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In This Issue

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2014: A Year Focused on Transparency, Drug Safety and a Crisis in West Africa

Last year saw major strides in increasing transparency around clinical trial data in the EU and trial safety and compensation in India. An international group also set the gears in motion for a harmonized guideline on multiregional clinical studies. Manufacturing quality was also on everyone's radar, with major changes in the way U.S. regulators conduct inspections and stepped up U.S. audits of Chinese and Indian drug plants. Other driving issues during 2015 included the Ebola crisis in West Africa, price controls in India and anticounterfeiting efforts around the globe. In this article, International Pharmaceutical Regulatory Monitor *brings you some of the highlights of 2014. Use them as a guide for staying in compliance in the year ahead.*

Transparency. In June, the European Parliament adopted new clinical trial regulations, paving the way for qualified researchers to access detailed clinical trial data submitted in support of drug approvals. The regulation requires companies that redact commercially confidential information from clinical study reports to justify their actions. Such information must fall within one of three categories: novel analytical methods, manufacturing methods or exploratory endpoints.

The regulation also creates an EU portal that would allow sponsors to submit a single application anywhere in the union regardless of whether the trial is a single or multistate study. And it requires the European Medicines Agency to establish an electronic database for safety reporting related to clinical trials.

The European Parliament also advanced major data privacy legislation, but not before removing a provision that would have allowed clinical research subjects to demand that personal data be erased from all records, even after they were incorporated in regulatory filings.

In late September, the U.S. government began publicizing drugmaker payments to physicians, the latest provision of the Physician Payment Sunshine Act to take effect. Industry complained that the Open Payments Database lacks context, making it difficult for the public to gauge whether a payment was appropriate or not. The Centers for Medicare & Medicaid Services further riled industry by not including a reporting exemption for payments made to continuing medical education programs in final guidance.

Members of the Hellenic Association of Pharmaceutical Companies in Greece committed to disclose the details of interactions with healthcare professionals and organizations, in line with similar measures adopted by European drugmakers. A similar plan in Australia was criticized for allowing doctors to opt out.

Clinical Trials. The EU wasn't the jurisdiction to advance clinical trial regulations last year. In India, drugmakers saw a flurry of activity as the government issued draft standards on accreditation and ethics of trial sites and finalized formulas for determining compensation for trial-related injuries and death.

On a global level, the International Conference on Harmonisation announced plans to develop a guideline on the conduct of multiregional clinical trials. The guideline will focus on issues such as the usefulness of MRCTs in drug development, the importance of ethnic factors on drug safety and efficacy and controls for dosing and handling concomitant medications.

Anticounterfeiting. In 2014, international authorities seized more than $31 million in potentially counterfeit and dangerous drugs and shuttered over 10,600 websites for peddling unapproved and substandard drugs, in a global dragnet that involved law enforcement, customs officials and regulators from 111 countries. In the U.S., the Food and Drug Administration, partnering with Customs and Border Protection, detained or seized 583 packages at mail facilities in Los Angeles, New York and Chicago. Most of the drugs hailed from India.

Meanwhile, Indian authorities unveiled a scheme to reward whistleblowers for providing information leading to the seizure of spurious, adulterated and misbranded drugs. The country also surveyed pharmacists and tested drug samples to get a better grasp on the extent of its counterfeit and substandard drugs problem.

Drugmakers also prepared to meet a Jan. 1, 2015, deadline to begin complying with new U.S. track-and-trace requirements aimed at combatting counterfeiting. The FDA issued guidance detailing how companies should capture and maintain such information. And the FDA and European Medicines Agency launched an information-sharing initiative aimed at speeding international responses to drug safety problems.

Inspections and Audits. In October, the U.S. FDA unveiled a broad plan to create investigative teams to conduct quality inspections, changing the way the agency inspects drugmakers, approves recalls, reviews and enforces compliance decisions, screens imports and tests products for quality. Under the reorganization, investigators will be accompanied by microbiologists, chemists and engineers during facility inspections. Also, the approval authority for class I recalls has been decentralized, eliminating the requirement that an associate commissioner approve them.

The FDA also ramped up inspections of manufacturing plants in India and announced plans to boost its China staff from eight direct to 26 hires to increase the number of inspections it conducts there.

Drug Pricing. India's National Pharmaceutical Pricing Authority enacted price controls on scores of essential medicines. In September, NPPA set limits on the costs of 43 drugs, including antibacterials and diabetes treatments. Price caps for 52 additional drugs were announced in December, including treatments for cancer, pain and skin disorders.

The moves by NPPA followed a decision in July to set price controls on 108 drugs that treat diabetes and cardiovascular disorders but are not listed as essential medicines in India. Over the summer, the Organization of

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The following documents covered in this issue of the *International Pharmaceutical Regulatory Monitor* are available for download at www.fdanews.com/IPRMdocs.

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Pharmaceutical Producers of India and the Indian Pharmaceutical Alliance sued NPPA over its pricing policies, arguing that the agency doesn't have authority to fix prices on drug formulations. In September, the Department of Pharmaceuticals ordered NPPA to withdraw an internal guideline that set the July price caps in motion.

