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Editor's Note: The *International Pharmaceutical Regulatory Monitor* is available in an electronic edition, which includes web access to seven years of archived issues. For information on converting to an electronic subscription, contact us at (888) 838-5578.

India Steps Back on Trial Compensation Rules, Proposes Central Drug Authority

India's Ministry of Health and Family Welfare on Aug. 30 gave notice that it plans to scale back some elements of the clinical trial compensation rules released early this year.

The new plan would eliminate mandated compensation for study subjects who receive no therapeutic benefit from a trial. It retains other compensation requirements, however, for subjects injured in trials.

Mark Barnes, a partner and healthcare specialist with Ropes & Gray, says he expects the compensation rules are on a fast track and will be implemented quickly, despite remaining questions such as: What's an appropriate amount of compensation? Who decides when compensation is warranted? And is there an option to appeal?

India's Central Drugs Standard Control Organization released finalized guidelines on clinical trial death and injury in January (*IPRM*, February). In a backlash to the compensation policy, the U.S. National Institutes of Health said it was withdrawing from clinical trial research in India because of uncertainties posed by the new requirements (*IPRM*, August).

Extended Reporting Timelines

Other proposed revisions to the trial rules include:

- Extending the time frame for sponsors and investigators to report serious adverse events from 10 days to 14 days;
- Extending the time for ethics committees to forward analyses and opinions of SAEs from 21 days to 30 days; and
- Extending the timeline for independent expert committees to examine SAEs and report their findings to the Drugs Controller General of India (DCGI) from 30 days to 60 days.

"The bottom line is: The notification of rulemaking about the compensation rules promises to eliminate some major problems, or solve some from the first issuance — but we have to wait and see what the final proposed version is," Barnes says.

The Aug. 30 notification will be followed by a formal proposal, according to Barnes. The next step is for the ministry to

open the proposal to public comment, after which a final rule will be published in the *Official Gazette*. Barnes says he understands that the specific draft regulations "will be issued within days or at most a couple of weeks."

New Central Authority

The revisions to the compensation rules come one day after Indian lawmakers introduced a bill to replace the Central Drugs Standard Control Organization with a Central Drugs Authority overseen by a council of permanent secretaries from related ministries. The new authority would operate as an independent agency similar to the U.S. Food and Drug Administration. "This idea of elevating the status of the drug control authority and the DCGI … has had a lot of discussion among the higher echelons of Indian academics and government staff for the past couple of years," Barnes notes.

Under the proposed legislation, the CDA would designate, through regulations and guidelines, all functions of a central licensing authority and state licensing authorities and periodically assess their performance. The CLA would be responsible for issuing certificates and licenses for 17 categories of drugs. State authorities would need the CLA's permission before licensing a drug.

Document Index

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

India's Trial Compensation Notice

Drug & Cosmetics (Amendment) Act, 2013

Indian Parliament Committee's Report on FDI in the Pharma Sector

EMA's Report on Routine vs. For-Cause GCP Inspections

Brazil's Antibribery Law (In Portuguese)

Brazil's Decree on New GMP Framework (In Portuguese)

EU Parliament Committee's Amendments to Precursor Regulations

U.S. FDA-EMA Joint Assessment of Qbd Pilot

ASEAN Draft Guidance on Qbd Validation Approach

U.S. FDA's Draft Rule on Border Medicines Detentions

Notice of EMA-U.S. FDA Joint Orphan Product Meeting

U.S. Federal Trade Commission's Amicus Brief

Colombia's Vaccine Regulation Proposal (In Spanish)

The 17 drug categories are:

- Sera;
- Solution of serum proteins intended for injection;
- Vaccines, including DNA vaccines and ones containing living genetically engineered organisms;
- Toxins;
- Antigens and antitoxins;
- Antibiotics (betalactums and cephalosporins);
- Parenteral preparations;
- Hormones and preparations containing hormones;
- Recombinant DNA-derived drugs;
- RNA interference-based products;
- Monoclonal antibodies;
- Cellular products and stem cells;
- Gene therapy products;
- Xenografts;
- Cytotoxic substances (anticancer drugs);
- Blood products; and
- Modified living organisms.

The bill clarifies that "new drug" covers any bulk drug substance that has not been recognized as safe and effective by the CLA; any approved drug which is proposed for marketing with modifications; approved drugs that are being proposed as a fixed dose combination therapy; and vaccines intended to be used as drugs.

The bill, which amends the 1940 drug and cosmetics law, also creates new regulatory frameworks for medical devices and clinical trials and strengthens provisions on imports and exports and supplies of spurious goods.

The government introduced the bill Aug. 29 in the upper house of Parliament, which includes the Departmental Committee on Health and Family Welfare. As of press time, the legislation had not been assigned to the committee and no time frame has been established for debating it.

However, Barnes says industry tends to favor rule-making legislation "because it clarifies [the government's] authority and gives [industry] a clear regulatory process rather than an ambiguous one." He adds, though, that violations of the regulatory requirements would be met with "strict" and "very tough" civil and criminal penalties. According to the bill, an adulterated drug could land its maker in prison for life.

