seeks to reverse the Supreme Court’s decision in *Riegel v. Medtronic*, which confirmed preemption of state tort suits for medical devices that have U.S. Food and Drug Administration (FDA) premarket approval (*IMDRM, March*).

When the *Riegel* decision was handed down, Kennedy, who chairs the Senate Education, Labor, Health and Pensions Committee, threatened to create legislation to override the court. He said Congress never intended for FDA approval to give immunity to manufacturers from liability for injuries caused by faulty devices.

“Congress obviously needs to correct the court’s decision,” Kennedy said. “Otherwise, FDA approval will become a green light for shoddy practices by manufacturers.”

Sen. Barbara Mikulski (D-Md.), a co-sponsor of the bill, said, “The FDA used to be the gold standard, but the agency has come under scrutiny recently. If manufacturers are putting faulty devices on the market, they must be held accountable to the patients who use them, the way Congress always intended. I will continue to fight for legislation like this that puts the health and safety of Americans ahead of manufacturers’ interests.”

The device industry warns the bill would result in more lawsuits and ultimately higher healthcare costs. “If enacted, this legislation would create a patchwork approach to medical device approvals where state courts would effectively review and regulate medical devices,” AdvaMed President and CEO Stephen Ubl said.

“It would likely result in a dizzying array of conflicting labeling and indications for use and ultimately may result in

life-saving, life-enhancing technologies simply not being available for patients,” he added.

The senators’ statement can be viewed at leahy.senate.gov/press/200808/080108a.html. H.R. 6381 is available at www.house.gov/waxman/pdfs/bill_MDSA_2008.pdf. — Renee Frojo

Access to Unapproved Devices Outlined in TGA Draft Guideline

Medical devices that are not approved in Australia may be used in patients with life-threatening illnesses provided the Therapeutic Goods Administration (TGA) is informed of the use within 28 days, according to a new draft guideline.

Australia’s Special Access Scheme (SAS) considers the treating physician to be the approving authority for a device used with Category A patients — those with serious illnesses likely to result in death within months if early treatment is denied. But the physician must complete a special form authorizing the sponsor to supply the device, the draft says.

Under the SAS, the import or supply of unapproved devices for all other patients requires prior approval by the TGA, which will evaluate the applications on a case-by-case basis.

The guideline also provides information on when medical devices are exempt from inclusion in the Australian Register of Therapeutic Goods (ARTG).

Australian law provides four avenues for accessing unapproved devices: clinical trials in Australia, authorized prescribers, SAS and personal importation. In each case, applicants must justify the use of the unapproved device over available approved alternative devices, the TGA says. Supplies of unapproved devices are considered temporary pending general authorization to market the product in Australia.

In the clinical trial avenue, sponsors may use either clinical trial notification (CTN) or clinical trial exemption (CTX) for unapproved devices. Both schemes apply to devices that are not listed on the ARTG or that are used for unapproved indications.

For CTN, all materials relating to the proposed trial must be presented to an ethics committee, and a notice of intent to conduct the trial must be submitted to the TGA. “Notification of the CTN Form with the appropriate fee automatically creates the exemption necessary to allow lawful supply of the unapproved medical devices for the clinical trial,” the draft says.

Under the CTX scheme, sponsors must submit a seven-part application covering risk analysis, serious adverse events, administrative and scientific aspects of the trial, product design and manufacturing information, preclinical and clinical data, and information for ethics committees. The time frame for decisions on CTX applications is 50 days with an additional 30

days allowed for sponsors to respond to objections, the guideline says. Once a trial is approved, sponsors may conduct additional trials without further assessment if they notify the TGA.

The “authorized prescriber” avenue is open to physicians, who may apply for the designation when they need an unapproved device for the immediate care of a patient with a life-threatening or serious illness or condition. This avenue may be used when a device has been withdrawn from the Australian market, is marketed elsewhere but not in Australia or has concluded clinical trials and is awaiting authorization. It also may be used when no approved device is available to meet the patient’s needs.