Ebola Response. The World Health Organization and regulators around the globe rushed to respond to the last year's Ebola outbreak in West Africa, pledging millions of dollars to Ebola research and fast-tracking promising vaccines and treatments. In October, the EMA established a rolling review process whereby companies must show that a candidate is safe and effective, but the benefit-risk balance is largely determined by the public health need. Increasingly robust scientific opinions are provided as new data emerges.

The U.S. FDA also announced it would expedite reviews of investigational new drug applications for Ebola products. Applications for two Ebola vaccines were reviewed and allowed to proceed in less than a week.

Pacific-Rim Harmonization. After several starts and stops, Australia and New Zealand abandoned plans to create a joint regulatory authority, but said they would continue to explore other means of regulatory harmonization. Drugmakers in both countries welcomed the decision, saying the merger would have created a costly reregistration and repackaging nightmare and costs to consumers. — Jonathon Shacat

EMA Adaptive Pathway Pilot Underway With Initial Group of Six Medicines

European regulators have selected six drugs out of 34 applicants that submitted proposals for the EMA's adaptive pathway pilot project. The initiative aims to speed access to promising therapies by authorizing products in stages for targeted populations.

The European Medicines Agency will meet with the companies for the second phase of the pilot, which will entail face-to-face, in-depth discussions about their proposals.

The announcement of the first group of participants, which weren't identified, comes as momentum is building for the adaptive pathway concept. An article in the Nov. 27 issue of *Clinical Pharmacology & Therapeutics* argues that changes in the political and scientific landscape will make adaptive licensing the preferred approach to bringing new medicines to patients going forward.

According to the authors, a confluence of factors is fueling the adaptive licensing movement — advances in science, patient demand for timely access to new treatments, mounting pressure on healthcare systems to control spiraling costs and pressure on industry for R&D sustainability.

The UK BioIndustry Association has actively lobbied for the adaptive pathway and encouraged its members to respond to the EMA's call for participation in the pilot project. European drugmakers see the pathway as a stark contrast to the U.S. regulatory system, which is focused on accelerating approvals via breakthrough designations (*IPRM*, Oct. 14).

But the system could pose challenges to how new drugs are assessed by health technology assessment bodies in EU member states. The adaptive pathway will require HTAs, which make recommendations on coverage policy, to assess the cost-effectiveness of these products based on earlier and less certain data, says Johan Strömquist, CEO of NDA Group, which advises industry on drug development and HTA issues.

The European Federation of Pharmaceutical Industries and Associations says a more flexible pathway would not only accelerate patient access to crucial therapies, but would increase the likelihood of their success as they would be given to populations most likely to respond. Costs for industry and healthcare providers could drop significantly as well, the group says, adding that the program's success hinges on an appreciation of its value across the innovation lifecycle — regulators, HTAs, payers, clinicians and patients.

The journal article, *From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients*, is available at http://onlinelibrary.wiley.com/doi/10.1002/cpt.59/pdf.
— Jonathon Shacat

UK Lags Behind Other Countries In Adopting New Meds: Report

Overly zealous national and local healthcare funding schemes have put the UK far behind other industrialized countries in providing patients access to the latest drug therapies, an industry report concludes.

The Association of the British Pharmaceutical Industry compared new drug usage in the UK and 12 other countries in areas such as cancer, diabetes and hepatitis C.

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For chemotherapies less than five years old, the UK ranked seventh in rate of adoption in 2013, up from 11th place in 2009, according to the report. Austria ranked No. 1, while Switzerland moved to second place from sixth in 2009, the report shows.

In the booming field of diabetes drugs, the UK ranked eleventh in 2013 in adopting new products such as GLP-1 agonists and DPP-4 inhibitors — outpacing only Sweden and New Zealand. Spain and Italy led this category.

For hepatitis C treatments, the UK placed 10th in adopting new protease inhibitors, such as Gilead Sciences' blockbuster Sovaldi (sofosbuvir).

Many new drugs, particularly for cancer, are approved by the European Medicines Agency but rejected by healthcare cost-evaluation agencies such as the UK's National Institute for Health and Care Excellence, says David Watson, ABPI's director of pricing and reimbursement. He blames NICE in large part for the UK's low uptake of new medicines.

NICE responded to similar criticism in September by saying it would expand reviews to involve patients, National Health Service staff, industry and researchers. The government watchdog unit has also suggested that an innovations office be created to assist industry with development, evaluation and eventual adoption of new drugs by the NHS.

But Watson says uptake of new drugs is further hindered by local funding groups or formularies that sometimes contradict national guidelines.

View the report at www.fdanews.com/12-01-14-UK-drugs.pdf. — Lena Freund

China Agrees to Reforms to Speed Innovative Drugs to Market

Foreign companies seeking to market novel drugs in China should have an easier time, thanks to an agreement by Chinese officials to cut regulatory red tape.