View the compensation notice at www.fdanews.com/ext/files/09-13-Compensation.pdf. The Drug & Cosmetics (Amendment) Act, 2013, is at www.fdanews.com/ext/files/09-13-IndiaBill.pdf. — Nick Otto

Foreign Investments Under Fire in India; Panel Urges Ban on 'Brownfield' Buys

Indian policymakers are calling for a blanket ban on new foreign investment in existing domestic pharma companies, cautioning the government that any more takeovers of large manufacturers by outsiders could destroy the benefits flowing from India's "generic revolution."

In a report issued Aug. 13, the Indian Parliament's commerce committee notes that of 67 foreign direct investments, or FDI, made through September 2011, only one was a "greenfield" investment in a fresh project. All of the rest were "brownfield" buys involving legacy businesses.

The committee notes that many of the recent FDI brownfield investments have predominantly fueled mergers or takeovers of domestic pharmaceutical companies.

When asked about the statistics, the Reserve Bank of India said it doesn't distinguish between greenfield and brownfield deals, making it difficult to assess the impact of incoming equity flows, according to the report.

The committee calls that argument "naïve" and is urging the government to "stop behaving like an ostrich" and "take cognizance of … reality." India's generic drug industry is booming, but "the country has not yet reached a position to control the international market," the panel says.

Misguided Protectionism

Amy Hariani, director and legal policy counsel for life sciences at the U.S.-India Business Council, is hopeful the government will dismiss the report. "I think there is legitimate concern, but at the same time people in the government are really mindful of investment opportunities," she tells *IPRM*.

According to Hariani, several acquisitions were being considered before the change in the FDI rule was even contemplated.

"To change the rule in the middle of the process for a lot of companies that are in the middle of doing acquisitions really is a difficult investment environment in terms of predictability," she said. "It shows a signal that the government could always be changing their rules at any time."

India has been revolutionizing a number of policies regarding patent rights and clinical trial initiatives. Meanwhile, it has revoked a slew of patents on breast-cancer drug Tykerb (lapatinib), leukemia drug Glivec (imatinib mesylate) and diabetes drug Januvia (sitagliptin) (*IPRM*, April).

More recently, changes in clinical trial compensation policies have moved research giants like the U.S. National Institutes of Health to suspend trial funding in the country (*IPRM*, August) (*see story, page 1*).

The committee's report has already sparked criticism from pharma defense lawyers in the U.S., who describe the effort as misguided protectionism. Whether FDI in India increases or not, there is little market barrier to a new generic drugmaker starting up and competing, one source told *IPRM*.

View the committee's report at www.fdanews.com/ext/files/09-13-13-FDI.pdf. — Nick Otto

EMA Clarifies 'Triggers' for Routine Versus For-Cause GCP Inspections

As drug sponsors make their way through the EU approval process, there are "triggers" that can help European Medicines Agency inspection coordinators determine whether a clinical trial should undergo a routine or for-cause good clinical practice inspection, an agency working group says. Determining factors include trial size, complexity and site selection.

While every trial could benefit from closer scrutiny via inspection, "this is not feasible and not always necessary," the EMA's GCP Inspectors Working Group says in a report posted Aug. 21.

"A GCP inspection is a time and resource consuming process and therefore a request for an inspection should be considered when triggers are identified and [an] alternative method cannot provide the necessary assurance, or when unresolved issues remain" post-evaluation, the group adds.

Routine Triggers

Routine GCP inspections, carried out in the absence of a specific trigger or concern, "should have a random element in that not all [marketing authorization] applications would necessarily give rise to a GCP inspection," the report states. But there are numerous factors that underscore the need for a routine GCP inspection and the agency should be aware of these. They include:

- There are inconsistencies in an application dossier or missing GCP-related documents;

- The candidate being studied is a recombinant product, monoclonal antibody, cell therapy, gene therapy, new chemical entity, blood product or orphan drug;
- The applicant is not the sponsor of the proposed trial;
- The trial supports a sponsor's first marketing authorization application; or
- The scope of a supporting trial is unusually minimal.

Pivotal trials "will usually be the ones selected" for routine GCP inspections, the working group says. But if more than one is planned, trial size, complexity, design and site selection will all be taken into consideration when determining inspection priorities.

For-Cause Factors

When making determinations about possible for-cause inspections, requested by assessors when concerns arise about GCP deviations, the agency should consider many of the same factors that go into routine inspection decisions. However, there are other factors specific to a for-cause inspection request that should be taken into account. Among these are the following:

- There is a lack of information about an ethics review;
- The study's administrative structure involves an unusually large number of researchers;
- Major changes to study protocol have occurred or troublesome treatment issues emerged;
- There are unexplained differences in the number of patients per treatment arm; or
- Efficacy and safety variables regarding definitions and/or measurements.