Applications for authorized prescriber must include information on the indication, clinical justification, product details, prescriber details, safety and performance data, endorsement from an ethics committee and a signed “Agreement to Treatment Directions” form. Informed patient consent also is required in these cases.

The TGA emphasizes that devicemakers are not required to supply an unapproved device that has been requested by an authorized prescriber. Firms that do so must monitor use of the device, submit twice-yearly reports on the supply of the product, consider whether to apply for market authorization if there is a long-term need for the device, report any serious unanticipated adverse events and inform the TGA of any changes in the benefit-risk assessment of the device.

Individuals may import devices that are not included in the ARTG if the product:

- Is for use by the importer or an immediate family member;
- Does not contain a substance prohibited for import;
- Is not made using nonviable substances of animal origin or substances of bacterial or recombinant origin;
- Does not incorporate human blood or plasma; and
- Complies with regulations regarding poisonous substances.

Requests to import a Class IIa (low-medium risk) or higher category device “must not exceed the amount required to deliver three months’ treatment using the device according to a treating medical practitioner’s directions,” and the total annual supply cannot exceed 15 months’ treatment, the guideline says.

The draft, “Access to Unapproved Medical Devices in Australia,” also describes which forms are required and where to submit applications. The draft is the latest addition to TGA’s *Australian Regulatory Guidelines for Medical Devices*, which is intended to be a single reference source for all regulatory guidance documents. The agency announced its plan for the compendium in July and has held consultations on three of the sections — conformity assessment evidence, essential principles of safety and performance, and fees and charges (*IMDRM, August*).

Comments on the draft guideline are due Sept. 22. It can be accessed at www.tga.gov.au/devices/argmd-drunapp.pdf. — Meg Bryant

To view the full text of this document, [click here](#).

Draft Guidance Explains When to File HDE Versus IDE

Investigators, institutional review boards (IRBs) and device trial sponsors can distinguish humanitarian device exemptions (HDEs) from investigational device exemptions (IDEs) by consulting a new draft guidance issued by the U.S. Food and Drug Administration's Center for Devices and Radiological Health (CDRH).

An HDE approval is based on safety and probable benefit, and makers of humanitarian use devices (HUDs) are exempt from the requirement to provide a reasonable assurance of effectiveness. They also may be exempt from certain statutes and regulations when legally marketing the device, according to the draft, which is written in a question-and-answer format.

With an IDE, on the other hand, an exemption means that certain statutes and regulations need not be followed to conduct a clinical trial of an unapproved or uncleared device. It also may refer to trials of an approved or cleared device for an unapproved or uncleared indication, the draft says.

When they initially review an application to conduct an IDE study, "most IRBs will not know whether the device is a HUD because the IRB review and approval is for an IDE device being used in a clinical investigation," the draft says.

The HDE holder is responsible for ensuring that the HUD is used only in facilities with properly constituted and functioning IRBs. The healthcare provider at such facilities is responsible for obtaining IRB approval before the device is used, except in emergencies where the physician in charge determines there isn't time to get prior approval. In such cases, the physician must report the emergency use within five days and provide written notification to the head of the IRB, identifying the patient involved, the date of the use and the reason.

The FDA recommends that IRBs reviewing HUD studies use an expedited procedure because a HUD is a legally marketed device and no safety and effectiveness information is being collected systematically as is required for a research protocol.

The draft is updated from a 2006 version to include requirements set forth by the Pediatric Medical Device Safety and Improvement Act of 2007. Those new provisions include:

- A requirement that all original HDE applications contain a description of any pediatric subpopulations that suffer from a condition the device is intended to treat, diagnose

or cure and the number of patients affected;

- An amendment allowing some HUDs to be sold for profit; and
- A requirement for the FDA to provide guidance to IRBs on how to review HUDs.

The draft also provides a list of definitions and information on HUD designations and HDE applications as well as whom to contact at CDRH about the applications.

The draft clarifies that companies with HDEs for devices used with pediatric patients may not profit from their sale if the product was approved before Sept. 27, 2007.

Device companies may sponsor a study to collect safety and effectiveness data to support a PMA for the HDE-approved indications without applying for an IDE, but IRB approval and informed consent still are required. If the HUD is studied for uses beyond its approved indications, the sponsor needs to get an IDE as well as IRB approval and informed consent.