Under the agreement, the China Food and Drug Administration will accelerate reforms of its regulatory review and approval system, including eliminating a drug approval backlog within two to three years. The agreement was announced last month at the conclusion of the U.S.-China Joint Commission on Commerce and Trade meeting in Chicago.

Excessively long timelines for getting innovative drugs to market in China is problematic for drugmakers and deprives Chinese patients of important healthcare options and benefits, the U.S.-China Business Council says. According to industry sources, it has taken some companies as long as eight years to get their drugs on the market.

The trade deal should ease entry for all foreign drugmakers, not just those in the U.S., says Mark Grayson, spokesman for U.S. brand manufacturers association PhRMA.

Among the expected reforms are measures to allow experimental drugs to be tested in China while they undergo clinical study in other countries, which should shorten the drug's time to market, and clinical trial waivers for applications based on multiregional studies that include data from China, provided the applications comply with technical review requirements.

According to the U.S. Department of Commerce, annual exports of U.S. drugs to China exceed $1.2 billion. — Jonathon Shacat

Brazil Clarifies Rules on Public-Private Product Development Partnerships

The Brazilian government is providing more clarity around a voluntary program that encourages public-private partnerships to expand access to affordable drugs, but questions remain about the program's transparency and how the market would be divided among competing partnerships.

A final ordinance issued last month by the Ministry of Health establishes a new framework for local laboratories to enter into agreements with the government under its Product Development Partnerships program. The initiative was created in 2008, in part to help grow a domestic pharmaceutical industry.

Under the PDP program, a manufacturer sells a product to the government and transfers the technology — or the know-how used to produce the product — based on a price proposed to the health ministry and negotiated with between the company and the local public laboratory. To be eligible for the program, products must be deemed strategic for the country.

With the new ordinance, prices for products obtained through PDPs will decrease over time to reflect domestic and international markets, fluctuations in exchange rates and the government's official indices. Pricing was not covered under the previous rule, Roberto Rodrigues, with Licks Attorneys in Rio de Janeiro, tells *IPRM*.

The new framework also extends the maximum timeframe for PDP agreements — from five years under the old ordinance to 10 years, notes Justin Duarte Piné, a U.S. lawyer and consultant with Dannemann Siemsen Advogados in Sao Paulo. The extra time gives manufacturers the chance to recoup the costs of their product and successfully transfer the technology, he says.

And the new ordinance provides more details on how PDPs will be proposed, structured and monitored by the government. Drugmakers had complained that the previous regulations lacked a clear regulatory framework for structuring PDPs and guidelines on pricing and market exclusivity, Piné says.

The transparency concerns center on the lack of a provision allowing access to information about the government's public health concerns. Industry believes this information should be available as significant public resources are being invested in the program. Questions also remain over how the government would divvy up the market for biosimilars of the same reference product, which are produced by multiple competing PDPs, Piné says.

Read an English translation of the document, provided by Licks Attorneys, at www.fdanews.com/12-14-ANVISA-PDP.pdf. — Jonathon Shacat

Office of Pharmaceutical Quality Revs Up Process to Accelerate U.S. ANDA Reviews

In a preview of how the U.S. Food and Drug Administration's new Office of Pharmaceutical Quality will speed generic drug approvals, the office is rolling out a framework for filers of abbreviated new drug applications to respond to minor queries regarding chemistry, manufacturing and control early in the review cycle.

OPQ, which officially started operations Jan. 1, is the agency's central office for all drug quality issues and is charged, as part of its mission, with speeding up ANDA reviews.

One key tool the office will employ is so-called real-time communications. These will be issued to applicants directly from OPQ, rather the Office of Generic Drugs, and will replace the previous controlled correspondences that had to be used for even minor queries.

ANDAs will be eligible for the real-time communications only when the FDA's query doesn't require a major expenditure of agency resources and won't result in a missed ANDA target action date. Such cases might include a request for additional chemistry information or a clerical clarification on an application.

A query that doesn't meet these criteria will instead be submitted formally as a minor controlled response, says Susan Rosencrance, director of OPQ's Office of Lifecycle Drug Products. Queries that will incur a significant amount of FDA resources will continue to be treated as major deficiencies.

The stringent requirements to qualify for real-time communication are meant to encourage more high-quality ANDAs, Rosencrance told generics makers on a Dec. 5 conference call.

All ANDAs filed after Oct. 1, 2014, are eligible for real-time communications under the 2012 Generic Drug User Fee Act response times goals. The FDA says it will apply this process as much as possible to ANDAs filed prior to Oct. 1, on a case-by-case basis.

Response Timelines Laid Out

Real-time communications will generally be transmitted by secure email. Upon receipt, ANDA filers will have up to 30 days to respond to a query, says Glen Smith, deputy director of the OLDP. The FDA will have 45 days to respond to the first answer and 30 days for the second, he adds.

Real-time communications will typically be limited to two per ANDA, says Robert Gaines, an acting director in the agency's Office of Program and Regulatory Operations.

The response framework is part of a series of moves announced by the FDA in recent months to speed generic drug approvals and respond to industry calls for greater transparency. Rosencrance says the agency wants to drive down the number of review cycles ANDAs need before approval. Currently, most filings take between two and five cycles.

