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In This Issue

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Indian Bill Would Create New 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.

Medical products covered under the bill include DNA vaccines and vaccines containing living genetically engineered organisms, cellular products such as pancreatic islet cells for transplantation, recombinant gene therapy products, transgenic blood- or plasma-derived products, stem cell-based products, RNA interference-based products and products of synthetic biology for human or animal use.

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."

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. Momentum to shore up control of all healthcare products has gained steam in the wake of a May 2012 parliamentary report challenging CDSCO's review of 31 new drug approvals (*IPRM*, May 2012).

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

Document Index

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

Biotechnology Regulatory Authority of India Bill, 2013

CDSCO Draft Rules on Compensation in Death or Injury

India Draft Guideline on Trial Compensation

EMA Guideline on Qualified Persons and Batch Releases

WHO Quality Risk-Management Guideline

ICH *Guideline for Elemental Impurities Q3D*

U.S. FDA Proposed Rule Granting Detention Authority for Drugs

U.S. FDA Guidance on Penalties for Refusing an Inspection

EU Q&A on Postauthorization Updates

EC Update on Drug Labeling Requirements

EMA Draft Trial Transparency Policy

PhRMA and EFPIA's Principles for Trial Data Sharing

Ombudsman Report on Pediatric Trials Waiver Process

Ruling Overturning EMA's Decision on Orphacol

EUCERD Report on Orphan Drugs in the EU

CHMP Decision on GLP-1 Diabetes Drugs

TGA Listing of Biosimilar Guidelines

Ontario Health Ministry Report on Drug Compounding

Mexico Drug GMP Regulation

EMA Member State Contacts for Translation Review

U.S. NIH Halts Clinical Trials in India, Cites Uncertainty Over 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 Indian 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.

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. The court gave the Central Drugs Standard Control Organization four weeks to comply.

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.

Revisions Likely, but When?

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 *IPRM*.

"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."

NIH's decision to stop funding trials is important because it's symbolic, Mark Barnes, a partner and healthcare specialist with Ropes & Gray, told *IPRM*. "It is just a very stark illustration" of the regulation's impact regarding compensation of subjects, he said.

Barnes, who met recently with industry and government officials in India, said the government is "well aware of the drastic effect" of the new 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 guideline on trial compensation is available at www.fdanews.com/ext/files/09-12-Trial Compensation.pdf. — Nick Otto

EU, WHO Update Key GMP Guidelines; EMA Revision Focuses on Remote Sites

European regulators want to revise good manufacturing practice guidelines to clarify how quality personnel oversee batches manufactured at remote sites. And on a global scale, the World Health Organization is updating its GMPs to reflect industry trends.

Last month, the European Medicines Agency released a draft revision to Annex 16 of the GMP guidelines, bringing it up to date with current trends in the drug industry. The annex, introduced in 2002, provides guidance on how a qualified person (QP) can certify a batch release.

According to the revision, the QP can delegate some of the tasks required to certify a batch is safe and rely on the quality management system. But they must ensure that this "reliance is well-founded," the guideline says.

Some of these tasks address:

- Starting material compliance and supply chain security, including GMP assessments by third parties;
- Manufacturing and testing performance;
- Manufacturing and testing processes validation; and
- Changes and investigations completion.

The EMA emphasizes that the QP is still responsible for ensuring that a particular batch was manufactured in accordance with EU GMPs.

Petra Rybackova, EMA scientific administrator for manufacturing and quality compliance, told *IPRM* the revision brings the annex in line with the International Conference on Harmonisation's Q8, Q9 and Q10 quality system guidelines. The update also clarifies what documentation is needed to accompany batches that move between EU member states.

WHO Risk Guidelines

Meanwhile, WHO recently updated a guideline for quality risk management (QRM), also aimed at addressing current trends. The update contains advice for global regulators and drugmakers on how to install QRM principles, described as the evaluation of the risk to quality based on science and patient protection and the process of documenting QRM practices commensurate with the level of risk.

WHO said the QRM principles can help regulators allocate inspection resources and aide manufacturers in implementing a corporate culture of quality.

Drugmakers have been stepping up such efforts. Ranbaxy, like many of its peers, recently trumpeted a list of quality "enhancements" that closely track recommendations the U.S. Food and Drug Administration persistently promotes to prevent problems. Among other things, the Indian company is encouraging its workers to communicate quality issues with upper management, as well as through a new whistleblower program.

