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EU Internal Trade Rapporteur Further Refines Notion of "Single-Use Device"

Devicemakers that label their products for single-use only should be able to back that claim with objective evidence that reuse of the device is impossible, an EU lawmaker says.

Minus such demonstration, such devices are only "intended" for single use and may be reprocessed according to the legislation, writes Nora Berra, rapporteur for the EU Parliament's Committee on Internal Trade and Consumer Protection.

Berra also suggests that distinct definitions be drawn up for "multiple-use device," "single-use device" and "intended single-use device." Her July 30 opinion on the proposed medical device regulation takes issue with a number of provisions in the European Commission's proposal and an earlier report by another parliamentary committee.

In an April report on the legislation, Dagmar Roth-Behrendt, rapporteur for the Committee on the Environment, Public Health and Food Safety, recommended allowing any device to be labeled single-use provided the company could demonstrate that fact. That view was widely criticized by industry as being too broad and placing the onus on original equipment makers, rather than reprocessors, to finance the needed studies (*IMDRM*, May). It is likely that Berra's recommendation will draw similar concerns.

Berra also expresses concern that adoption of common technical specifications could undermine the European standardization system and offers several amendments aimed at ensuring that CTS are limited to areas "where no harmonized standards exist." The Medical Devices Control Group, which would be created by the regulations, should serve as a forum for stakeholders to consult on the appropriateness of individual CTS, she says.

With regard to innovative high-risk devices, Berra says devicemakers should inform competent authorities early in the development stage of a product's uniqueness and that clinical and scientific assessment should be allowed to proceed in the absence of common technical specifications.

Once experience is gained on a new technology, guidelines and CTS should be established, Berra says. "This would progressively reduce this European assessment mechanism to first-in-class and innovative devices."

Another amendment would prohibit member states from requiring national registration for products that are already centrally registered. "While the overriding objective must be the safety of patients and users, steps must also be taken to safeguard the free movement of products," Berra writes.

The rapporteur would require manufacturers of devices comprised of more than one implantable part to ensure the compatibility of parts supplied by different manufacturers. In particular, the Commission should look into the need for further checks on the compatibility of hip implant components sourced from different manufacturers, given the large number of elderly who have hip replacements, she says.

Other amendments Berra proposes would:

- Require the Commission to produce guidelines on the procedures for assessment, designation and notification of conformity assessment bodies and monitoring of notified bodies within two years of the regulations taking effect;
- Limit subcontracting of product reviews to "only specific tasks" connected with the conformity assessment, and those must be justified by the national authority;
- Allow unannounced inspections to count as regular inspections, with the offsetting of the devicemakers' costs, provided that no significant nonconformities are recorded during unannounced inspections;
- Require summaries of safety and performance of Class III and implantable devices to be updated annually;
- Establish requirements for the submission of periodic safety update reports on Class III devices;
- Authorize unannounced inspections of manufacturers located outside the EU if the device will be sold in the European market; and
- Phase out the use of phthalates and other substances known to be carcinogenic, mutagenic or toxic to reproduction within eight years of the regulation coming into force, unless no safer alternative materials are available.

The call for an eventual phaseout of phthalates, a known endocrine-disrupter, echoes recent statements by the Danish health minister and French officials (*see story below*).

View the rapporteur's opinion at www.fdanews.com/ext/files/08-13-IMPC.pdf. — Meg Bryant

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Denmark Wants Device Reg Negotiations To Include Phase-Out of Phthalates

Denmark's health minister is spearheading an effort to include the phase-out of phthalates in medical devices in revisions to EU device regulations. And she has the backing of the country's device trade group, Medicoindustrien.

"Patients must be able to be confident that the medical equipment used in healthcare — whether in plastic tubing, catheters, blood bags or other — does not expose them to unnecessary risks," said Astrid Krag, the health minister. Scientific studies have shown phthalates to be endocrine-disrupters.

Industry has agreed to support the phaseout if it allows a reasonable timeline.

The compounds are used to soften PVC and make it more resilient in devices such as endotracheal tubing and blood bags and tubing used to provide respiratory therapy for premature infants. The phthalate most often used in medical devices is di(2-ethylhexyl)phthalate, or DEHP.

According to the trade group Eucomed, a blanket ban on phthalates in medical devices could impact the availability of products used in medical procedures such as blood transfusion, hemodialysis and enteral feeding.

"Eucomed would strongly oppose any arbitrary or unscientific ban of any material that could be essential to the functioning of medical devices and a proven benefit to patients," spokesman Brett Kobie told *IMDRM*.

"The discussion about phthalates in devices has been going on for years and was also hotly debated in the 2007 revision of the medical devices directive," said Erik Vollebregt, a partner at Axon Lawyers in the Netherlands. The compromise reached at the time requires manufacturers to incorporate risk reduction in design and include the presence of phthalates in product labeling.

"The complexity here is that phthalates are already covered under the EU REACH [Registration, Evaluation, Authorisation of Chemicals] regulation on chemicals safety, so the question is whether the EU can provide additional design requirements based on safety for chemicals that are permitted in articles under REACH, which restricts some phthalates but not all and only restricts these particular ones under certain conditions of application," explains Vollebregt.

In 2009, the European Chemicals Agency proposed DEHP as one of six chemicals that would comprise the initial list of substances subject to REACH authorization (*IMDRM*, February 2009). The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks has called for more studies to address concerns about testicular toxicity in infants and for the evaluation of suitable alternatives (*IMDRM*, April 2008).

The Danish health ministry and Medicoindustrien said they will explore options for a public-private partnership to identify devices or product areas where phthalate-free alternatives don't exist. The ministry recently released a set of guidelines to municipalities on reducing the purchase of devices containing phthalates.

Meanwhile, France announced it would ban all phthalates in medical devices for children beginning July 1, 2015. — Meg Bryant

Survey Points to Jump in Issued Certificates From Notified Bodies

The number of valid certificates issued by EU notified bodies grew markedly between 2010 and 2012, but so did the number of certificate withdrawals, a new report finds.

According to a survey by The European Association for Medical Devices of Notified Bodies, issuances of valid certificates totaled 21,530 in 2012, up 55 percent from 13,899 in 2010. TEAM-NB notes, however, that 2012 is the first year all notified bodies have participated in the survey.

The report comes as scrutiny of notified bodies has intensified in the wake of concerns about the safety of high-risk medical devices authorized in European markets.