The FDA's decision to shift chemistry, manufacturing and control functions from OGD to the newly formed OPQ has not been without controversy. The realignment prompted then-acting OGD director Greg Geba to resign after less than a year on the job.

FDA officials on the conference call cautioned that the real-time communications initiative will not replace OGD's formal communication methods. Nor will it provide updates on application status, despite frequent criticism by generics makers that learning where an ANDA stands in the process is virtually impossible.
— Bryan Koenig

Biosimilars Makers Press for Dose API as Reference Comparator

Companies developing biosimilars for the European market want regulators to revert to comparing therapies with the reference product based on the amount of active ingredient in a dose, rather than a proposed standard that compares dose with route of administration.

When posology, or nominal dosage, is used as the standard of strength rather than the actual measure of active ingredient, biosimilar developers may believe they are formulating their product to the true label strength when in fact the reference product's dosage strength is in error, say manufacturers in comments on a European Medicines Agency draft guideline.

The concern stems from a provision in the guideline that says the posology and route of administration of the biosimilar and reference must be the same. Under the previous guideline, companies were required to assess similarity based on the measured amount of the active ingredient.

It is not sufficient to specify that the products should have the same posology, says Amgen. That sentiment was mirrored by trade group EuropaBio.

Boehringer Ingelheim and European Biopharmaceutical Enterprises also warn that the guideline's continued use of the word "comparability" could sew confusion by conflating the term with biosimilarity. They urge the EMA to clarify that comparability is only in reference to manufacturing process changes between batches of the same product and not between the biosimilar and its reference.

Several of the 24 commenters, including EuropaBio and Pfizer, caution against confusing biosimilars with generic drugs. They say the EMA has done just that with several recent products by labeling the biosimilars as if they were generic versions of the reference therapy.

Separately, the European Generics Associations' biosimilars group endorsed the EMA's position on biosimilar labeling, which requires the product's label to be consistent with that of the reference product.

Labeling has been a major point of contention in the U.S., where industry is awaiting an FDA decision on the matter. The Generic Pharmaceutical Association argues that requiring different labels for biosimilars would hinder acceptance of the therapies, while brand companies believe patients and prescribers should be notified of the difference between reference and biosimilar.

An EMA final guideline, published in October, focuses in large part on letting biosimilar applicants use comparator data from biologics approved outside the EU bloc (*IPRM*, December 2014). That guideline takes effect in April.

View the comments on the draft guideline at www.fdanews.com/12-02-14-EMABiosimilarComments.pdf.
— Bryan Koenig

EU States Suspend Marketing Nods For Generics Vetted by GVK

Several EU member states suspended marketing authorization for therapies that underwent bioequivalence testing at contract research organization GVK Biosciences' facility in Hyderabad, India, citing serious concerns about deviations from good clinical practice.

The European Medicines Agency has said that the precautionary suspensions are up to individual countries and that a review of noncompliance findings with good clinical practice at the facility is underway. Part of that review includes assessing exactly which therapies are affected. The agency promised a recommendation, expected this month, on what member countries should do with the affected products.

France, Belgium and Germany have all opted to suspend marketing authorizations as a precautionary measure pending the outcome of the EMA review, the European Generic medicines Association says. EGA member companies are currently conducting their own in-depth investigations into the matter, the group says.

Germany's BfArM published a list of 80 generic drugs whose approvals were yanked due to the GVK concerns. Among them were me-too versions of Forest Laboratories' Lexapro (escitalopram), AstraZeneca's Nexium (esomeprazole), Novartis' Diovan (valsartan) and Pfizer's Effexor (venlafaxine), from generics giants such as Mylan and Dr. Reddy's Laboratories. All of the products had been approved based on bioequivalence studies performed by GVK Biosciences.

The 80 drugs can't be sold in Germany until the companies submit new bioequivalence studies, the agency says. No shortages are expected as other versions of all of the drugs remain available.

The EMA review was triggered by a French medicines agency inspection at the Hyderabad plant, which raised questions about the reliability of bioequivalence testing going as far back as 2008. The plant performs bioequivalence testing for generic drugs and late-phase clinical studies conducted by brand name companies. According to an EMA document, a May 2014 inspection by the French authority turned up falsified electrocardiograms in each of nine clinical trials reviewed.

GVK says it is disappointed with the continuing doubts about its bioequivalence testing and believes it has addressed concerns over the electrocardiograms raised by the EMA's Committee for Medicinal Products for Human Use. The CRO expects marketing authorization holders affected by the suspensions will need to repeat their bioequivalence testing within the next 12 to 15 months and is working with its clinical development customers to provide data that meets regulatory requirements.
— Bryan Koenig, Lena Freund

India Releases Draft Standards On Trial Ethics, Accreditation

India's Central Drugs Standard Control Organization has proposed accreditation and ethics standards for clinical trial sites, investigators and ethics committees.

The draft standards are mostly procedural, requiring trial personnel to be registered and to follow written standard operating procedures for documenting all functions.