The guidance can be found at www.fda.gov/cdrh/ode/guidance/1668.pdf. Comments are due Oct. 3. — Renee Frojo, Martin Gidron

To view the full text of this document, [click here](#).

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FDANEWS

Canada: Research Needed on Use Of FDG-PET in Infections

More clinical studies are needed to support the use of fluorodeoxyglucose-positron emission tomography (FDG-PET) in the detection and evaluation of infections, the Canadian Agency for Drugs and Technologies in Health (CADTH) concludes in a recent report.

The technology, which involves nuclear medicine imaging, is indicated to diagnose and manage cancers and cardiac and neurological problems. Its use in infections is relatively new, but it has the potential to improve disease management and patient outcomes if it results in earlier and clearer diagnoses, the report says.

Using FDG-PET to diagnose infections also could swell the patient base for the technology, the report notes.

The CADTH assessment compares the safety, performance, cost-effectiveness and clinical impact of FDG-PET with other imaging methods. The report will help shape policy and guidance on the use of this technology in infections.

Two meta-analyses and seven prospective observational diagnostic studies demonstrated the clinical efficacy of the technology over other methods, according to the report. It adds that FDG-PET proved superior to other techniques in analyzing peripheric bone and prosthetic joint implants and infections of the vertebral column.

The technology also outperformed scintigraphy in detecting periprosthetic hip infection and MRI in characterizing Charcot's neuroarthropathy. One meta-analysis showed FDG-PET was superior to MRI in osteomyelitis, but the results in another osteomyelitis study demonstrated it was less effective than MRI. The efficacy of FDG-PET was inconclusive in studies of patients with multiple infections.

"The results of this review suggest that FDG-PET may be more effective in diagnosing certain types of infection relative to other imaging techniques, but more intensive studies or systematic reviews and analyses of specific indications are needed, as well as evidence for this technology's potential to alter patient treatment and outcomes," the report says.

CADTH also calls for cost-effectiveness studies of FDG-PET, noting the high cost of the technology relative to other diagnostic methods. Average per-service costs range from \$1,231 to \$7,869, the agency says.

The report, "FDG-PET to Assess Infections: A Review of the Evidence," is available at www.cadth.ca/media/pdf/I3016_FDGPET_Assess_Infections_htis-3_e.pdf. — Meg Bryant

To view the full text of this document, [click here](#).

Small Device Firms Often Unprepared For Bioresearch Monitoring

The U.S. Food and Drug Administration (FDA) is getting tougher when it comes to conducting device clinical trials — if the increased number of violations coming from its Center for Devices and Radiological Health's Bioresearch Monitoring (BIMO) program is any indication, an expert says.

As a result, small device firms are being hit the hardest, Carl Anderson, senior consultant for Biologics Consulting Group, told *IMDRM*.

Because clinical trials for PMAs or 510(k)s rarely draw inspections, there is a smaller body of knowledge around compliance standards. "When FDA does inspect device sponsors, they are frequently unprepared. The result is an increased number of warning letters for easily avoidable violations," Anderson said.

Last year, the FDA came up with a Top 5 list of sponsor violations cited on Form 483. Monitoring the progress of a clinical trial investigation has been the top item for the FDA's compliance program and the No. 1 violation every year, Anderson said at an FDAnews audioconference. Failure to submit progress reports, failure to secure investigator compliance, inadequate unanticipated adverse device event reporting and failure to inform investigators also made the cut, followed by inadequate device accountability and failure to obtain a signed investigator's agreement.

Suggestions Anderson offered to facilitate compliance include conducting internal audits to verify a study is on track and submitting timely, detailed annual reports that contain a study progress section and risk analysis. "Good reporting includes narrative paragraphs and not just check boxes," he said.