The report does not cover triggers specific to inspections of bioequivalence trials. It is available at www.fdanews.com/ext/files/08-22-13-EMAinspections.pdf.
— Johnathan Rickman

British Pharma Group Promotes Trial Transparency Checklist

A UK industry group has released a clinical trial disclosure toolkit on its website to help drugmakers comply with growing transparency requirements.

In a timely addition to the ongoing debate over clinical trial transparency, the Association of the British Pharmaceutical Industry has posted 11 documents on its website. Included are:

- Points to consider when managing disclosure;
- Process flow maps to map companies' disclosure processes relating to trial registration and results disclosure;
- A template standard operating procedure on clinical trial registry; and
- Self-training and Q&A documents.

ABPI hopes the documents will help drugmakers navigate the research landscape, which has become an obstacle course in recent months with regard to data transparency.

However, the group — which represents more than 180 pharma companies — stresses the toolkit "is not intended and should not be construed as regulatory or legal advice."

ABPI notes its code of practice already requires members to register current and future trials within 21 days of enrolling the first patient. The organization also requires members to publish trial results within a year of a drug's marketing authorization or a year post-study completion for products already on the market.

Debate over trial transparency has seen a recent upsurge as various stakeholders continue to push and pull on the need for more trial data. Recently, the European Medicines Agency released a draft policy paper on its plans to proactively publish data submitted for product approvals in the EU (*IPRM*, August).

And in July, U.S.-based PhRMA and the European Federation of Pharmaceutical Industries and Associations released joint principles for sharing clinical trial data.

Amidst all this, ABPI has been a key player in discussions with regulators, industry stakeholders and advocacy groups on balancing the need for more trial transparency with the need to protect trial participants and intellectual property.

"Research is a truly global activity, with the UK supplying less than two percent of patients to global clinical trials," ABPI Chief Executive Stephen Whitehead said. "As part of a global industry, we are actively engaging with our European and international counterparts, as well as many other stakeholders, to input into ongoing discussions around clinical trial transparency."

The clinical trial transparency checklist and related documents can be found at www.abpi.org.uk.
— Ferdous Al-Faruque

UK Regulators, Industry Spar Over Drug Development Costs

British regulators are questioning whether the cost of drug development is unnecessarily high, in response to editorials in *The Times of London* warning of a potential manufacturing exodus.

In an Aug. 30 opinion article, Jonathan Emms, Pfizer's managing director in the UK, says the National Institute for Health and Care Excellence has created a regulatory environment that is stifling drug development. He cites the agency's recent rejection of a slew of cancer drugs.

Emms calls on the government to reevaluate the policies and practices employed by NICE, which assesses whether drugs are safe and cost-effective for use by National Health Service beneficiaries.

"Companies like ours cannot go on creating innovative new medicines if ultimately they are blocked from the people who need them most," Emms writes. "It's time for ministers to look again at the way NICE makes its decisions to ensure innovation is better recognized and used."

According to Pfizer, developing a new drug costs upward of $2 billion. Ninety-five percent of drug candidates fail to make it to market, the company says. Last year, NICE turned down 40 percent of new drugs and more recently denied Pfizer's Xalkori (crizotinib) for non-small cell lung cancer despite the drug getting conditional approval from the European Medicines Agency, Emms says.

The refusal is part of a long line of cancer drug rejections NICE has issued since tightening its review policy for oncologics in 2010 (*IPRM*, September 2010).

NICE's Rebuttal

In a response editorial, the paper's business editor, Ian King, agreed.

"This cannot be allowed to continue," King writes. "If nothing else, it raises the risk that many drug makers will decide not to bother developing medicines here."

NICE struck back in a follow-up editorial on Sept. 3, with Chief Executive Andrew Dillon saying he suspects the UK R&D and clinical trial environments still hold "too many advantages" for companies to pack up and take their business elsewhere. Instead, he asks whether drugmakers are "absolutely confident" that average development costs reach $2 billion.

"Companies are entitled to expect a return on their investment, but health services have to be confident that the extra benefit to patients justifies the price," Dillon writes. "NICE is, quite properly, scrutinized closely on its decisions and the methods we use to arrive at them. We are not perfect, but we are respected throughout the world for the quality of our work."

Alasdair Breckenridge, former chair of the UK's Medicines and Healthcare products Regulatory Agency, says the sparring reflects an ongoing struggle between industry and regulators over drug pricing in the UK. "It is a ritual flexing of muscles between the money men behind industry who dislike NICE and the response from NICE," he tells *IPRM*. "NICE does a good job and approves over 80 percent of products it considers."

Echoing Dillon's concerns, Breckenridge said industry needs to be more forthcoming with data and justify how much it spends on drug development.
— Ferdous Al-Faruque

Brazil Enacts Strict Anticorruption Law, Implements New GMP Framework

Brazilian President Dilma Rousseff has signed into law legislation aimed at stemming corporate bribery of government officials across all business sectors. The law brings the country's antibribery policies in line with other major nations and the Organization for Economic Cooperation and Development (OECD).