The standards also explain what should be included in the SOPs. For example, an ethics committee's SOP should include the names and qualifications of all members, a confidentiality agreement and documentation of any conflicts of interest, frequency of the meetings, declarations of payments made and received, training policies for all members, including new arrivals, and policies laying out how to communicate with various parties.

The standards also specify responsibilities such as investigators' accreditation and proper human subject protection and lay out expectations for site infrastructure and documentation.

Vince Suneja, CEO of TwoFour Insight Group, says most established companies are already following these recommendations. Those that will be most affected are smaller firms with fewer resources to ensure compliance.

The comment period closed Dec. 15. View the draft at www.fdanews.com/12-02-14-IndiaCTStandards.pdf.
— Lena Freund

India's Drug Pricing Authority Sets Prices on 52 More Products

India's drug pricing authority has placed 52 additional drugs under price control, including treatments for cancer, skin disorders and infection, as part of a program to provide life-saving and essential medicines to the public.

Thirty-two companies — including Cadila Healthcare, Lupin and Merck — are affected by the retail price caps, which are based on specific formulations, strengths and units. However, because the National Pharmaceuticals Pricing Authority didn't publish the prior price of each drug, it's difficult to gauge how much the new caps will impact companies.

NPPA's notice, issued in early December, follows a September decision to limit prices on 43 other essential drugs, including therapies for diabetes and infections.

In July, NPPA imposed price controls on 108 drugs that were not on the essential medicines list. The Indian Pharmaceutical Alliance and the Organization of Pharmaceutical Producers of India pushed back with a lawsuit claiming NPPA lacks the authority to fix prices on these formulations. The litigation is ongoing (*IPRM*, Oct. 14).

NPPA's notice is available at www.fdanews.com/12-14-NPPA-PricingNotice.pdf. — Jonathon Shacat

U.S. FDA May Recognize Firms That Go Extra Yard in GMP Compliance

The FDA is considering a new inspections scoring system that would, for the first time, recognize drugmakers that go beyond normal compliance with good manufacturing practices.

The system, which has yet to be finalized, would offer six scores: critical failure, major failure, minor failure, acceptable, exceeds and superior. Drugmakers would receive a score for each aspect of an inspection, including whether a facility meets GMPs, has an adequate quality system and quality culture.

The proposed system is part of an inspections protocol project aimed at revamping the inspection process so that officials in the Center for Drug Evaluation and Research have a better idea of a facility's state of quality.

The scores would be in addition to the traditional overall inspection classifications: no action indicated, voluntary action indicated and official action indicated, Neil Stiber, CDER senior operations research analyst, tells *IPRM* during a session at the Parenteral Drug Association's recent quality metrics conference in Washington, D.C.

The scores are intended to provide more information to drugmakers than the current broad classifications and won't interfere with the process for levying enforcement actions like Form 483s, Stiber says. The scores would also not directly translate into an inspection classification such as NAI, OAI or VAI.

Inspection classifications depend on many factors, including prior issues, drug availability and how well the facility responded to previous problems, Stiber explains. Those issues will help to determine the inspectional outcome.

More Specific Feedback

One goal of the scoring system would be to recognize manufacturers that go beyond meeting agency regulations and GMPs. High-quality facilities could act as role models for the rest of industry and encourage quality improvements, Stiber says.

The scoring system also would provide more specific feedback on inspection results than the broad, overall classifications, he says.

Any score would be in addition to the upcoming ranking that a facility will receive based on a series of quality metrics. The rankings will be used to compare manufacturers with the rest of industry and determine inspection frequency.

Stiber declined to comment on when CDER will make a decision on the scoring system.

Agency officials have offered details on other parts of the inspection protocol project. This year, for instance, CDER will launch an internal pilot to train investigators to examine a facility's quality culture for the first time. The idea is to have investigators looking for quality culture indicators during inspections within the next few years. — Robert King

Consolidation of Drug Import Oversight Aimed at Harmonizing U.S. Port Policies

The FDA plans to consolidate its 16 districts overseeing pharmaceutical imports into just four or five under a reorganization plan designed to make inspection policies and procedures more uniform across all ports of entry.

The consolidation is part of the agency's Program Alignment Group initiative to reorganize investigators into specialized teams focused on product type — e.g., pharmaceuticals, devices or food — rather than on all FDA-regulated products generally.

It remains undecided how such product specialization will be addressed within import inspections, says Domenic Veneziano, director of the FDA's Division of Import Operations. But import operations will remain in the Office of Regulatory Affairs, he told a Food and Drug Law Institute conference on enforcement, litigation and compliance.

Under the reorganization, the ORA and the Center for Drug Evaluation and Research will create a strategy by fall 2015 to expedite the way imports are screened, using risk-based import entry reviews to identify adulterated products more quickly.

Veneziano tells *IPRM* that he can't predict when the reorganization of import operations will be finalized, but he is confident the restructuring will make the FDA more efficient.