The deadline for comments on the EMA guideline, *Certification by a Qualified Person and Batch Release*, is Nov. 5. View the update at www.fdanews.com/ext/files/7-16-13-GMPGuideline.pdf. The WHO guideline is at www.fdanews.com/ext/files/7-16-13-WHORiskGuideline.pdf. — Robert King

Strict Metal Impurity Controls Detailed In Long-Awaited ICH Draft Guideline

The International Conference on Harmonisation released a draft guideline with tighter limits on the amounts of metals that can be in finished drug products, representing a drastic departure from the status quo.

The Q3D guideline sets permitted daily exposure (PDE) limits for certain metals based on safety and toxicology data. Experts say manufacturers must work with their suppliers to meet the new limits for finished drugs and for new drugs that employ existing drug substances.

Manufacturers currently abide by liberal impurity limits set by the U.S. Pharmacopeia, which are not

strictly based on safety. And the screening method drugmakers use to gauge the presence of metals "[is] probably 100 years old," Janeen Skutnik-Wilkinson, chair of the International Pharmaceutical Excipients Council Federation and a prior member of the ICH working group that developed the guideline, told *IPRM*.

The guideline will "significantly change what people have done in the past, because there are expectations for much lower levels," Skutnik-Wilkinson said.

The draft guideline divides metals into four classes based on toxicity:

- Class 1 metals include mercury, lead, cadmium and arsenic. These metals are significantly toxic across all routes of administration and typically have limited or no use in the manufacturing of pharmaceuticals;
- Class 2 metals include vanadium, molybdenum and cobalt — metals considered toxic to a greater or lesser extent based on how they are administered;
- Class 3 impurities have a relatively low toxicity if taken orally, but require consideration in the risk assessment for other types of administration such as inhalation. Metals in this class include chromium, copper, tin and nickel; and
- Class 4 metals don't have a PDE because their toxicity is very low. Such metals include sodium, manganese, calcium and zinc.

A Call for Collaboration

Skutnik-Wilkinson stresses that drugmakers should collaborate with excipient and active pharmaceutical ingredient (API) makers to communicate their expectations on impurity testing. A key concern is that some excipient makers test their products for heavy metals infrequently, in some cases testing only once a year, according to David Schoneker, director of global regulatory affairs with excipient maker Colorcon.

Drugmakers need to discuss impurity limits early and often with excipient and API makers "and get a sense of what is in their products," Skutnik-Wilkinson said.

ICH is accepting comments on the guideline, and no deadline on the comment period has been set. Skutnik-Wilkinson said the goal is to finalize the guideline by next summer.

ICH's *Guideline for Elemental Impurities Q3D* is available at www.fdanews.com/ext/files/08-6-13-ICH MetalGuideline.pdf. — Robert King

Proposed Rule Aims to Close Gap In U.S. FDA's Drug Import Powers

The U.S. Food and Drug Administration has moved to close a glaring gap in the agency's import powers, issuing a proposed rule that grants detention authority for drugs. The FDA also issued a draft guidance outlining penalties for refusing, delaying or limiting an inspection.

The proposed measures were mandated by last year's FDA Safety and Innovation Act, or FDASIA, and address a growing and complex supply chain for pharmaceuticals, according to FDA Commissioner Margaret Hamburg.

"We now receive imports from more than 150 countries, many with much less sophisticated manufacturing," Hamburg said during a July 12 meeting to get stakeholder input on the new import powers granted by FDASIA. "Over time, our authorities couldn't keep pace with the challenges of this global marketplace."

The proposed rule is intended to give the FDA the same authority over imported drugs that inspectors believe to be adulterated or misbranded that currently exists for medical devices and foods.

Under the proposed rule, an inspector can detain a drug for up to 20 days if he or she believes it is adulterated or misbranded. The importer has five days to appeal the detention order.

The FDA maintains the rule will not hurt small businesses financially, but Rick Quinn, a principal at the import consulting firm FDAImports.com, isn't buying that. Noting that about 80 percent of importers are small businesses, Quinn scoffs, "Importers must pay for an attorney to respond to the detention in 20 days, and it won't have an economic impact?"

What Constitutes Refusal?

The same-day draft guidance provides details on the circumstances that constitute delaying, denying or limiting an inspection and refusing inspectors access to a facility and its records. Such actions can result in criminal penalties.

Examples of violative actions, outlined in the guidance, include:

- A facility doesn't agree to a proposed inspection start date and doesn't give a reasonable explanation;
- The facility's designated contact ignores the FDA;

- A facility doesn't allow an FDA inspector to go to a specific area until a future date and time;
- An FDA inspector asks for specific records, but the facility fails to produce them and does not provide an adequate justification; and
- The agency cannot inspect the facility because certain staff members aren't present.