The "Clean Company Act" requires the government to establish procedures for investigating alleged bribery and corruption and sets fines and penalties for companies that run afoul of the law. Companies found guilty of offering bribes may be fined up to 20 percent of their gross annual revenue from the previous year, or a maximum of about US $26 million. The government can also suspend or dissolve the company's operations and confiscate its assets, depending on the egregiousness of the bribes.

The law calls on competent authorities to establish policies, at the penalty phase, that take into account whether a company has a compliance program in place. Those that do could fare better than those that don't. And it calls for the establishment of credits for companies that voluntarily disclose corrupt practices.

"I think this law fills some gaps, and the legislation shows that Brazil is compliant with the international

agreements," attorney Carlos Ayres, co-chair of the Brazilian Institute of Business Law's anticorruption and compliance committee, tells *IPRM*.

The legislation was prompted by a 2007 peer review of Brazil's anticorruption efforts by the OECD's Anti-bribery Convention, Ayres says. While not an OECD member, Brazil has participated with the convention and was asked to take "urgent steps" to make companies liable for bribing foreign officials.

"This new law is a tough law," Ayres says. The government needs only to show that bribes were paid — a lower bar for prosecution than the U.S. Foreign Corrupt Practices Act, which requires the government to show intent to corrupt.

Decentralized Enforcement

Before signing the bill on Aug. 1, Rousseff vetoed three provisions she believed would weaken the law. For instance, the legislation approved by the Brazilian Senate would have limited financial liability to the value of the contract obtained with the bribe. Rousseff said this could impair the government's ability to "effectively punish offenders and deter future violations."

Also nixed were provisions on the establishment of intent and on leniency for less-extensive crimes.

The new law says nothing about gift-giving. Ayres says a law already on the books limits company gifts to public officials to about US $45.

The "Clean Company Act" will be enforced by the compliance offices of the competent authorities responsible for various market segments. Drugmakers will answer to investigators from the Ministry of Health. During debate on the bill, industry had asked that a neutral, centralized agency handle the inspections, to avoid the potential for conflicts of interest.

GMPs Revised

Brazil's law comes as other governments have been cracking down on foreign corrupt practices. The most recent case, involving China's investigation of GlaxoSmithKline, has now mushroomed into an industrywide probe (*IPRM*, August) (*see story, page 7*).

Separately, Rousseff signed a decree giving Anvisa the authority to implement a new good manufacturing practice framework that is more in line with U.S. drug GMP.

The new framework "corrects the root problem of the GMP certificate problem," whereby companies had to have a Brazilian GMP (B-GMP) certificate in order to register their products, says Marcelo Antunes, regulatory affairs strategy consultant with SQR Consulting in São Paulo. The problem stemmed from a 1988 decree that "explicitly tied the presentation of the B-GMP certificate to the registration," Antunes explains.

Among other changes, the new GMP framework:

- Eliminates certain requirements limiting registration transfers and gives Anvisa additional authority to define other options to transfer registrations; and
- Permits manufacturers to outsource the quality control of products to third parties that adhere to criteria defined by Anvisa.

View Brazil's "Clean Company Act," in Portuguese, at www.fdanews.com/ext/files/09-13-Brazil.pdf. The GMP decree, published in the Aug. 14 *National Gazette*, is at www.fdanews.com/ext/files/09-13-BrazilGMP.pdf. — Nick Otto

GSK Bribery Scandal May Go to the Top, *Xinhua* Reports; Broader Probe Underway

Chinese police now believe GlaxoSmithKline's China division, rather than just individual employees, organized an alleged bribery scheme — an allegation one expert says increases GSK's chances of becoming a target of U.S. law enforcement.

Police officials claim that sales teams assigned to big customers had been given nearly $1.6 million in "public relations funds" to preserve close ties with staff in major hospitals, according to *Xinhua*, the country's state news organization.

"Huang Hong, a high-ranking executive of GSK China, said the parent company had assigned annual growth rates as high as 25 percent in recent years, seven to eight percentage points more than the average growth rate of the industry," *Xinhua* reports. The sales reps' salaries were linked to volume and missed targets could mean lost money, the news service adds.

Huang admitted that salespeople couldn't reach such a high number without "dubious corporate behavior." Police investigators also found that "GSK China went through the motions in internal auditing so as not to discover these violations," *Xinhua* said Sept. 3.

The alleged bribery scandal first erupted in July when Chinese officials started investigating whether high-ranking senior officials gave kickbacks to government officials, hospitals, doctors and medical associations in the cities of Changsha, Shanghai and Zhengzhou, with the aim of boosting sales and prices for GSK drugs (*IPRM*, August).

DOJ, SEC Could Step In

GSK CEO Andrew Witty blamed senior managers in the company's China arm for the alleged fraud and said the company was investigating the situation. Four senior GSK executives reportedly have been detained in connection with the flap.

In mid-August, the State Administration for Industry and Commerce announced a nationwide probe running through November to root out other possible instances of drug industry bribery and wrongdoing.