TEAM-NB published the data in an effort to increase transparency around issuances of certificates by notified bodies, said Gert Bos, head of regulatory and clinical affairs at BSI and president of TEAM-NB.

IVD Certificates Up 1 Percent

The report shows the distribution of certificates between different directives and between different conformity assessment modules under those directives. While the medical device directive took the lion's share of certificates, a modest distribution was associated with the directives on in vitro diagnostic devices and active implantable medical devices. Disbursements of IVD certificates grew 1 percent from 2010 to 2012.

Within the main device directive, 46 percent of certificates related to CE marking, 24 percent involved production quality assurance and 19 percent were for device design examination.

The study's biggest reveal was a nearly 280 percent jump in withdrawals of device certificates — from 240 in 2010 to 915 last year. These were mostly due to companies refusing to allow audits, evidence of major nonconformities or company acquisitions, the survey shows.

Bos isn't worried by the higher number of withdrawals, given the overall rise in valid certificates. "The data show that more strict actions are [being] taken in case of nonadherence to requirements," he told *IMDRM*. "This might be attributed to increased requirements enforced in 2007/47/EC, more supervision by the competent authorities and the general drift towards stricter compliance that is the basis of discussion for future regulation."

View the survey at www.team-nb.org. — Nick Otto

IMDRF Provides Harmonized Definitions For When Standalone Software Is a Device

The International Medical Device Regulators Forum has issued a draft paper aimed at facilitating global regulatory convergence in the management of standalone medical software.

Current regulations "do not readily translate or address the unique public health risks posed by standalone software nor assure an appropriate balance between patient/consumer protection and promoting public health by facilitating innovation," IMDRF says. The paper defines key concepts regulators should consider when classifying SMDS.

IMDRF defines SMDS as software that is "intended to be used for one or more medical purposes and is able to perform its medical purpose without being embedded in a hardware medical device or being dependent on specific or proprietary medical purpose hardware." As such, it qualifies as a medical device.

Characteristics of SMDS include the capability to run on general computing platforms and accomplish tasks without the use of device hardware, the paper notes. Regulators should also consider whether the software is intended for use in combination with medical devices or as an interface with other device hardware and software.

The paper lists four medical purposes for SMDS:

- Mitigating a disease;
- Providing information for determining compatibility, detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities;
- Aiding in diagnosis, screening, monitoring, predisposition, prognosis, prediction and determination of physiological status; and
- Aiding persons with disabilities.

Disinfection of devices and reproductive purposes are specifically excluded for SMDS, the paper says.

Some regulators, such as Sweden's Medical Products Agency, have already taken steps to classify standalone software as a device (*IMDRM*, March). IMDRF says that while these individual approaches have a common public health goal, adopting a set of harmonized definitions will help to foster innovation and ensure patient access to novel technologies that are safe.

Comments on the document are due Aug. 30. View IMDRF's proposal at www.fdanews.com/ext/files/08-13-Standalone.pdf. — Nick Otto

Aussies: In-House, Commercial IVDs Should Meet Same Conformity Standards

Australian devicemakers are criticizing a government proposal to allow modified conformity assessment procedures for Class 4 in-house in vitro diagnostics, saying it would put commercial assays at a disadvantage.

Under the proposal — one of six options for amending the Therapeutic Goods Administration's regulatory framework for IVDs — laboratories creating Class 4 IVDs would have to be accredited as medical laboratories by either the National Association of Testing Authorities or the Royal College of Pathologists of Australasia or maintain good manufacturing practice — but not both.

"This would create an uneven playing field where a de novo Class 4 in-house IVD is not subject to the same conformity assessment procedure as equivalent commercial assay," writes IVD Australia in comments on the TGA proposal.

Abbott concurred, saying the change would allow laboratories to develop Class 4 IVDs with minimal scrutiny. Incorrect results from a de novo in-house hepatitis C virus assay was one of the catalysts for the introduction of the proposed IVD regulatory framework in 2002, Abbott adds.

Longer Transition Urged

Laboratories must follow GMP and have NATA/RCPA accreditation if they manufacture Class 4 IVDs that are used for diagnosis or donor screening in Australia, industry says.

"If this proposal were to be implemented, these assays should not be registered on the ARTG [Australian Register of Therapeutic Goods] and available for supply to any and all laboratories. They should be assessed prior to use by the laboratories and a publically viewable database maintained by TGA," Abbott writes.

Industry said it would support a modified conformity assessment procedure for Class 4 in-house IVDs predicated on a commercial assay, but urged the TGA to "produce a prescriptive list of modifications that would be acceptable" under this option.

Industry also took issue with the TGA's proposal to retain the current time frames for transition to the three-year-old IVD regulatory framework, saying it could disrupt supplies of essential tests (*IMDRM*, September 2010). "Under proposal 1B (status quo), it is quite likely that a number of products will not be included on the ARTG before 30 June 2014, given the current TGA backlog and the rate at which applications are being processed," writes IVD Australia.

The trade group threw its weight instead behind a proposal that would extend the transition period for all IVDs to June 30, 2015.

If the revised deadline is adopted, Class 2 and 3 IVDs made in Australia and all Class 4 inclusion entries should not have to pay annual fees until 2015, writes IVD maker Alere. "This will ensure that manufacturers/sponsors who have submitted valid inclusion applications by the original deadline are not penalised by this change in timelines."

The TGA also has proposed selective performance reviews of Class 4 IVDs that are submitted for design examinations and amendments to the definition of "medical device" to include predisposition and susceptibility tests. IVD makers expressed only minor issues with these proposals.

In all, 29 comments were received on the consultation. View it at www.fdanews.com/ext/files/08-13-TGAconsult.pdf. IVD Australia's comments are available at www.fdanews.com/ext/files/08-13-IVDAustralia.pdf. Abbott's and Alere's comments are at www.fdanews.com/ext/files/08-13-Abbott.pdf and www.fdanews.com/ext/files/08-13-Alere.pdf, respectively. — Nick Otto

Devicemakers Reject TGA Proposal To Ban Ads for High-Risk Devices

Prohibiting all direct-to-consumer advertising of higher-risk medical devices could result in patients ferreting information from less reliable sources, industry warns in comments on proposed revisions to the Therapeutic Goods Administration's advertising regulations.

The proposal — one in a series of options floated by the TGA in a May consultation document — would bar all forms of advertisements of high-risk devices in mainstream media. This would include Class III devices, active implantable medical devices and Class IV in vitro diagnostic devices.