During the public meeting, stakeholders called for caution and clarity in exercising the agency's new import powers.

In addition to the detention authority, FDASIA's Title VII allows the FDA to register importers and directs it to establish good importer practice regulations — the subject of a 2009 draft guidance that was never finalized.

As these new regulations roll out, the FDA needs to provide "clarity of expectations on standards of importation," said David Gaugh, vice president for regulatory science at the Generic Pharmaceutical Association.

PhRMA urged the FDA to limit the documentation and data low-risk importers must submit. This will enable the agency and customs officials to focus on imports that are more likely to be diverted, counterfeit and substandard, the group said.

The FDA is seeking comments on the proposed rule, docket no. FDA-2013-N-0365, through Sept. 13. View it at www.fdanews.com/ext/files/07-12-13-DetentionRule.pdf.

Comments on the draft guidance, docket no. FDA-2013-D-0710, are also due Sept. 13. View it at www.fdanews.com/ext/files/07-12-13-PenaltiesGuidance.pdf. — Robert King

EMA Updates Guidelines on Postauthorization Variations

The European Medicines Agency issued a last-minute update to guidelines on changes to approved product applications. The update came just under two weeks before the Aug. 4 effective date of revised rules on variations.

Under the new rules, all study submissions concerning marketing authorizations must be submitted as a type II variation application, with few exceptions, the agency explains in a question-and-answer document.

Studies to support postmarketing variations will be considered final reports and should include both clinical and nonclinical study material, the EMA says. Examples include clinical efficacy/safety studies, drug-drug interaction studies, results from toxicology studies, pharmacokinetic/pharmacodynamic studies, meta-analyses and reviews of risk-minimization measures defined in the risk-management plan.

Marketing authorization holders also should determine if their data fall under either of two new classification categories included in annexes to the variation guideline. C.1.11 covers obligations and conditions of a marketing authorization, while C.1.13 relates to submissions of studies to a competent authority.

The EMA said it plans to publish an additional regulatory update on worksharing procedures for variations to marketing authorizations, as well as an amended template table to be used for any variations submitted to the agency and a tabular overview with detailed information on the updated documents.

View the Q&A on implementation of the variations guideline at www.fdanews.com/ext/files/07-26-13-Variations.pdf. — Nick Otto

European Commission Revises Guideline On Drug Package Information

The European Commission has released a final revision to its guideline on packaging information, detailing new provisions for drugmakers seeking EU marketing authorization. The guideline pays particular attention to label content, companion leaflets and package design.

EU law allows some leeway for member states to require labeling information beyond that which is mandated by the law, including the following:

- Product price;
- Reimbursement conditions of national coverage organizations;
- Legal status for supplying the product to patients; and
- Authenticity and identification in accordance with labeling and package leaflet rules.

Information specific to a member state should be located in a single boxed area — the so-called "blue box" — and appear on one side of the package. Each "blue box" should be presented in the country's official language or languages, the guideline notes. When one pack is intended for marketing in several member states, the box should contain different information relevant for each state.

Drug packs must include a companion leaflet unless the required information is fully presented in the

labeling. The leaflet should be in the local language and "reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use," the guideline says.

If the medicine is not intended for direct dosing to the patient, or if serious availability issues exist, the concerned competent authority may grant a full or partial exemption to the language obligations, the guideline adds.

Presentation

The guideline provides details on label presentation, noting the requirements for size, design and composition.

An appropriate range of package sizes should be selected based on the duration of treatment and dosing outlined in the summary of product characteristics. Package size should not be influenced by local prescribing habits.

To minimize the chance of confusion due to linguistic variations, the guideline advises drugmakers to use the same logo, format, layout, style, color scheme and, if possible, package dimensions on all versions of a drug marketed in the EU.

View the updated guideline at www.fdanews.com/ext/files/07-22-13-Packaging.pdf. — Nick Otto

EMA Calls for 'Considered Approach' In Draft Trial Transparency Policy

The European Medicines Agency is seeking feedback on a proposed policy for increasing access to clinical trial data, offering a "considered approach" to transparency that respects patient and commercial interests.

The plan is to proactively publish trial data in tandem with regulatory decisions about drug candidates, irrespective of whether they are approved, rejected or withdrawn. Since November 2010, the EMA has released some 2 million pages of trial data in response to specific requests — a "controlled access" policy that will continue under the agency's transparency proposal as it pertains to patient-specific trial data.

Documents that might contain commercially confidential information, or CCI, would be bound by access controls. But the EMA says clinical trial data generally would not be considered commercially confidential since "the interests of public health outweigh considerations of CCI."