Ben England, founder of FDA imports.com and a former counsel to FDA's associate commissioner for regulatory affairs, is skeptical of that conclusion, saying the import district consolidation plan will create a more centralized bureaucracy. It represents a further paring back of inspector discretion and power at the local level, and could make it more complicated for industry to resolve import issues, he tells *IPRM*. — Bryan Koenig

EFPIA Proposes Process for Early Resolution of Patent Disputes

Brand drugmakers in Europe are calling on the European Commission to implement a system to facilitate the resolution of patent disputes before a generic version is launched, a move they say would curb inefficiencies in the current patent litigation system.

The three-step process, put forward by the European Federation of Pharmaceutical Industries and Associations, would require the innovator company, at least one year before loss of exclusivity, to release details of certain patents so that generic companies could assess the risks of early entry. Medicines agencies would, in turn, be required to disclose information about generics makers' applications so that the innovators could evaluate the likelihood that the generic might infringe its intellectual property rights.

Following the filing of a generics application, the innovator firm could initiate infringement proceedings.

The proposal comes amid reports that brand and generic firms increasingly are settling patent disputes out of court. In 2013, the number of patent settlements jumped to 146, compared with an annual average of 24 settlements from 2000 to 2008, according to a Commission report released last month.

The report concludes that companies generally are able to resolve their disputes in a way that is nonproblematic from a competition law perspective. For example, settlements that included payments by brand firms to generics makers to delay generic entry represented just 8 percent of the total settlements in 2013, down from 22 percent during the 2000 to 2008 period. Settlements without payments accounted for 47 percent of the total in 2013, a 51 percent drop from the prior year but significantly higher than the 26 percent for 2000 to 2008.

Read the Commission's report at www.fdanews.com/12-14-EC-Report.pdf. — Jonathon Shacat

New Zealand Moves Forward On Updating Recall Procedures

New Zealand's regulatory authority is updating its uniform recall procedure for drugs, following a recent decision not to pursue a joint authority with Australia.

Manufacturers, suppliers and importers of drugs in New Zealand must have written procedures in place that describe how recalls are initiated and carried out, according to draft guidance issued last month by the Medicines and Medical Devices Safety Authority. The document clarifies the responsibilities of the various parties and describes ways to improve communications during a recall.

Before initiating a recall, companies must discuss the matter with Medsafe and determine the level of risk to public health.

Once a recall is deemed necessary, companies must prepare correspondence for wholesalers, retailers, hospitals and pharmacists, as well as media releases and consumer advertisements. Progress reports are required, normally at two and six weeks. A final report, including certificate of product destruction, confirmation of product correction and an investigation of root cause and remedial actions, must also be submitted to Medsafe.

The review of the recall process was triggered by a small cluster of consumer-level recalls in 2010. A working party prepared a draft recall code for consultation in August 2010, but it was never formally adopted because of the separate effort to merge Medsafe and Australia's Therapeutic Goods Administration.

In November, the countries unexpectedly abandoned the trans-Tasman plans. The updated draft recall code is based on the 2010 consultation and processes agreed to with the TGA in anticipation of the merger (*IPRM*, Dec. 16).

Comments are due Feb. 27. Read the draft *Uniform Recall Procedure for Medicines and Medical Devices* here: www.fdanews.com/12-14-Medsafe-RecallCode.pdf. — Jonathon Shacat

Ebola Vaccine Developers Protected From Liability Under U.S. Law

Ebola vaccine manufacturers Janssen, GlaxoSmithKline and NewLink Genetics will be sheltered from legal liability under a law that protects companies that produce treatments to combat public health emergencies, the U.S. government says.

According to a Dec. 9 *Federal Register* notice by the Department of Health and Human Services, none of the three companies can be sued for any claim of loss caused during the manufacture, testing, development, distribution, administration or use of the vaccines, unless it is attributed to willful misconduct by the drugmaker.

The companies' immunity kicked in Dec. 3 under the 2005 Public Readiness and Emergency Preparedness Act, and lasts for one year without geographic limitation, HHS says.

GSK's vaccine, developed jointly with the National Institutes of Health, is the furthest along the development path, with positive results of a Phase I trial announced recently. NewLink Genetics began Phase I trials of its vaccine in September, and Janssen expects to start trials in the middle of 2015.

View the *Federal Register* notice at www.fdanews.com/12-09-14-Ebolavaccines.pdf. — Lena Freund

Japan Clarifies Premarket Review Routes for Combination Products

Manufacturers that combine drugs with either medical devices or cellular or tissue-based products must determine which category the product falls under before filing a marketing application in Japan, the Pharmaceutical and Medical Devices Agency says. The regulatory category should be based on the primary function and purpose of the product.

Examples of combination products that correspond to drugs include prefilled syringe injections and asthma agents with inhalers, according to a wide-ranging guideline on marketing applications for combos released last month by the PMDA.

Combination products that correspond to devices include drug-eluting stents, heparin-coated catheters and antibacterial bone cements, while ones falling under the cellular and tissue-based products category include cell suspensions in prefilled syringes and scaffolding, the guidance says.