According to the agency, advertising of high-risk devices "would be on the same basis as the prohibition on advertising of higher-risk medicines given the similar risk profiles and that there is a need for the involvement of a healthcare practitioner to ensure safe use of the product."

But in comments to the TGA, the Medical Technology Association of Australia says drugs and devices should not be aligned because the risk profiles of the two industries differ greatly.

While drugs and devices both require some contact with a health practitioner, implantable high-risk medical devices can't be implanted without physician involvement, MTAA says. "This is contrary to prescription medicines that could be obtained illegally and taken without further healthcare professional involvement."

High-Risk Devices 'Rarely' Advertised

The trade group also rejects the TGA's assertion — as a reason not to impose a ban — that prohibiting ads of higher-risk devices might harm sales, noting that high-risk devices are "rarely" advertised but instead recommended through healthcare providers.

Instead of banning direct-to-consumer information on high-risk devices, the trade group says sponsors of all classes of devices should be allowed to provide information that is within the scope of the intended use of the device. "[T]he determination of risk categorization criteria should be linked to advertisement risk categorization and not to device risk classification," MTAA writes.

The group also questions the need for broad-based prepublication approval of device ads, saying an industry review of the TGA's Complaints Resolution Panel found only about 3 percent of complaints involved devices on the Australian Register of Therapeutic Goods (ARTG). A June 2012 proposal would have required devicemakers to get preapproval of advertisements intended for mainstream media, similar to rules for non-prescription drugs (*IMDRM*, June 2012).

MTAA supports the creation of a dedicated complaints office within the TGA, but says there should be distinct pathways for complaints about ARTG and non-ARTG devices.

Read MTAA's comments at www.fdanews.com/ext/files/08-13-MTAA.pdf. The TGA consultation is at www.fdanews.com/ext/files/08-13-Advertising.pdf. — Nick Otto

Europe's FaBiMed Project Aims to Revamp Custom Manufacturing

Two Irish devicemakers are the latest to be selected for FaBiMed, an EU-funded pilot project to develop new cost-effective, flexible manufacturing techniques for patient-specific microdevices.

There is a growing need for such devices in point-of-care diagnosis, advanced therapies and other applications, said Pablo Romero of the nonprofit association Aimen, which is coordinating the project. But devicemakers have run into a "big barrier" manufacturing these highly customizable, disposable devices.

"Micromanufacturing and microassembly methods nowadays are inherited from microelectronics," he told *IMDRM*. While cost-effective for producing high volumes, "they are not suitable to variable batch size, flexible design, 3-D geometries, etc."

Promising direct-manufacturing technologies exist, such as 3-D printing and laser micromachining, but they are far from cost-effective, Romero added. FaBiMed aims to find more immediate solutions via "revolutionary" injection mold design and a concurrent design of the mold and replication process, he said. Molds will be designed specifically for device materials, such as polymers and biocompatible ceramics.

Slated for a September launch, the project should deliver several functional prototype products and prototype manufacturing equipment in about three years, Romero said. New products enabled by the technology are expected to hit the market within another two years.

FaBiMed's benefits for devicemakers could include:

- More cost-effective manufacturing;
- More flexibility in microdevice design;
- Wider selection of processable materials;
- Ability to incorporate nanosized features;
- Use of a single manufacturing technique from the prototype to the serial production phase; and
- Reduced development time, time-to-market and costs.

FaBiMed falls under the European Commission's FP7-NMP initiative, intended to boost the region's competitiveness. According to the commission's website, "the competitiveness of the industry of the future will largely depend on nanotechnologies and their applications."

Participating in FaBiMed are Irish devicemakers Adama Innovations and Crospon Limited; the UK's Applied Functional Materials; the Netherlands' Promolding BV; Spain's Servizo Galego de Saúde and Twoptics Systems Design; Portugal's Universidade de Aveiro and Instituto de Engenharia Mecânica e Gestão Industrial; Germany's SensLab and Fraunhofer-Gesellschaft; and Austria's Research Center for Non-Destructive Testing.

The EU is injecting about U.S. $4 million into the initiative. Total cost is estimated at roughly $5.5 million. — April Hollis

EUnetHTA Renal Nerve Denervation Pilot Now Covers Entire Class

An EU pilot for a rapid health technology assessment of a Medtronic renal nerve denervation device is now a class assessment, according to the EU Network for Health Technology Assessment's response to public comments on the project.

The pilot was originally intended to provide information on the safety and efficacy of Medtronic's Symplicity device to countries making coverage decisions.

However, in comments on the draft project plan, Johnson & Johnson, which also makes an RND device, recommended a class assessment and EUnetHTA agreed.

The HTA umbrella group said research questions have been reformulated and, where appropriate, all five manufacturers may submit their documentation. The pilot, which will compare RND with drug therapy, will look at safety and efficacy data and will not consider cost.

In its comments, J&J took issue with EUnetHTA's rationale for undertaking the review as a "rapid" assessment, calling it unclear and potentially unjustified. The company asked for "a more robust and comprehensive review of the procedure and potential technologies available."

Specifically, J&J urged that the review consider three points: whether the procedure has value; if yes, which of the available technologies are safe and effective; and what is needed for future RND technologies to demonstrate safety and performance.

In the meantime, J&J said EUnetHTA should create an explicit rule regarding the eligibility criteria for technologies or procedures seeking a rapid core HTA. The organization agreed and plans to bring this up for discussion at a general level.

J&J also suggested changes to the outcomes the pilot will assess, recommending a decrease in blood pressure as the primary outcome.

"There is a validated correlation between blood pressure level and cardiovascular morbidity/mortality," the company writes. "Considering realistically the feasibility of clinical studies to evaluate the therapies, primary outcomes should not be 'overall mortality and cardiovascular morbidity.' Those outcomes would require a long-term study of several years and a very high number of patients."

Despite these concerns, EUnetHTA plans to keep mortality and morbidity as primary outcomes. "We perfectly understand the limitations of providing data on mortality at this point, hence this needs to be stated in the review," the group says, adding, "blood pressure decrease now figures as primary outcome in the project plan."

EUnetHTA did agree with J&J that changes and adjustments may be needed to make the pilot work for devices, as the company noted the plan lifts heavily from procedures and methods designed for pharmaceuticals.