At least two U.S. companies — AbbVie and InterMune — have challenged that contention in court (*IPRM*, May). The outcome of those cases could impact policy implementation, the EMA says.

An ongoing legislative effort to replace the current EU clinical trials directive could also throw off the implementation timeline, the agency notes. In a recent report backing the European Commission's proposal, the Parliament's health committee said that trial data generally should not be considered CCI once a drug has been approved or the application process has been completed (*IPRM*, February).

U.S. regulators have waded into the debate as well, albeit more cautiously. Speaking at the Drug Information Association's annual meeting in Boston in June, FDA Commissioner Margaret Hamburg said the agency is watching the EMA's trial transparency efforts "with great interest." The benefits to industry and researchers from careful disclosure of regulatory review data — particularly that lost when a drug candidate is rejected — represents one of the next "frontiers" of transparency at the FDA, Hamburg said (*IPRM*, July).

A public consultation on the EMA's proposal ends Sept. 30, and the agency expects to release a final policy document by the end of the year. It would take effect Jan. 1.

Industry Adopts Selective 'Blueprint'

Meanwhile, U.S. trade group PhRMA and the European Federation of Pharmaceutical Industries and Associations (EFPIA) released a set of industry principles for "responsible" data sharing. The July 23 joint transparency blueprint comes amid accusations that both organizations are seeking to enlist patient groups to help them beat back increasing calls for full disclosure of trial data.

The blueprint includes a commitment by the groups' members to provide summaries of trial results to participating patients to further layman understanding of the clinical trial process. Synopses of clinical study reports will be submitted to EU and U.S. regulators upon approval of a new medicine or indication. Companies are encouraged to publish results from all Phase III trials, regardless of a positive or negative outcome.

The principles are in large part a response to the EMA's transparency push. In testimony before U.S. lawmakers last month, PhRMA CEO John Castellani said disclosure of unpublicized data sets could be damaging to both public health and patient welfare. It could also stifle investment in innovation, he said. "We want to engage with the EU to ensure proper data sharing."

Castellani's comments came during a hearing of the House Energy and Commerce Committee's trade subcommittee on ongoing EU-U.S. trade talks. Aside from seeking alignment between the two regions on regulatory data protection for biologic drugs (PhRMA proposes a 12-year time frame in line with U.S. law), Castellani called for increased harmonization of technical requirements for registration of human drug products.

Memo Controversy

Both PhRMA and EFPIA have been accused of asking members to recruit patient groups as supporters in a campaign against the EMA's trial transparency push. PhRMA spokesman Mark Grayson told *IPRM* the fracas stems from an internal EFPIA memo.

While neither confirming nor rejecting rumors of a leaked memo, EFPIA spokesman Nick Elles told *IPRM* the EU association works with patient groups on a range of issues and values the "independent perspective" they bring. "We consider it our responsibility to take into account opinions and views from all stakeholders involved in issues that have the potential to impact them directly — especially patients," Elles said.

View the industry joint principles at www.fdanews.com/ext/files/07-25-13-DataSharing.pdf. The EMA's draft transparency policy is at www.fdanews.com/ext/files/06-24-13-EMATrialTransparencyDraft.pdf.
— Nick Otto, Johnathan Rickman

EU Ombudsman Review Leads to Changes In EMA Pediatric Trials Waiver Process

As it pushes industry to share more clinical trial data, the European Medicines Agency is promising to shed more light on its pediatric trials waiver process, the EU's ombudsman says.

In a case involving complaints that the agency unfairly singled out AstraZeneca and Takeda over other hypertension drugmakers for pediatric heart failure studies, EU Ombudsman P. Nikiforos Diamandouros last year deemed the EMA's 2009 decision to be justified. But he criticized the agency for not backing up its decision with adequate reasoning and for not being open about its process for reviewing requests for pediatric trial waivers (*IPRM*, June 2012).

Citing "maladministration" of the process, the ombudsman called for a reform of the system.

In a new report detailing the agency's response to his draft recommendations, Diamandouros says

the EMA continues to contest that it handled the case improperly. But he is unswerving in his opinion, writing that the agency failed to "respect the principles of good administration" when it waived studies for Merck and Novartis and not for AstraZeneca and Takeda. Simply following established rules and meeting applicable timelines is not enough, he says.

The EMA also contested the assertion that its 2009 decision lacked an adequate rationale. Diamandouros acknowledged "confusion" on his part concerning that matter and now finds the agency's arguments "convincing" and "unproblematic." The case involving AstraZeneca and Takeda's Atacand (Candesartan), Merck's Cozaar (losartan) and Novartis' Diovan (valsartan) had complexities unlikely to be duplicated again, especially in light of the EMA's reform promises, he says.