If GSK China had a major role in the transgressions, it could spell trouble with the U.S. Justice Department and Securities and Exchange Commission under the Foreign Corrupt Practices Act, Arnall Golden Gregory partner Mike Burke told *IPRM*.

Companies have some leeway with DOJ if only a rogue employee violates the FCPA. "The fact that this now looks like GSK China had a role in the bribery … removes an impediment to the Justice Department in going after [GSK]," Burke said. The $1.6 million in "public relations funds" could also catch the attention of the SEC, he added.

Under the FCPA, a company that lists securities in the U.S. must keep accurate books and records. If the public relations funds were used for bribery, then the SEC could intervene.

GSK responded that the *Xinhua* reports relate to an ongoing investigation. "As we said previously, we are fully cooperating with the investigation and we completely share the desire of the Chinese authorities to root out corruption wherever it exists," spokeswoman Mary Ann Rhyne told *IPRM*. "We will take all necessary actions as this investigation progresses," she said.
— Robert King

U.S. FDA's China Office Expansion Stymied by Visa Holdup: Official

The U.S. Food and Drug Administration's expansion into China is well underway, but additional inspectors are on hold because Chinese officials are not issuing visas to agency employees, Christopher Hickey, director of the FDA's China Office, said last month at a roundtable hosted by the Alliance for a Stronger FDA.

"This issue is being addressed at the highest level of our governments, and there has been significant activity in recent weeks," Hickey told a Washington, D.C., audience via webcast from Beijing.

Obtaining visas can be a lengthy process, Arnall Golden Gregory partner Mike Burke said. "It's possible that the visa delay is aimed at trying to secure something for the People's Republic of China side, which may or may not be related to FDA's work," he told *IPRM*.

Hickey stressed the importance of the FDA strengthening its international force. "Not only is the desire to have just more personnel in the country — but [there is] responsibility that FDA has under [the FDA Safety and Innovation Act] and [Generic Drug User Fee Act] … to increase the number of inspections that we're doing," Hickey told attendees.

In late March, the U.S. Senate passed a continuing resolution providing an additional $24 million to help fund new safety inspectors in China and pay for rented

properties. The FDA currently has one drug, one device and two food inspectors in China. The additional funding would increase that number significantly, adding 10 more drug inspectors.

Both Hickey and Burke said the visa delay could also be reflective of Chinese sensitivity to outside regulators within the country.

Referencing past Chinese supply chain issues involving melamine, Burke told *IPRM* "there was a sense that the Chinese regarded these issues as a domestic problem that they would address, notwithstanding the fact that the items in question were in an international supply chain."

Back at the roundtable, Hickey said any government would think twice before allowing foreign inspectors to take root. "The idea of having FDA inspectors — and not just a few, but a large number of them — based in your country is a big lift and a new concept," he said. — Nick Otto

MHRA Details Plan for Enforcing EU API Import Rules

To comply with the EU's new import rules for active pharmaceutical ingredients, the UK's Medicines and Healthcare products Regulatory Agency plans to review APIs during plant inspections rather than rely on assessments made at the border.

The EU's Falsified Medicines Directive took effect July 2, requiring all API makers operating outside the EU's 28-member bloc to get written confirmation from their national regulators that their facilities meet EU good manufacturing practice standards.

The MHRA will review imported APIs during the "inspection of manufacturers and, where there is a risk trigger, at inspection of [API] importers and distributors," the agency said.

The MHRA is the competent authority for APIs and pharmaceuticals, "not UK border control," agency spokesman Matthew Niizeki told *IPRM*, explaining the move.

Niizeki said Germany and Spain have adopted the same approach.

The MHRA previously said it could inspect roughly 1,200 sites in order to comply with the EU's new rules. The EU granted the U.S. Food and Drug Administration a waiver to the new import rules earlier this year, relieving U.S. API makers from having to file cumbersome GMP documentation before importing products to EU markets (*IPRM*, July).

Preventing Shortages

The MHRA has voiced concern that the additional inspection requirements could "in some instances make the sourcing of [APIs] from some third countries difficult," leading to drug shortages.

To prevent shortages, the agency has adopted contingency plans that apply to third-country API makers that are not covered by a written confirmation, reside in an exporting country that hasn't been assessed by the European Commission as having EU-equivalent GMP standards, and lack a certificate of compliance with EU GMPs.

The plan was initially floated in June. Drugmakers must provide evidence that they or a third party audited the API manufacturing site within the past three years and that it meets EU GMPs. Drugmakers must also show that the API site is in compliance with a recognized regulator such as the FDA. — Robert King

EU Trade Committee Would Limit Access to Drug Precursor Database

The European Parliament's Committee on International Trade (INTA) wants revised regulations on drug precursors to include language restricting police and other law enforcement officials from using a future database on companies that use precursors.