The draft pilot plan is available at www.fdanews.com/ext/files/07-29-13-RNDdraftpilot.pdf. View the consultation response at www.fdanews.com/ext/files/07-29-13-RNDcomments.pdf. — April Hollis

UK's NICE OKs Tracheal Endoscope, Vaginal Acidity Reader for Pregnancy

The UK's benefit-cost agency last month issued two recommendations on devices for use in tightened tracheal airways and identification of vaginal wetness in pregnant women.

CommonSense's Vision Amniotic Leak Detector, or VALD, assesses unexplained vaginal wetness during pregnancy, which could be due to leaking urine or could be leaking amniotic fluid, indicating a possible rupture in the fetal membranes and the potential for infection. According to Wednesday's guidance, the noninvasive diagnostic has a central polymer-embedded strip that turns blue-green on contact with fluid that has a pH higher than 5.2; normal pH is 3.5 to 4.5, while amniotic fluid is 6.5 or above.

Clinical evidence for VALD was based on three comparative diagnostic studies evaluating the noninferiority of VALD to speculum examination, the National Institute for Health and Care Excellence says. In two of the studies, the comparator was speculum examination or a positive nitrazine (pH) and fern test.

"The device can reliably distinguish whether unexplained vaginal wetness in pregnancy is due to amniotic fluid leaking, or if it's due to urine which is less of a concern," said Carole Longson, director of the NICE Centre for Health Technology Evaluation. "This will free up clinical time and resources and is estimated to save the NHS up to £24 [US $36.44] per woman compared to standard management."

Breathing Room

The same day, NICE released guidance recommending Ambu's aScope2 for use in people with unexpected, difficult airways requiring emergency intubation. The device employs a single-use, flexible endoscope and video camera to help healthcare practitioners correctly place the breathing tubes.

Conditions that can hamper intubation include limited mouth opening or cervical spine movement, trauma to the face or neck, respiratory tract infections and some cancers.

According to NICE, the aScope2 is an acceptable alternative when the current gold standard for managing

difficult intubation — a multiple-use fiber optic endoscope — is unavailable.

"There are an estimated 22,000 instances each year in the UK where there are unexpected difficulties with endotracheal intubation in patients," Longson said. "In some cases, this can result in patients being brain-damaged or dying because unexpected problems with keeping the airway open have left the patient starved of oxygen."

The economic models presented by Ambu indicate the highest savings with aScope2 if used in the intensive care setting — about US $4,563 per unit annually in specific circumstances.

A positive recommendation from NICE is needed to support payment by the National Health Service. On May 1, NICE took over the NHS' technology adoption program, ensuring a "more seamless and effective route" to the adoption of novel diagnostics, surgical implants and other devices (*IMDRM*, June).

View the VALD and aScope2 guidances, respectively, at www.fdanews.com/ext/files/08-13-pregnancy.pdf and www.fdanews.com/ext/files/08-13-Airways.pdf. — Nick Otto

Industry to U.S. FDA: Draft Guidance On ISO-10993 Could Delay Reviews

A U.S. Food and Drug Administration draft guidance instructing sponsors on how to use International Organization for Standardization (ISO)-10993 Part 1 to test the potential toxicity of devices that come into direct or indirect contact with the body "may result in even slower development and review times," AdvaMed says.

The guidance makes several recommendations to contact the FDA review division prior to beginning biocompatibility testing. But it takes a minimum of 60 days to get an in-person meeting with the FDA, the group points out in comments on the guidance. Additionally, some of the required tests are lengthy, AdvaMed adds.

The draft covers test selection, sample preparation, general testing considerations and specific considerations for certain tests, including carcinogenicity and reproductive toxicity tests. AdvaMed calls for a transition period after the guidance is finalized for companies to implement the changes.

In its comments, AdvaMed urges the FDA not to require testing to address "speculative considerations, which can have a chilling effect on innovation because of the inefficient use of FDA's time (i.e., multiple review cycles, etc.) and extension of the product development time to rule out theoretical concerns." Instead, the final guidance should recommend testing of materials with unknown or inadequately characterized toxicological risk. In some cases, material characterization and toxicity risk assessment may be preferable options.

AdvaMed hopes the new guidance will help address transparency issues. A review the group conducted of recent premarket submissions showed inconsistencies in the FDA's policies on biocompatibility testing requirements and its data interpretation. As examples, the group notes:

- Lack of reviewer experience in interpretation/use of the ISO 10993 standard. "It appears that many reviewers are unfamiliar with common materials and processes that have been used by industry for many years. Many reviewers are also unfamiliar with the tests and how to interpret the results (e.g., hemocompatibility tests, such as complement and coagulation)";
- Inconsistencies in the FDA's interpretation of a device's body contact, leading to data requests for incorrect or overly conservative durations;
- Refusal to accept alternative test data despite adequate supporting data and consistency with recognized standards; and
- Lack of acceptance by many FDA reviewers of the ISO 10993-1 allowance for reference to commercial experience of a material.

To address the last issue, the agency should define its expectation for materials with a "sufficient history of use in medical devices," including identifying any limitations, AdvaMed says.

AdvaMed is also concerned that the draft guidance is not consistent with ISO 10993-1:2009. The draft emphasizes biological test selection without much discussion of the Part 1 standard's three-step process for biological evaluation: material characterization, toxicological risk assessment and biological testing, the group says. The final document should acknowledge acceptance of ISO 10993-1:2009 and state that it is intended to be applied in the context of a risk-management system. It also should clarify that risk management will be used to help determine the level of chemical testing and toxicological assessment needed, the group adds.

In addition to clarifications and changes, AdvaMed calls for more guidance on the evaluation of biological materials. In particular, the group seeks guidance on

special considerations for testing the chemical characterizations of biologics, which is difficult to perform.

Comments on the draft guidance were due July 22, but none have been posted online by the FDA. The guidance is available at www.fdanews.com/ext/files/04-23-13-10993.pdf. — April Hollis

China FDA Issues Field Results From Random Device Quality Tests

The China Food and Drug Administration released its first national medical device quality report of 2013, showing results from random quality inspections of hospitals and other facilities where the devices are used. Optical therapy equipment was the big loser, failing to meet standards in 22 of 38 cases.

The CFDA periodically investigates device quality by random inspections in the field, Daniel Huang, a quality systems and regulatory affairs officer at consulting firm Celestica, told *IMDRM*. "Each time, they will select several types of devices marketed in China and announce the inspection results to the public."

In addition to optical devices, the latest round of inspections focused on:

- Balloon dilatation catheters;
- Metallic bone plates;
- Endoscopy devices (fiberscope and other rigid optical endoscopy except uteroscope and peritoneoscope); and
- Low- and intermediate-frequency therapy apparatuses.