The agency has agreed to:

- Adopt guidelines that assist its Pediatric Committee with application reviews and address, in detail, the issue of proper justification of opinions;
- Disclose decisions resulting from the application of pediatric regulations; and
- Publish an online lay language summary of assessments and outcomes of all waiver applications adopted by the Pediatric Committee.

View Diamandouros' full report at www.fdanews.com/ext/files/07-31-13-Ombudsman.pdf. — Nick Otto

Court Overrules EMA Rejection of Orphan Liver Treatment Orphacol

A European court has overturned the European Medicines Agency's refusal to grant marketing authorization for a drug to treat rare liver diseases, saying the safety and effectiveness of the active ingredient have been well-established for over 10 years.

The French drugmaker, Laboratoires CTRS, applied for marketing authorization of Orphacol (cholic acid) as an orphan treatment for rare but life-threatening liver diseases in October 2009. The EMA's Committee on Medicinal Products for Human Use issued a positive opinion for the drug the following year, but the agency submitted a draft decision denying marketing authorization to its Standing Committee on Medicinal Products for Human use.

The standing committee also weighed in in favor of authorizing Orphacol. The EMA took that opinion to an appeals committee, which issued a negative opinion of the agency's proposed denial of marketing authorization. In 2012, CTRS sued to force the EMA to make a final determination on Orphacol. The agency subsequently denied authorization.

In annulling the EMA's decision, the General Court for the European Union notes that cholic acid "has been used to treat patients in France between 1993 and October 2007 in the form of hospital preparations provided on medical prescription, prepared individually in accordance with the prescriptions of a pharmacopoeia and in compliance with the rules of good practice laid down in French legislation."

Under the EU's orphan drug law, CTRS was not required to provide the results of preclinical and clinical trials for the rare liver diseases because cholic acid's safety and performance were well-established, the court says. Moreover, participation in a clinical trial would expose patients to the risk of serious liver disease or even death, the court adds.

The court notes that at the time CTRS submitted its application in 2009, only 90 people had been diagnosed with the conditions Orphacol was intended to treat, 19 of whom were in France.

View the court's July 4 decision at www.fdanews.com/ext/files/08-13-Orphacol.pdf. — Nick Otto

More Drugs Winning Orphan Status in EU, But Reimbursement Hinders Access

Reimbursement now outpaces marketing authorization as the lead barrier to accessing orphan drugs across EU member states, according to a new report by the European Committee of Experts on Rare Diseases.

Health technology assessments, which determine which drugs will be covered, vary among individual member states, due to gaps in information and knowledge of a product's risks and benefits, EUCERD says. But two initiatives could help to remedy the problem and ensure broader access to orphan products, the panel adds.

The first initiative is the Clinical Added Value of Orphan Medicinal Products, or CAVOMP, information flow. CAVOMP capitalizes on existing regulatory, clinical, HTA, pricing and reimbursement processes without adding new obstacles, the report, released last month, says. The idea is to bridge the knowledge gap between different member states and between member states and EU bodies.

The second initiative is the Mechanism of Coordinated Access to Orphan Medicinal Products. A MoCA-OMP working group has developed a definition of "coordinated real life access" — the time when the product in on the market, affordable and easily accessible to the patient—and is encouraging early dialogue between stakeholders and member states to achieve this goal, the report says.

Orphan Designations Increasing

Struggles aside, since orphan drug legislation was passed in 1999, the European Medicines Agency has granted more than 1,120 orphan product designations, the report notes. In 2012, the Committee for Orphan Medicinal Products adopted 139 positive opinions on orphan designations, covering approximately 90 conditions and diseases. The bulk of those opinions — 39 percent — involved antineoplastic agents.

View EUCERD's report at www.fdanews.com/ext/files/08-13-Orphan.pdf. — Nick Otto

CHMP Renders Positive Opinion On GLP-1 Diabetes Drugs

The European Medicines Agency has reaffirmed its positive stance on the benefit-risk profile of incretin-based, glucose-lowering drugs to treat type 2 diabetes.

According to a final review of glucagon-like peptide 1 (GLP-1) diabetes therapies by the agency's Committee for Medicinal Products for Human Use, the available data show no new concerns of increased pancreatic risks associated with the class of diabetes drugs.