Precursors are chemicals that are used in a variety of products — including cold, flu and allergy treatments — that also may be illegally diverted to produce narcotics. The database, which would be created under the proposed amendments, would store licensing and registration information on businesses that trade and use these substances.

In a May 6 report on the recast that was released in late August, INTA says the European Commission and other competent authorities should be the only entities authorized to use the database, to ensure that activities aimed at keeping precursors off the black market are effective and well-coordinated.

In addition to controlling the database's usage, INTA seeks to close some loopholes in the current precursor legislation that have previously been exploited, commission spokeswoman Natasja Bohez-Rubiano told *IPRM*. Specifically, the committee would strengthen customs controls on

two drug precursors — ephedrine and pseudoephedrine. Currently, most customs authorities can only seize ephedrine or pseudoephedrine as raw substances.

The proposed recast stems from a 2010 report on the current system. While it was agreed the EU's drug precursor regulations were effective overall, the commission found gaps in the barriers aimed at stopping illegal diversion of ephedrine and pseudoephedrine in human medicines.

The commission tabled its proposal in September 2012, along with a separate, but similar amendment aimed at tightening rules for companies that use acetic anhydride — an ingredient used in the manufacture of heroin, Bohez-Rubiano said. Acetic anhydride was also cited in the 2010 report.

Current EU legislation contains 23 drug precursors that can be subject to customs controls at EU borders.

Fall Plenary Vote Planned

Both Parliament and the European Council still have to formally approve the amendments, Bohez-Rubiano said. The committee's amendments will move to a plenary vote in Parliament this fall, after which the legislation will move to the Council for final adoption.

The Chinese government has also taken action recently to curb the illegal diversion of drug precursors. In May, the China Food and Drug Administration put in place conditions, procedures, data requirements and processing times for drug precursor chemicals, and specified acceptable channels for the purchase and distribution of raw materials, prescribed preparations of ingredients and small packages of ephedrine (*IPRM*, May 2010).

View INTA's amendments to the regulation at www.fdanews.com/ext/files/09-13-precursor.pdf. — Nick Otto

FDA, EMA Joint Assessment of QbD Review Pilot Offers Filing Advice

The U.S. Food and Drug Administration and European Medicines Agency released a joint assessment last month of their quality-by-design pilot, which involves parallel reviews of new drug applications with QbD components.

Lauding the pilot as another useful regulatory team-up, the Q&A-style assessment includes a number of "lessons learnt," including that critical quality attributes for a drug substance should always be classified as critical rather than broken down into tiered degrees of criticality.

"The fact that a risk of failure is mitigated by applying a robust proactive control strategy should not allow for the underestimation of assigning criticality," the joint assessment states.

Quality target product profiles, or QTPP, which summarize the desired quality characteristics of a drug product, are most helpful to reviewers when presented in tabular format, the regulators say.

The assessment also touches on an emerging industry trend: the application of QbD concepts in the area of analytical methods using risk assessments and statistically designed experiments to define methods' analytical target profiles and method operational design ranges.

Noting a current lack of consensus on the definition of ATP and MODR, which parallel the QTPP and design space defined for a manufacturing process, the agencies say NDAs and EU marketing authorizations that include such proposals will be evaluated on a case-by-case basis.

The agencies launched the pilot in 2011 (*IPRM*, April 2011). They will continue to make QbD recommendations as more assessments of the pilot are conducted through 2014. Design space verification, continuous process verification and continuous manufacturing are expected to be topics of future assessment summaries, the agencies add.

The joint assessment is at www.fdanews.com/ext/files/08-22-13-QbD.pdf. — Nick Otto

ASEAN Document Draws on FDA, ICH Process Validation Guidelines

The Association of Southeast Asian Nations recently released draft guidance that updates process validation processes using a quality-by-design (QbD) approach.

The ASEAN guideline includes recommendations from the U.S. Food and Drug Administration and the International Council on Harmonisation. *Guidance for Quality by Design as an Alternative Approach to Process Validation* is appended to a larger ASEAN guideline on submitting process validation data.

The FDA released final guidance in 2011 on process validation, replacing a document issued in 1987. The ASEAN document notes that the guidance incorporated QbD, process analytical technology, risk management and "the concept of life cycle approach to process validation … [which] emphasizes a more holistic approach to process validation."

The ASEAN guideline adopts the FDA's method of dividing process validation into three stages: process design, process qualification and continued verification.

Process design provides an understanding of the manufacturing process. Information such as the intended dosage form and general manufacturing pathway affects process design, the ASEAN guideline explains. During the process validation stage, the company determines if the process design is capable of reproducible commercial manufacturing.

In the final stage, continued process validation, the aim is to provide assurance that the process remains in a state of control during commercial production.

The guideline also cites ICH Q8 though Q11 at certain points. For instance, it references ICH Q11, which focuses on the manufacture of drug substances, regarding how material attributes of active pharmaceutical ingredients affect critical quality attributes (CQA) for both chemical and biological drugs.