The CFDA found no faults with the 11 balloon dilation catheters it inspected. Metal bone plates and endoscopes also performed well, meeting standards in 31 of 35 and 21 of 23 examinations, respectively, the report says. Quality results for low-frequency therapeutic equipment were split, with seven devices meeting national standards and six failing the exam.

When a manufacturer fails to meet the relevant quality standards, the CFDA will halt production of any affected devices, impose a warning and fine the company, Huang said, referencing article 37 of the CFDA's Decree on Medical Device Supervision, State Council Order no. 276. If the device exhibits serious deviations, the agency can revoke its registration certificate.

Huang noted that the CFDA is reluctant to re-register devices whose registration certificates have been revoked. Devicemakers have seen harsher penalties and fines for quality violations since the CFDA began enforcing a new policy in January aimed at stemming the flow of counterfeit and substandard medical products (*IMDRM*, December 2012).

Huang recommends devicemakers strictly follow the CFDA's approval registration standards to avoid quality problems. — Nick Otto

UK Pharma Giant's China Woes Offer Cautionary Tale for Devicemakers

As senior officials of GlaxoSmithKline face accusations of bribing Chinese government officials, experts on the U.S. Foreign Corrupt Practices Act (FCPA) say the case offers a cautionary tale on how to conduct — or not conduct — business in a foreign market.

The alleged kickbacks — described by the Ministry of Public Security as "serious economic crimes" — were given to government officials, medical associations, hospitals and doctors in the cities of Changsha, Shanghai and Zhengzhou and were aimed at increasing sales and prices of GSK drugs, the ministry said in a statement early last month.

Among enticements the UK drugmaker allegedly offered physicians and others were travel rebates and speaker fees.

"This is the first official communication that has been published by the PSB [Ministry of Public Security] in relation to the specific nature of its investigation," GSK said in response to the probe. "We take all allegations of bribery and corruption seriously. We continuously monitor our businesses to ensure they meet our strict compliance procedures."

"All we know about the situation comes from the release issued by the Chinese authorities," GSK spokeswoman Mary Anne Rhyne told *IMDRM*.

Developments in FCPA

Similar corruption allegations have put many drug- and devicemakers in the "crosshairs" of the FCPA, the U.S.-based law firm Arnall Golden Gregory posted online.

"The principal take-away here is that all companies, regardless of size or business focus, need a robust FCPA compliance policy that sets the tone from the top of the organization," AGG partner Mike Burke told *IMDRM*.

One aspect of the FCPA that frequently trips up companies is the expanded definition of what constitutes a "government official," Burke notes.

In most situations, it's easy to discern a government employee. But, Burke posits, "What about a person who works for a state-owned hospital? Or someone who works for another state-owned enterprise or sovereign wealth fund? These may be considered 'quasi' government officials in the normal sense, but they are foreign government officials under the FCPA."

Burke cautions that the definition of "foreign official" is "broad, and is potentially getting broader."

Gifts and entertainment are another potential stumbling block under the FCPA, Burke says. While the FCPA allows for "reasonable business-related" gifts, the challenge is in the details.

According to Burke, companies can offer guidance to their employees on determining what is "reasonable" by:

- Setting a dollar limit on expenditures;
- Requiring advanced approvals for expenditures; and/or
- Requiring that certain conditions be met for a proposed entertainment expense. — Nick Otto

Guidance Lays Out Good Distribution Practice for Devices in Malaysia

Malaysia's Medical Device Authority has issued guidance on good distribution practices for medical devices. The document — which addresses certain quality, safety and performance provisions in the country's year-old device regulation — applies to authorized representatives of foreign devicemakers, importers and distributors. It does not cover manufacturers and device retailers.

The GDP certification should specify the scope of activities performed by the establishment and the devices it deals with; outsourced activities, if applicable; any special storage and handling conditions; and applicable sections of the Medical Device Act 2012 and accompanying legislation (*IMDRM*, April 2012).

Certification should be conducted by a registered conformity assessment body. Malaysia's Medical Device Control Division began accepting applications from parties interested in registering as CABs earlier this year (*IMDRM*, March).

The document provides guidance on establishing responsibilities, organizing a compliance system and maintaining surveillance and vigilance following distribution. It also describes requirements for active medical devices.

The guidance offers supply chain specifics on a number of issues, including how an establishment should implement a traceability plan and steps to take if tracking is not possible for individual products.

For implants, establishments must create a tracking record down to the patient level, the MDA says. The agency is especially concerned with the ability to track and trace the following high-risk implantable devices: mechanical heart valves; pacemakers, including electrodes and leads; defibrillators, including electrodes and leads; ventricular support systems; and drug infusion systems. Surveillance reports on the aforementioned devices must be submitted at least annually.

GDP certification does not imply compliance with the law, the MDA emphasizes, adding it is the devicemaker's responsibility to ensure compliance with all applicable laws in the country.

View the GDP guidance at www.fdanews.com/ext/files/08-13-malaysia.pdf. — Nick Otto

India Considering Separate Regulatory Authority for Biotechnology Products

Indian lawmakers are giving stakeholders until Aug. 25 to weigh in on a bill that would create a new regulatory authority for biotechnology products.

The Committee on Science & Technology, Environment and Forests, which is considering the bill, extended an earlier deadline for comment due to widespread interest. The bill would establish a government agency with distinct divisions and requirements for medical, agricultural and industrial biotech products, each headed by a chief regulatory officer with advanced degrees in biotechnology or medicine.

According to the bill, India's biotech industry has been growing at an average annual rate of 20 percent to 30 percent over the past five years, with 2011-2012 revenue exceeding about US $204 billion. "The potential of biotechnology with respect to food security, public heath, employment generation, intellectual wealth creation, expanding entrepreneurial opportunities and augmenting industrial growth warrants a focused approach towards innovation, regulation and commercialization," an explanatory note states.

The new authority would regulate the research, transport, import and manufacture of organisms and products of modern biotechnology. In addition to the three divisions, the authority would have a risk-assessment unit and an enforcement unit and would oversee trials of organisms and products preceding clinical trials in the health sector. The authority also could recommend and evaluate clinical trials in applications forwarded by the Central Drug Standards Control Organization.

To prevent overlap with drug regulations, the bill would amend section 37 of the Drugs and Cosmetics Act, 1940, to state: "Nothing contained in this Act shall apply to the genetically modified or engineered organisms or any matter or thing connected with it to which are covered the Biotechnology Regulatory Authority of India Act, 2013."