"Data from clinical trials do not indicate an increased risk with these medicines. However, the number of events is too small to draw final conclusions," CHMP says. "Due to their mechanism of action, some uncertainties remain in respect to the long-term effect of these medicines on the pancreas and more data collection efforts are under way."

Recent concerns with the drugs stem from debates in academic journals that GLP-1 receptor agonist drugs — as well as incretin-inactivating protease dipeptidyl peptidase-4 (DPP-4) therapies — could increase the risk of pancreatitis and pancreatic cancer.

The EMA says a rise in type 2 diabetes is causing a major public health challenge. Its opinion could be a boon for drugmakers with currently marketed GLP-1-based products, including Merck's Januvia (sitagliptin), Bristol-Meyers Squibb and AstraZeneca's Onglyza (saxagliptin), Boehringer Ingelheim and Eli Lilly's Trajenta (linagliptin), and Novo Nordisk's Victoza (liraglutide).

The U.S. Food and Drug Administration has not given its final word on use of GLP-1 or DPP-4 drugs. The American Diabetes Association earlier this year said it could find no evidence to support modifications to current GLP-1 treatment recommendations.

View CHMP's decision at www.fdanews.com/ext/files/07-29-13-diabetes.pdf. — Nick Otto

GSK's China Woes Offer 'Teachable Moment' for Other Drugmakers

As senior officials of GlaxoSmithKline face accusations of bribing Chinese government officials, experts on the U.S. Foreign Corrupt Practices Act 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.

Chinese investigators say GSK managers funneled the illegal payments through travel agencies to cover their tracks.

Certain senior managers in the Chinese arm of GlaxoSmithKline "acted outside of the company's processes and controls to defraud the company and Chinese officials," GSK CEO Andrew Witty said July 25, addressing questions about the company's brewing bribery scandal. "To be crystal clear, we have zero tolerance for this behavior."

Similar corruption allegations have put many drugmakers in the "crosshairs" of the Foreign Corrupt Practices Act (FCPA), law firm Arnall Golden Gregory posted recently online.

"The principal takeaway 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 tells *IPRM*.

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, Burke says. "But 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 fluid, saying it "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.

Last year, employees at Eli Lilly's China subsidiary falsified expense reports to provide spa treatments, jewelry and other improper gifts and cash payments to government-employed physicians, one of many complaints ending in a $29 million fine from the U.S. Securities and Exchange Commission.

Sources tell *IPRM* that in light of the China/GSK incident, the U.S. Department of Justice is considering a sweep of life science companies for FCPA compliance — allegations DoJ wouldn't comment on either way. — Nick Otto, Melissa Winn

Market Data, Government Program Point To Growing Global Trials Role for S. Korea

A government effort to attract more clinical trials to South Korea seems to be paying off, according to new data from Industry Standard Research.

ISR's report on *South Korea: Clinical Trial Development Country Profile,* released last month, shows a 360 percent jump in the number of clinical trials approved in 2012 versus 2003, when upward trending began.

That dovetails with the 2007 launch of KoNECT — Korea National Enterprise for Clinical Trials — a

government-financed organization aimed at fostering the human resources, core technology and infrastructure necessary to make South Korea a global clinical trial hub. Since then, KoNECT has established a network of 15 regional clinical trial centers with 132 investigational sites nationwide, all certified by the Ministry of Food and Drug Safety, formerly the Korea Food and Drug Administration.

"The nature of KoNECT … [is] to improve the clinical trial conduct and the infrastructure of clinical trials in Korea," said Julie Lee, the group's external affairs manager. KoNECT has recently added a certification system for clinical investigators, research coordinators and research associates.

According to ISR, evidence of South Korea's rise as a clinical trials hot spot includes:

- Samsung Electronics' plan to invest $260 million in a joint venture with Quintiles to make generic drugs by the first half of 2013 and biosimilars by 2016;
- INC Research's opening of a new clinical development facility in the country; and
- PAREXEL's partnership with the Korea Drug Development Fund to create and commercialize therapies in South Korea.

To purchase a copy of ISR's report, visit www.isrreports.com. — Nick Otto

TGA Posts Advice on Registering Biosimilar Drugs in Australia

Australia's Therapeutic Goods Administration has assembled a raft of guidelines and forms online to help biosimilar drugmakers identify the data necessary to support registration and clarify the scientific and regulatory principles used to evaluate applications.

Sponsors must ensure the biosimilar has the same formulation, strength and dosage form as the reference product, or include scientific justification for any differences. The following information should be included in the presubmission planning form:

- Chemistry, manufacturing and quality control data (Module 3);
- Preclinical data (Module 4);
- Clinical data (Module 5); and
- Risk-management plan.