And the document also notes risk-assessment tools located in the risk-management guideline ICH Q9 to help in process development. "Initial risk assessment can be performed to study the impact of unit operation to CQAs," the ASEAN guideline says.

The association is comprised of 10 nations: Vietnam, Cambodia, Brunei Darussalam, Indonesia, Laos, Malaysia, Singapore, Thailand, the Philippines and Myanmar.

To read the guideline, visit www.fdanews.com/ext/files/09-13-ASEAN-QbD.pdf. — Robert King

Pharma: Exempt Research Drugs From U.S. FDA Border Processes

Imports of drugs intended for research should be exempt from new U.S. Food and Drug Administration border processes implemented under the FDA Safety and Innovation Act (FDASIA), industry stakeholders say.

Those that import such materials should not be required to submit additional information at the time of entry to demonstrate compliance with the 1938 FD&C Act, because to do so would be redundant, Pfizer writes in an Aug. 8 letter to the agency. The comments are in response to an FDA request for feedback on its implementation of new import authorities under Title VII of FDASIA.

In each phase of research, agency regulations require drugmakers to submit information assuring the proper identification, quality, purity and strength of the investigational drug. These controls are "dynamically sufficient to satisfy FDA's [current good manufacturing practice)] concerns," writes Anthony Barone, Pfizer's director of global logistics policy.

Instead, the agency should establish an "affirmation of compliance" code for research to be used alongside the other codes the agency uses during the import screening process, Barone suggests.

In separate comments, David Gaugh, senior vice president for science and regulatory affairs at the Generic Pharmaceuticals Association, notes that research materials are typically imported in small "negligible quantities." Inactive ingredients should be exempt as well because "most … are commodity materials used in many industries."

"By definition, inactive ingredients do not exert a pharmacological effect nor are targets for counterfeiting," Gaugh writes.

Risk-Based Policy Urged

Pfizer and GPhA urge the FDA to give "trusted importers" a break by categorizing them as such. Importers with negative or nonexistent compliance histories should be required to file additional information at the U.S. border, they say.

Importers that don't fall into the trusted camp should face "both document and physical exams with particular emphasis on the ability to demonstrate the inbound logistics of the consignment," Gaugh suggests. Those with negative compliance histories should be required to file, at the time of entry, data now required for processing under the agency's Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting, or PREDICT, program, he adds.

Importers whose history is unknown should also be required to file PREDICT data, as well as other proofs of product integrity, such as cGMP or facility inspection certificates covering the production date of the imported lot. And they should submit shipping and conveyance security data, Gaugh says.

PREDICT uses several factors to calculate a risk score for imports so that FDA inspectors can check the riskiest items first.

Pfizer's and GPhA's comments expand on those made during an FDA public meeting in July to get stakeholders'

input on the agency's enhanced import powers. The same day, the agency issued a proposed rule granting detention authority for drugs (*IPRM*, August).

Meanwhile, the FDA's 2009 draft guidance on good importer practices has yet to be finalized, a cause of frustration for some stakeholders who say their clinical materials and biological products are treated differently at different points of entry.

The FDA is taking 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. — Melissa Winn

Orphan Sponsors to Get One-on-One Talks With U.S. FDA, EMA Officials

The U.S. Food and Drug Administration and European Medicines Agency will hold a joint workshop this fall for makers of orphan drugs and medical devices to discuss both agencies' rare disease programs.

In addition to overview sessions by both regulators, manufacturers will have the opportunity on Oct. 4 to register for one-on-one video teleconferences with FDA and EMA staff to discuss the specifics of applying for an orphan product grant or designation.

During the morning, there will be concurrent sessions providing an overview of the regulators' orphan drug designation programs and an overview of the FDA's orphan designation and grant programs for medical devices. Both sessions will be available by webcast.

FDA orphan drug designations have increased markedly in recent years, and the agency has handed out more than 70 candidates already in 2013. Hundreds of such products have been approved since passage of the 1983 Orphan Drug Act — a feat orphan drugmakers attribute to the FDA's "historic flexibility" during reviews (*IPRM*, May 2012).

Across the pond, the EMA has strengthened its partnership with drugmakers, updating guidance on filing applications for orphan designation and fee reductions and encouraging parallel applications for designation with international partners (*IPRM*, June).

The EMA has granted more than 1,120 orphan product designations since EU legislation passed in 1999. A recent report by the European Committee of Experts on Rare Diseases shows reimbursement outpacing marketing authorization as the lead barrier to accessing orphan drugs across EU member states (*IPRM*, August).

View the notice of the joint meeting at www.fdanews.com/ext/files/08-21-13-Orphan.pdf. — Nick Otto

U.S. FTC Says No-AG Agreements Are Antitrust Concerns a la *Actavis*

Patent litigation settlements with "no-authorized generic" agreements qualify as "payment in return for staying out of the market" and should be considered an antitrust concern under the U.S. Supreme Court's recent ruling in *FTC v. Actavis*, the U.S. Federal Trade Commission says.