Michael Marcarelli, BIMO director, gave five basic recommendations to guarantee compliance:

- Follow good clinical practices. This includes submitting annual reports that FDA managers consider "critical to ongoing oversight";
- Develop clinical standard operating procedures that include a systematic plan to qualify vendors and govern how records are kept. Each stage of data handling should be recorded;
- Monitor the data life cycle. A quality system should be in place at the beginning of the trial, not the end, and be conducted throughout the entire course of the study. Also, clinical investigators should be consulted in protocol development to determine whether the protocol is reflective of what happens in real life;
- Conduct internal audits. Independent specialists could be used to periodically conduct mock FDA audits; and
- Implement corrective and preventive action procedures with management participation and review.

Anderson said device sponsors should expect to receive an FDA inspection when filing a PMA. By ensuring that high-quality

data is recorded and maintained, sponsors can benefit from quicker approvals. He said the best advice he can give any size firm is “monitor, monitor, monitor.” — Renee Frojo

US FDA Finalizes Tougher Rules on Advisory Panel Conflicts of Interest

Individuals may not participate on a U.S. Food and Drug Administration (FDA) advisory committee after Dec. 3 if they play a crucial role or have a financial interest greater than \$50,000 in companies that may be affected by the committee’s actions.

While some committee members are government employees who must make regular financial disclosures, most are experts hired as “special government employees” (SGEs) for whom disclosure rules are needed, according to one of five new guidances on advisory panels issued last month.

The guidance follows congressional and media attention that focused on FDA advisory committee members’ potential conflicts of interest. Several lawmakers urged the House Energy and Commerce Committee last December to investigate why the FDA did not approve Dendreon’s prostate cancer vaccine Provenge and charged that advisory committee conflicts of interest may have been part of the reason.

The new guidance also calls for disclosure of financial interests held by the spouses or minor children of SGEs. All such financial interests must be disclosed, and the agency may bar participation by individuals whose financial interest is less than the \$50,000 maximum in some circumstances.

For example, the ban applies if the SGE is or will be the principal investigator, co-principal investigator or head of the relevant research department for the product or indication to be discussed at the meeting or for a directly competing product. This restriction extends to SGEs receiving personnel or salary support for designing, advising or reviewing data on any aspect of relevant clinical trials.

If the FDA grants a waiver for a member with a potential conflict of interest, the agency “will make it clear and transparent,” Randall Lutter, deputy commissioner for policy, said in a conference call. Before issuing a waiver, the agency will have to prove the committee needs the person’s expertise. The agency also will limit the number of waivers it grants as required by law.

The new recommendations are stricter than those

implemented in 2000 and are necessary because of the passage last year of the FDA Amendments Act, the agency says in its final “Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees.”

The guidance on conflicts of interest can be viewed at www.fda.gov/oc/advisory/GuidancePolicyRegs/ACWaiverCriteriaFINALGuidance080408.pdf.

The agency released three related final guidances, which became effective last month:

- The first one requires the FDA to post all waivers and disclosures of potential conflicts of interest to its website, usually at least 15 days before the relevant advisory committee meeting. It also provides disclosure templates for candidates for advisory committees to use. It is available at www.fda.gov/oc/advisory/GuidancePolicyRegs/ACDisclosureFINALGuidance080408.pdf.
- The second guidance stipulates that votes at advisory committee meetings must be cast simultaneously rather than sequentially to avoid “voting momentum” in which members may be unduly influenced by preceding votes. It is available at www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2007-D-0196-gdl.pdf.
- The third one advises industry sponsors on preparing briefing materials before advisory committee meetings and informs them of timelines for submission, review and public availability of the briefing materials. The FDA intends to notify sponsors about open meetings involving their products approximately 55 business days in advance. The guidance is available at www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2007-D-0425-gdl.pdf.

The agency also proposed in a draft guidance to consider three factors when deciding to refer an issue to an advisory committee — whether it requires special expertise, is controversial or is of significant public interest. For all first-of-a-kind products, the FDA either will refer the product to an advisory committee or explain in a complete response letter why it did not do so, the draft says. Public comments on the draft, which can be seen at www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0417-gdl.pdf, are due Oct. 6.

A fact sheet about the guidances can be found at www.fda.gov/oc/advisory/factsheet080408.html. — Martin Gidron

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