The TGA will meet with sponsors prior to submission of an application, if desired. Once the planning form has been accepted by reviewers, the TGA will set milestones for evaluation, feedback and decision, the guidance states.

Last year, the U.S. Food and Drug Administration released a draft guidance setting out a stepwise approach to approving biosimilars. And just last month, the European Medicines Agency issued revisions to a 2006 guideline, clarifying clinical and nonclinical requirements for marketing biosimilars (*IPRM*, June).

The TGA's information on biosimilars is available at www.tga.gov.au/industry/pm-argpm-biosimilars-00.htm. — Nick Otto

Report Finds No Malice in Diluted-Drug Scare, Calls Health Canada to Action

Ontario's Ministry of Health and Long-Term Care (MHLTC) released a report calling on Health Canada to regulate all drug preparation entities and services beyond community pharmacies, which are already regulated by the Ontario College of Pharmacists.

The report comes in the wake of a cancer drug scare earlier this year involving reports of more than 1,000 patients receiving diluted chemotherapy treatments (*IPRM*, May).

Following the incident, MHLTC tapped Jake Thiessen, founding director of the University of Waterloo's School of Pharmacy, to lead an independent review of quality assurance in the heartland province's cancer drug supply chain and focus on the chemotherapy drugs in question.

In his report, Thiessen notes there was no evidence of a malicious or deliberate attempt to dilute the drugs. Rather, the weakened drugs were due to a series of operational failings.

For example, one case was linked to a compounder's failure to compensate adequately for an overfill factor in the supplier's normal saline bags. According to the report, "[t]here were shortcomings in the transition" from a previous saline distributor, Baxter, to the new vendor, Marchese Hospital Solutions, at several Ontario hospitals.

"Some of this is attributable to assumptions by the group purchasing organization (GPO) and its pharmacy committee, failure to accommodate the precise needs of the end-user (pharmacists) in the hospitals, and

short-sightedness in creating a seamless transition," the report says.

"However one views this development, it is clear that this entire incident underscores significant inadequacies in communication and implementation around specifications, preparing products, and the GPO-vendor handoff that safeguards patient care," the report adds.

It continues: "Notwithstanding the under-dosing incident, the continued use of GPOs to negotiate vendor product preparation pharmaceutical services shall not be discouraged. However, improvements are needed in the GPO-based processes."

Best Practices

In calling for comprehensive licensing of Canadian compounders, Thiessen suggests that all licensed businesses should maintain specialized electronic records detailing each product's drug identification, lot numbers and expiry date. Records of certificates of analysis of all materials should also be maintained electronically.

The report also calls on Health Canada to collaborate with the Ontario College of Pharmacists on a list of best practices and contemporary objective standards for the preparation of nonsterile and sterile products within a licensed pharmacy.

"Given the array of possibilities regarding the magnitude of business activity, types of products or services offered, and the probability that such items may be crossing provincial or national borders, special precautions are needed to ensure high-quality companies that prepare excellent products and ultimately provide effective and safe treatments," the report concludes.

View the report at www.fdanews.com/ext/files/08-09-13-Canada.pdf. — Nick Otto

IN BRIEF

EU, U.S. Extend Scientific Cooperation

The European Commission's Joint Research Centre and the U.S. National Institute of Standards and Technology last month agreed to expand their current scientific cooperation to 10 areas, including healthcare, clinical measurements and nanotechnology. The arrangement covers scientific cooperation related to standards and measurements and was made possible by the 1997 bilateral Agreement for Scientific and Technological Cooperation.

Mexico Revises Drug GMPs

Mexico's Ministry of Health has updated its good manufacturing practice regulation for human medicines, bringing it in line with international GMP. The revised regulation, which takes effect Sept. 16, establishes minimum requirements for the manufacture of drugs made locally or elsewhere and intended for the Mexican market. It covers quality control tests, warehouse conditions, storage and distribution of drugs and raw materials for processing, among other issues. View the document, NOM-059-SSA1-2013, in Spanish at www.fdanews.com/ext/files/08-13-MexicoGMP.pdf.

New Zealand Pharma Groups Merge

Medicines New Zealand and its vaccine counterpart, the Vaccines Industry Association of New Zealand, have joined forces to represent all companies involved with the development, production and prescription of medicines and vaccines in the country, including the vaccine branches of GlaxoSmithKline, Novartis and Pfizer. The new organization will operate as Medicines New Zealand.

EMA Releases Member State Translation Contacts

The European Medicines Agency has released an updated list of member state contacts for translation reviews, as well as the minimum amount of information companies should include in requests for translation. View the list of contacts at www.fdanews.com/ext/files/08-13-Contacts.pdf.