Device Scheme in the Works

The push to create a separate authority for biotech products comes amid reports by the Indian press that the government is proposing to create a Central Drugs Authority with dedicated rules for drugs, medical devices and clinical trials. Currently, only certain categories of devices are regulated and those must comply with requirements that were designed for drugs. Previous attempts to create a regulatory scheme for devices stalled, but momentum to shore up control of all healthcare products has gained steam in the wake of a May 2012 parliamentary report challenging the CDSCO's review of 31 new drug approvals (*IMDRM*, February).

The Drug and Cosmetics Bill, 2013, reportedly was approved by the Union Cabinet but has yet to be introduced in Parliament. The biotechnology authority bill was introduced in Parliament's lower house in April.

View the legislation at www.fdanews.com/ext/files/08-13-BiotechRegAuthofIndia.pdf. — Meg Bryant

U.S. NIH Halts Clinical Trials in India; Experts Blame New Compensation Rules

The U.S. National Institutes of Health announced June 29 that it is withdrawing clinical trial research in India, and some experts are pointing to recent stringent regulations as a possible cause.

Recent amendments to India's drug and cosmetics law have affected some NIH studies and, due to uncertainties posed by the new requirements, the institute and some grantees have suspended new patient enrollment for some ongoing interventional trials, an NIH spokeswoman said. She added that the agency is waiting for additional clarity on how the new rules affect medical device trials.

NIH has expressed to the Indian government its concern and in the meantime will wait for New Delhi to complete its internal deliberations on the issue, the spokeswoman added. On June 26, the Supreme Court of India took up the issue and directed the government to develop a framework for regulating and monitoring interventional trials.

India's Central Drugs Standard Control Organization (CDSCO) released draft guidelines on clinical trial death and injury compensation last September, and NIH says it wants additional clarity on those before continuing trials in the country.

India is trying to put in place rules that protect patients and allow trial participants to know what they're getting into, Amy Hariani, director and legal policy counsel at the U.S.-India Business Council, told *IMDRM*.

"The government has instituted some new rules that have been, pretty frankly, bad for the clinical trial industry in India, which would, for example, provide compensation to a patient or his or her family if the outcome of the trial didn't go as intended," Hariani said. She noted that many Indian patients are illiterate and may not fully understand the purpose of a clinical trial.

The NIH announcement is the latest hit to India's clinical trial industry as a result of the new rules, which charge ethics committees with setting the amount trial sponsors must pay patients or their families based on a formula that considers the patient's age, income, risk factors, preexisting conditions and percentage of disability. Organizations that contract with sponsors to run clinical studies have been impacted to the point where trials have all but stopped, Hariani said. "This new rule … is really having a disastrous effect on the industry."

Revisions Likely, but When?

NIH's decision to stop funding trials is important because it's symbolic, Mark Barnes, a partner and healthcare specialist with Ropes & Gray, told *IMDRM*. "It is just a very stark illustration of the new regulations in regard to compensation of subjects."

Barnes, who met recently with industry and government officials in India, said the government is "well aware of the drastic effect" of the current regulations. "I think there will be amendments to the regulations, but the question is going to be when will the amendments come and what form will they take? That has yet to be decided," he said.

View CDSCO's draft rules on compensation in death or injury at www.fdanews.com/ext/files/07-30-13-India.pdf. The draft trial compensation guideline is available at www.fdanews.com/ext/files/09-12-Trial Compensation.pdf. — Nick Otto

IN BRIEF

Russia Extends Registration Deadline

Russia's Roszdravnadzor has extended the deadline for replacing registration certificates for medical devices, giving companies until Jan. 1, 2017, to obtain recertification. The agency earlier this year said that certificates obtained before Jan. 1, 2013, would be valid until their expiration date or 2016, whichever is later, but those with no expiration date would need to be replaced by the end of this year (*IMDRM*, April). The new system also creates a 50-day timeline for reviews and requires foreign devicemakers to have a local authorized representative.

U.S. FDA to Study Causes of MoM Hip Failures

The U.S. Food and Drug Administration is commissioning a study of corrosion in total hip replacements and any potential link to clinical outcomes. The agency plans to use the results to develop test methodologies and special controls for preclinical studies of total hip implants. Meanwhile, the FDA is waiting on requested postmarket studies from 21 manufacturers of the devices and is facing stakeholder calls to finalize a proposed rule that would require makers of MoM implants to file PMA applications. View the *Federal* Register notice at www.fdanews.com/ext/files/08-05-13-hips.pdf. Responses are due by Aug. 9.

And in Ireland, the Health Service Executive is conducting a review of metal-on-metal hip implants, focusing on four groups of devices that should be monitored throughout the product lifecycle. The review follows safety alerts by the UK Medicines and Healthcare products Regulatory Agency concerning the high rate of failure in the metal prostheses (*IMDRM*, April 2012). The HSE review, which affects about 8,000 patients, will focus on metal-on-metal hip resurfacing implants, stemless implants with a head diameter less than 36 mm, stemmed implants with a head diameter greater than 36 mm, and all types of DePuy ASR hip replacements.

Korea Requires STED for Class 4 Devices

Beginning Jan. 1, 2014, makers of all Class IV devices, excepting in vitro diagnostic reagents, must submit summaries of technical documentation (STED) to Korea's Ministry of Food and Drug Safety. A format for submitting STEDs is described in Article 24, Clause 2, asterisk 7 and 8 of the agency's Regulations on Review, Approvals and Register Notice. Manufacturers of Class I, II and III devices have the option of submitting a STED, but are not required to use it.

U.S.-Korea Patent Pilot Launched

The U.S. Patent and Trademark Office and Korean Intellectual Property Office announced a cooperative patent classification system, whereby KIPO will classify some of its patents according to the Cooperative Patent Classification system. USPTO and the European Patent Office launched the CPC in January to facilitate international harmonization of patent systems.

Health Canada Taps Acting Device Chief

Health Canada's Therapeutic Products Directorate named Cindy Evans acting director of the Medical Devices Bureau, effective June 17. Evans previously served as director of the Therapeutic Effectiveness and Policy Bureau.