The updated regulation also addresses premarket and postmarket reporting of adverse reactions. Clinical trial sponsors must report adverse incidents associated with any of the individual components that comprise a combination product.

PMDA's notice on the revised regulation and an application template are available at www.fdanews.com/12-14-PMDA-Notice.pdf. — Jonathon Shacat

IN BRIEF

Canada Updates Batch Certification Rules

Health Canada has updated its guidance on the content of batch certificates for drugs exported under the scope of a mutual recognition agreement, adding specific language on investigational products. The new document, which replaces information in the appendix of a 2009 good manufacturing practice guideline, is available at www.fdanews.com/12-14-Canada-2.pdf.

China Cracks Down on Illegal Codeine Sales

The China Food and Drug Administration is threatening to punish companies that illegally manufacturer and sell codeine in an effort to stem adolescent abuse of the drug. Two businesses have had their licenses revoked for allegedly selling bulk quantities of cough syrup containing codeine and their cases are under investigation, the CFDA and Public Security Ministry said Dec. 16. In recent years, the CFDA has increased production controls, limited marketing channels and implemented strict electronic monitoring requirements for products containing the addictive substance.

Thailand Standardizes Plastic Containers

The Thai Industrial Standards Institute has issued a draft mandatory standard on plastic containers for liquid sterile drug products intended for injection, specifying types, materials, requirements, marking and labeling, sampling and criteria for conformity and testing. The standard will replace TIS 531-2546(2003).

MHRA Updates Orange, Green Guides

Two guides compiled by the UK's Medicines and Healthcare products Regulatory Agency are now for sale, offering information on the latest drug regulations, EU directives and guidance for manufacturers and distributors of human medicines. The so-called Orange and Green guides are intended to help companies follow good manufacturing practice and good distribution practice in Europe.

India Clamps Down on Drug Ads

The Bombay high court has ordered the drug controller general of India to come up with a comprehensive plan for regulating drug advertisements to reduce misuse and abuse of medicinal products. Advertising controls would fall under a new regulatory authority, along the lines of a censor board, the court said.

Sweden to Broaden AR Reporting

The Medical Products Agency will conduct a pilot project on electronic reporting of adverse drug reactions from healthcare IT systems. The aim is to simplify reporting and increase the quality of information received directly from medical records, MPA says.

FDANEWS

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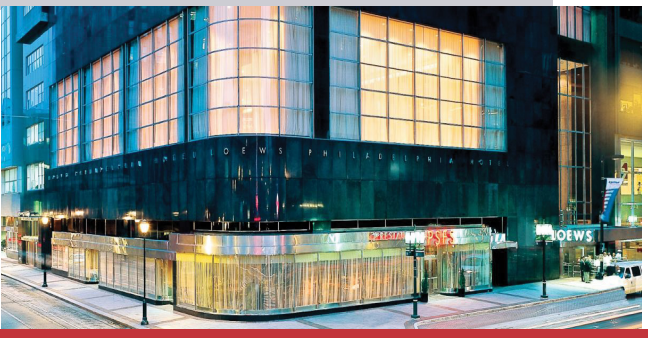

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FDANEWS

REDUCE HUMAN ERROR ON
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DAY ONE

8:00 a.m. – 8:30 a.m.
REGISTRATION/CONTINENTAL BREAKFAST

8:30 a.m. – 10:00 a.m.

Understanding The Basics of Human Error On The Manufacturing Floor

- How human errors intersect with manufacturing regulations
- Examples of applicable FDA requirements and what the FDA expects companies to be complying with
- A review of other industry standards that apply to drug and device manufacturing
- What FDA investigators look for during inspections and the most common violations found in Form 483s and Warning Letters
- Which violations tied to human errors and manufacturing are trending up
- The various types of human errors are commonly found on manufacturing floors
- How we got here — why is human error reduction such an important topic

Interactive Exercise! Do we also err? Attendees will be broken into groups and asked to describe the most common human errors within their facilities. The workshop will then reconvene and break-out group leaders will describe what they uncovered. A list of the most common problems will be tallied to help focus the future discussion.

10:00 a.m. – 10:15 a.m. BREAK

10:15 a.m. – 12:00 p.m.

Human Error In Context — What Are the Factors That Drive Human Errors?

- The taxonomy of human error; how and why drug and device companies need to focus on this in their investigation processes
- Why administrative and management systems factor so prominently into deviations and non-conformances
- The role of innovative operational controls and their role in reducing human errors
- Simple procedures that prevent human error -- how they should be described and presented to maximize human error reduction
- Common examples of poor human factors engineering and workplace conditions that contribute to human error
- When training is appropriate and when we should stop
- Learn how common day-to-day communication gaps contribute to human error
- How supervision can be one of the best human error reduction strategies at your site
- When is individual performance responsible for human error and when does it become a root cause
- How to address cognition, attention, and memory failures at your site

12:00 p.m. – 1:00 p.m. LUNCH

1:00 p.m. – 2:30 p.m.