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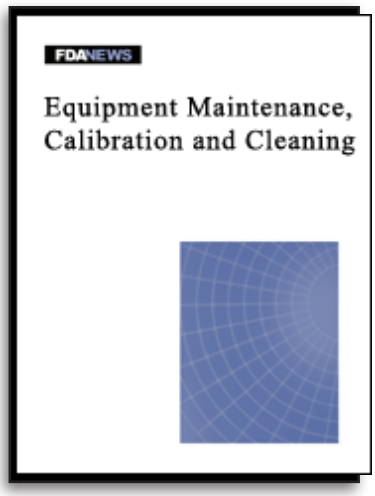

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WORKSHOP AGENDA

DAY ONE

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

8:30 a.m. – 12:30 p.m.
INTRODUCTION

- ACTIVITY: Connections between mountain climbing and pharma/ biopharma manufacturing
- VIDEO/DISCUSSION: Characteristics of a guide
- Key concepts important to regulators and industry
- ACTIVITY: Terms of compliance
- **GMP Expectations:** What they are and where they come from
- ACTIVITY: Identifying expectations for training and learning
- **Quality Systems:** GMPs as an example of a quality system
- ACTIVITY: GMP systems and your role
- VIDEO/DISCUSSION: Characteristics of systems

12:30 p.m. – 1:30 p.m.
LUNCH

1:30 p.m. – 4:15 p.m.

- The Seven Essentials of GMP
- **Essential 1:** Protect the product from contamination
- ACTIVITY: Sources of contamination and ways to prevent it
- **Essential 2:** Prevent mix-ups
- ACTIVITY: Minute mix-up mysteries
- VIDEO/DISCUSSION: Climbing essentials

4:15 p.m.
SUMMARY AND WRAP-UP

DAY TWO

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

8:30 a.m. – 12:30 p.m.

- ACTIVITY: Review of Day 1
- VIDEO/DISCUSSION: The real goal
- GMP Essentials - continued
- **Essential 3:** Know why, how and what you are doing before you do it
- **Essential 4:** Document all activities
- ACTIVITY: 10 Characteristics of a well-prepared document
- ACTIVITY: Dear Professor GMP
- **Essential 5:** Strive for consistency and control – qualification, validation and change management

12:30 p.m. – 1:30 p.m.
LUNCH

1:30 p.m. – 4:00 p.m.

- GMP Essentials - continued
- **Essential 6:** Have management that supports an independent group that makes final decisions on documents, product release and quality issues
- ACTIVITY: Management responsibilities and Q10
- **Essential 7:** Learn from mistakes, solve problems; monitor and continually improve
- **Case Study:** An examination of GMP compliance issues in an organization
- How I can apply this back in my job

4:00 p.m.
SUMMARY AND VIDEO/DISCUSSION:
On being a guide to others

ven Essentials of GMP

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WHO SHOULD ATTEND

- Compliance officers
- Engineering and design control teams
- Executive management
- Managers
- Manufacturing directors and supervisors
- Procedure writers
- Pharmaceutical and cGMP auditors
- QA/QC personnel
- R&D staff
- CAPA specialists
- Training personnel
- Instructional designers and technologists

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YOUR EXPERT INSTRUCTOR

JAMES VESPER designs and develops instructional courses and workshops for pharmaceutical and medical device companies. He established and is president of the firm LearningPlus, and has had more than 30 years' experience in the pharmaceutical industry.

Mr. Vesper worked eleven years at Eli Lilly and Co. His first assignment was as corporate industrial hygienist, followed by three years in corporate quality assurance. He was responsible for issues concerning the manufacturing and testing of parenteral products made at Eli Lilly facilities and third parties worldwide. His last assignment at Lilly was project leader of GMP education and instruction, establishing the department and its mission.

Since 1991, Mr. Vesper has been creating innovative instructional training products for the pharmaceutical and healthcare industries using video and computer technologies as more effective and efficient delivery media. Working as a consultant with a wide variety of clients, his firm creates integrated curricula for personnel and customized training courses targeted to specific needs. He presents papers and workshops at various international technical and professional meetings, including those of the International Society for Pharmaceutical Engineering, GMP TEA, PDA, Pharmaceutical Sciences Group and PharmTech. In 2001, he was awarded the PDA's Agallaco Award for Excellence in Training. He is also an advisor to the World Health Organization's Global Learning Opportunities/Vaccine Quality group, and has mentored, designed and developed learning programs that are in use worldwide.

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