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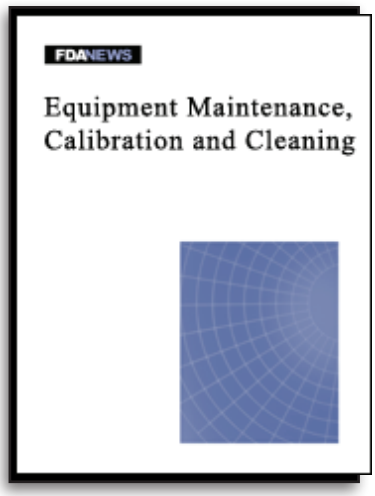

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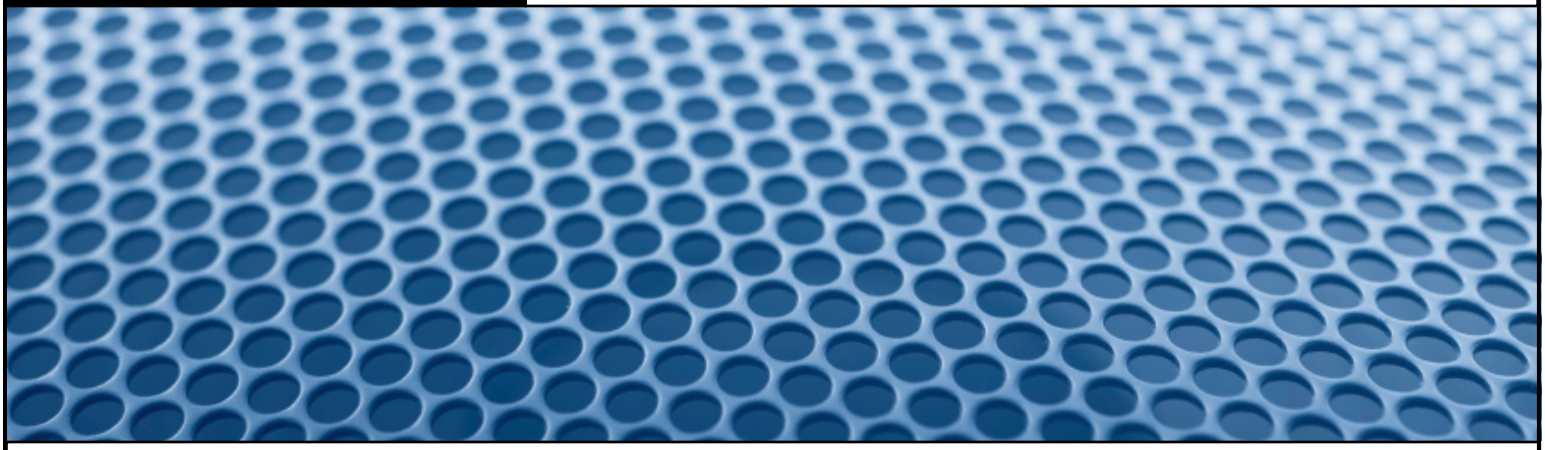

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DAN O'LEARY has more than 30 years experience in quality, operations and program management in regulated industries, including aviation, defense, medical devices and clinical labs. Mr. O'Leary is the president of Ombu Enterprises, a consultancy focused on operational excellence and regulatory compliance serving small manufacturing companies.

The FDA's QSR expert, Kim Trautman, on risk management:
"Are FMEA or FMECA… good tools? Yes. They are very good tools that can be utilized. Are they in and of themselves a risk management system? Absolutely not. I can't tell you how many manufacturers I have seen that have tried to present their risk management system by simply presenting a FMEA — that is not a risk management system. Do not make the mistake of presenting FMEAs as your whole risk management system."

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WORKSHOP AGENDA

DAY ONE

8:00 a.m. – 9:00 a.m. REGISTRATION AND CONTINENTAL BREAKFAST

9:00 a.m. – 10:15 a.m. Workshop Introduction and Concepts of Risk Management Overview

- The fundamentals of medical device risk management
  - Define common risk factors
  - Create a Consequence Diagram and extend it to multiple levels to build a Decision Tree
- Components of risk and potential problems to consider
  - The neonatal heal warmer example: an illustration of a Risk Analysis Procedure
- Definitions from ISO 14971:2007
  - Discuss the definition of a hazard and a harm
  - Risk defined: Identify the probability of harm and its severity to estimate risk
  - Assess the risk, including its formal definition
- Why FMEA is not sufficient for risk management

10:15 a.m. – 10:30 a.m. BREAK

10:30 a.m. – 11:00 a.m. INTERACTIVE EXERCISE
Importance of Risk Management — This exercise allows for an exchange of ideas among participants. They will discuss why risk is important and provide an example of failed risk management. They will discuss the various approaches their firms take to recognize the amount of impact and loss by developing three bullet points that describe the approach.

11:00 a.m. – 11:30 a.m. The Regulatory Structure: The Current Status of ISO 14971:2007

- ISO 14971:2007 as the current standard
  - Follow the development of ISO 14971:2007 and understand the new requirements
  - Outline the steps in the risk management process
  - First look at the implications of EN ISO 14971:2012
- The risk management requirements in FDA's QSR — Design Validation
  - Understand how risk management supports design validation
  - Recognized consensus standards and the FDA's declaration of conformity
- The Risk Management requirements in ISO 13485:2003
- Risk Management standards in the EU
  - Where to find the harmonized standards to the Medical Device Directive
  - Understand the status of EN ISO 14971:2012 and EN ISO 13485:2012
- Global Harmonization Task Force: Two important guidance documents for risk management
  - Understand the purpose of GHTF and its successor, IMDRF
  - Implementation of risk management principles and activities within a quality management system
  - Explore the purpose of the guidance; review and identify the four phases of risk
  - Highlight the two most important elements within the document
  - Identify essential principles of safety and performance of medical devices
- Review FDA warning letters
- Evaluate examples from companies that failed to address and design a valid risk analysis

11:30 a.m. – 12:00 p.m. Understanding ISO 14971:2007 (Part 1)

- Overview of the structure of ISO 14971:2007
- Explore the parts of a risk management plan: scope, responsibility, review, risk acceptability, risk verification, production activity, post-production activity
- How to create and administer a risk management file — Think of it as your risk management file cabinet
- Analysis of clauses 4–9 in ISO 14971
  - Ways to create a risk analysis (Clause 4)
  - Outline a risk evaluation (Clause 5)
  - Determine whether a risk reduction is required (Clause 6)
  - Highlight the importance of a residual risk evaluation (Clause 7)
  - Learn about the report on risk management of a device (Clause 8)
  - Look at production and post-production information (Clause 9)
- Components of risk — How to measure risk through hazards that create harm