Internal vs. External Factors

- How our biology affects our thinking process and individual performance
- Understanding the latest on cognitive load and attention, memory, and decision making errors — how they commonly occur on the manufacturing floor
- How our senses control how we react — it's more important that you think
- Best practices for controlling human factors for optimum people performance
- How to create an organizational environment that supports human error reduction initiatives — from senior management to floor level staff
- Why our culture with regards to human error has to change; it's not an easy process but vitally necessary for drug and device companies

2:30 p.m. – 4:30 p.m.

Corrective and Preventive Action (CAPA) — FDA's #1 Manufacturing Compliance Problem

- How to develop corrective actions that make sense —what's working and not working
- Creating preventive actions that truly prevent; how to stop errors that have not yet happened
- Understanding the human error prediction process and tools
- Prevention and human error control: proven ways to measure improvement and on-going trend analysis
- When to use detection mechanisms instead of preventive mechanisms — the pros and cons of each
- Human error detection and recovery rate — are you really uncovering all the errors within your facilities?
- Assuring for the FDA your CAPA program is effective and you've adequately focused on human error

Interactive Exercise! When to do what?

DAY TWO

8:30 a.m. – 10:00 a.m.

Human Error Reduction Techniques

- Discussion of insights from day 1
- When is human error a human resources issue?
- How and when to apply engineering controls to correct and prevent human error deviations
- What to do when individual performance is the major contributor
- Human error and documentation: from design, construction, change management and implementation
- Additional Contributors for human errors will be discussed

Interactive Exercise! Practice identifying techniques to be applied

10:00 a.m. – 10:15 a.m. BREAK

10:15 a.m. – 12:00 p.m.

Human Error Investigation

- Human Error investigation process defined from beginning to end
- How to gather data in the human error investigation process
- How to perform an effective interview
- Important steps foe effective human error investigations

- How to report issues to mae sure management listens

12:00 p.m. – 1:00 p.m. LUNCH

1:00 p.m. – 2:30 p.m.

Root Cause Analysis Tools

- A brief review of common tools used in determining root cause
- Hierarchy and use of the root cause determination tool for human error investigations
- How to perform a cognitive load assessment
- The interview process and interview techniques for human error root cause analysis
- When and how to use the human error prediction tool
- When to perform a Process vs. procedure analysis and why it is so important to do so before establishing procedure revision as a CAPA for human error

Interactive Exercise! Brainstorm root causes for real cases with peers. Using the situations identified in the first exercise we will try and apply the applicable tool.

2:45 p.m. – 4:45 p.m.

Metrics and Human Error

- KPI's
- Human Error rate
- 1st time pass rate
- Overall equipment effectiveness (OEE)
- Trending /Tracking

Interactive Exercise! Work with various common metrics and benchmarks. Determine what constitutes acceptable and non-acceptable results.

4:45 p.m. – 5:00 p.m.

Review and Key Insights/Materials

- Copies of the presentations
- Current FDA regulations
- Pertinent guidance documents
- Articles on Human Error
- Manual Tools
- Interviewing guide
- Report Example
- Root Cause Determination Tool

5:00 p.m. WORKSHOP ADJOURNS

WHO SHOULD ATTEND

- QA/QC directors and managers
- Process improvement/excellence professionals
- Training directors and managers
- Manufacturing operations directors
- Human factors professionals
- Device engineering
- Compliance officers
- Regulatory professionals
- Executive management

COURSE BINDER MATERIALS

- Root cause determination tool
- Interviewing guide – you can take back and use immediately
- Example of well-documented HE report
- Complete copy of slide deck materials
- Copies of applicable FDA regulations referenced in the course
- Copies of pertinent FDA guidance documents
- Articles focused on human error reductions

YOUR EXPERT SPEAKER

GINETTE COLLAZO, PH.D., — has spent more than 15 years in technical training, organizational development and human reliability. She has worked with Bristol-Myers Squibb, Johnson & Johnson, Schering-Plough, Wyeth and Medtronic, and many more small and mid-sized drug and device companies. An active researcher in specialized studies related to human reliability, she is the author of numerous publications on these topics.

"The topic is very relevant to the needs of our business at the moment. I learned several things associated with how to train and use lean techniques to reduce the opportunity for human error. It also reaffirmed the things we are doing well that are working."

—Richard Leach, Director of Quality, Nosco

"[Ginette is] very passionate [and] high energy. A lot of take aways. Reduction of human error has been a challenge and the tools provided will be put to the test."

—Alex Masso, QA In-Process Supervisor, Mylan Institutional Inc.

"[Ginette is] very knowledgeable with great industry examples. Very spunky! Great delivery."

—Irene Rockwell, Manufacturing Compliance, Biogen Idec

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To reserve your room, call the hotel at the number below. Be sure to tell the hotel you're with the FDAnews Workshop to qualify for the reduced rate. Only reservations made by the reservation cutoff date are offered the special rates, and space is limited. Hotels may run out of discounted rates before the reservation cutoff date. The discounted rate is also available two nights before and after the event based on availability. Hotel may require first night's room deposit with tax. Room cancellations within 72 hours of the date of arrival or "no-shows" will be charged for the first night's room with tax.

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