"The [Supreme] Court reaffirmed [in *Actavis*] that the legality of an agreement not to compete between a patent holder and a would-be rival is to be assessed using 'traditional antitrust factors,'" an amicus brief filed Aug. 14 by the FTC asserts. And under antitrust rules, no-AG agreements "are considered compensation," according to one attorney with the commission.

In fact, while many antitrust cases are difficult to prove because it's hard to compute a cost of damage, "it's pretty easy to value a no-AG agreement," FTC counsel Maren Schmidt says.

The FTC filed its brief in the U.S. District Court for the District of New Jersey in a private lawsuit concerning a patent settlement between Wyeth and Teva over Wyeth's blockbuster antidepressant drug Effexor XR (venlafaxine HCl). According to the suit, Teva, as part of the settlement, agreed to delay introduction of its generic version of Effexor XR until July 1, 2010, and Wyeth agreed not to market an authorized generic version of the drug for a period of time.

Wyeth and Teva contend antitrust concerns arise "only if parties use a monetary payment to share the supracompetitive returns preserved by their agreement to avoid competition," the FTC says in its brief.

But the commission concedes that the Supreme Court's opinion speaks in terms of payments and money, "as those were the allegations in *Actavis*."

Still, nothing in the opinion suggests the high court intended to limit its ruling to payments in cash, "nor would such an artificial limitation make economic sense," the commission argues. "Such a rule would allow settling parties to evade an antitrust challenge to a reverse payment settlement simply by transferring other valuable assets, such as gold bullion, stocks or real estate."

The FTC last year asked to file a similar amicus brief in the case, saying no-AG agreements are "without a doubt" anticompetitive pay-for-delay deals even though no cash payments are involved. At that time, the district court said the agency's brief failed to express an interest that is not already "represented competently" in the case.

More recently, an FTC report found that when a brand drugmaker refrains from launching an authorized generic during the 180-day exclusivity period reserved for the first-filing generic drugmaker under the Hatch-Waxman Act, consumers end up paying higher prices for the generic products.

The presence of authorized generic competition reduces the first filer's revenues by 40 to 52 percent, on average, and the impact of that competition on first filer revenues persists outside of exclusivity, the report says. A first filer's revenues in the 30 months following exclusivity are between 53 and 62 percent lower when facing an authorized generic.

View the FTC's amicus brief at www.fdanews.com/ext/files/08-19-13-ftc-amicus-brief.pdf. — Melissa Winn

Colombia Harmonizes Vaccine Regulations, Clarifies Preclinical, Clinical Requirements

Companies seeking to market vaccines in Colombia must provide the drug regulatory authority with the results of Phase IV studies, details of each study's protocol and a complete pharmacovigilance plan, new technical information released by INVIMA says.

Submissions for vaccines containing known or previously used antigens must include results of immunogenicity and safety studies, the agency adds. Such studies should take into account the justification of adjuvants and any potential interference with other vaccines.

Results — both favorable and unfavorable — must be provided with a verified manufacturer's declaration and all toxicity information. All studies must comply with global good clinical practice standards.

Preclinical requirements include studies of pharmacodynamics, immunogenicity, pharmacokinetics and adjuvants. Companies must also provide analyses of any toxicological studies, especially those conducted on special populations and for carcinogenicity and/or reproductive health, INVIMA says.

The draft resolution, issued last month, aligns Colombia's vaccine regulations with the Pan American Network for Drug Regulatory Harmonization.

To register a vaccine in Colombia, manufacturers must also provide:

- Names and contact information for all companies involved in the production process, along with any suppliers, vendors and contractors;
- Detailed list and analysis of every ingredient in the vaccine, including active pharmaceutical ingredients, along with study results;
- Justifications of the safety and stability of the vaccine and all of its components, including the processes and results of all studies;
- Analysis of any environmental risks associated with the vaccine;
- Name and contact information for a local technical director who will be responsible for the vaccine in-country;
- Details of each batch and lot, including shipping, packaging and labeling information. Labels must specify the brand and generic names, pharmaceutical form and concentration; and
- Validation of all studies, along with the manufacturer's certification.

Companies looking to renew their vaccine registrations should submit studies of any new ingredients incorporated into the vaccine formulation.

Stakeholders have until Nov. 1 to comment on the draft resolution. View it in Spanish at www.fdanews.com/ext/files/08-19-13-vaccines.pdf. — Lena Freund

FDANEWS

Customer Service: Kim Williams
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editor: Nick Otto
(703) 538-7639
notto@fdanews.com

Ad Sales: Jim Desborough
(703) 538-7647
jdesborough@fdanews.com

Content Sales: Nelly Valentin
(703) 538-7656
nvalentin@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • Fax: +1 (703) 538-7676
www.pharmaceuticalmonitor.com

Reporters: Johnathan Rickman, Elizabeth Orr, Ferdous Al-Faruque, Lena Freund, Robert King, Melissa Winn

President: Cynthia Carter; **Content Director:** Dan Landrigan; **Executive Editor:** Meg Bryant