12:00 p.m. – 1:00 p.m. LUNCH BREAK

1:00 p.m. – 1:30 p.m. Understanding ISO 14971:2007 (Part 2)

- Conclusion of Understanding ISO 14971:2007

1:30 p.m. – 2:30 p.m. Building a Risk Management File That Meets ISO 14971:2007 Requirements (Part 1)

- Understanding the purpose and contents of a risk management file
  - Assuring the file contains pointers to all relevant documents
  - Organizing documents by hazard and cause
  - Auditing the risk management file
- Risk management planning
  - Explore the role of the risk management plan and learn the scope of the plan
  - Designating someone to be responsible for the plan: qualifications for performing risk management tasks, RASI Matrix and example
  - Two sets of criteria for risk acceptability
  - Accessing risk severity and probability
  - Monitoring residual risk evaluations
  - Two aspects of verification activities provided in the standard
  - Post-production activity: how to collect data and review
- Hazard Analysis
  - Why FMEA is not the right approach
  - Hazards that are not failures
  - The fallacy of Risk Priority Numbers (RPN)
- Risk Assessment
  - Two parts of risk assessment: risk analysis and risk evaluation
  - Tips to develop a systematic approach to determine risk
  - Different components of risk
  - Tools for hazard identification — 5 standard methods to support risk analysis (PHA, FTA, FMEA, HAZOP, HACCP)
  - Understand how to score risks — how to use severity and probability

2:30 p.m. – 2:45 p.m. BREAK

2:45 p.m. – 3:45 p.m. INTERACTIVE EXERCISE
The Risk Management Plan — Participants will develop various sections of the plan based on the contents of a file as defined in ISO 14971. They will first develop a risk matrix. They will then define the structure of their matrix and include a description of each part. Finally, they will devise a plan for data collection, analysis and use of production and post-production issues and discuss how to incorporate it into the risk management file.

3:45 p.m. – 4:30 p.m. Building a Risk Management File That Meets ISO 14971:2007 Requirements (Part 2)

- Risk control
- Conducting a risk control completeness check
- Implementing risk controls: Strategies for the two elements of risk verification
- Overall residual risk evaluation
  - Seven methods to evaluate overall residual risk

Risk Management

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- Disclosing overall residual risk
- Risk management report
  - Strategies for reviewing the risk management process to ensure complete reports
  - A checklist to ensure your report is complete
- Production and post–production information
  - Review the production phase and the post–production phase
  - Evaluating final hazards and corrective processes to put in place

4:30 p.m. SESSION WRAP-UP, END OF DAY ONE DAY TWO

DAY TWO

8:30 a.m. – 9:00 a.m. CONTINENTAL BREAKFAST

9:00 A.M. – 10:00 A.M. INTERACTIVE EXERCISE
The Risk Management Report — This is a set of exercises designed to illustrate the sections of the report. Participants will develop various sections of the report based on the contents defined in ISO 14971. They will begin with deciding on someone to prepare the report. Then they will compose a checklist that acts as a guideline in reviewing the risk management plan. Finally, they will explore more about the residual risk evaluation.

10:00 a.m. – 12:00 p.m. (Includes a break)
Digging Deep Into the Risk Management Tool Kit

- Preliminary Hazard Analysis (PHA)
  - What is PHA and how can it be best used?
  - Developing a PHA worksheet
  - Sources of hazards using PHAs
- Hazard and Operability Studies (HAZOP)
  - Procedures for HAZOP
  - Developing a worksheet for HAZOP
  - Significant parameters for HAZOP
- Hazard Analysis and Critical Control Points (HACCP)
  - Using HACCP to identify hazards, establish controls, and monitor processes
  - Linking HACCP with corrective action
- Failure Modes, Effects and Criticality Analysis (FMECA)
  - Applications to discover known and probable failures in products and the failure impact
- Fault Tree Analysis (FTA)
  - Using this tool to analyze a particular event and its causes
- Event Tree Analysis (ETA)
  - Using this tool to evaluate barriers as risk reduction methods

12:00 p.m. – 1:00 p.m. LUNCH BREAK

1:00 p.m. – 2:30 p.m. APPLICATIONS IN THE EUROPEAN UNION
Understanding the 13485 and 14971 Applications to the Product Directives — From the EU harmonized EN ISO 13485:2012 and EN ISO 14971:2012 to the three product directives: MDD, IVDD, and AIMDD.

- Learn where ISO 14971:2007 deviates from the essential requirements and the implications for risk management
- Understand the linkages between conformity assessment and ISO 13485:2003

2:30 p.m. – 2:45 p.m. BREAK

2:45 p.m. – 4:15 p.m. Related Standards
There are standards and FDA guidance documents that relate to risk management and often call out ISO 14971:2007.

- IEC 60601-1 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
- IEC 62304 Medical device software – Software life-cycle processes
- FDA Guidance – Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
- FDA Draft Guidance – Applying Human Factors and Usability Engineering to Optimize Medical Device Design
- The Assurance Case as a new methodology

4:15 p.m. – 4:30 p.m. Summary, Conclusions, and Lessons Learned

4:30 p.m. ADJOURN WORKSHOP

"Overall for me it was a valuable workshop. There was a ton of information delivered in the 2 days. The handouts and 3ring binder will be a helpful resource upon return tho my company." –Barry Shaw, Quality, Arsenal Medical/ 480 Biomedical

[Dan] provided the material in an easy to handle method and the workbook is a good take-home reference." –Philip DiMascio, Quality Engineer, Covidien

WHO SHOULD ATTEND

- Project managers involved in design and development
- Design engineers
- Quality engineers
- Manufacturing engineers
- Quality auditors
- Production managers
- Scientists involved in device research and development
- Medical staff evaluating risk, safety or effectiveness
- Quality or regulatory staff assigned to complaint, CAPA or MDR management
- Training personnel
- General/corporate counsel

COURSE BINDER MATERIALS

- Slides from PowerPoint presentations
- Case review worksheets
- Interactive exercise worksheets
- Reference docs:
  - Design Control Guidance for Medical Device Manufacturers
  - Medical Device Use — Safety: Incorporating Human Factors Engineering into Risk Management
  - Medical Device Quality Systems Manuals: A Small Entity Compliance Guide
  - Essential Principles of Safety and Performance of Medical Devices
  - Implementation of Risk Management Principles and Activities Within a Quality Management System

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