Absence of Full API Export Rules in India, China Is Ongoing Source of Concern

Despite India and China being the top two active pharmaceutical ingredient exporters in the world, neither country has strict regulations governing API exports, a U.S. trade expert says.

The uptick in API production in both countries is due to their having rich deposits of the raw materials needed to make APIs, Jeffrey Gren, director of the Office of Health and Consumer Goods in the U.S. Department of Commerce, said during an Oct. 25 European Institute meeting on falsified medicines.

Currently, India regulates APIs only at the state level, while thousands of Chinese companies are manufacturing bulk APIs without any oversight, Gren explained. The issue of concern with China is that some products identified as chemicals may be used as APIs but are regulated by different Chinese authorities and under different requirements than for APIs, Gren said. The fact that export requirements for medical products are less strict than imports requirements is a concern cited in the Asia-Pacific Economic Corporation’s Life Sciences Innovation Forum’s Regulatory Harmonization Steering Committee Roadmap on Global Medical Product Quality and Supply Chain Integrity, he added. The lack of export controls ultimately shifts the regulation of APIs to the importing countries.

For the U.S. and Europe, which regulate the safety and quality of incoming products, suspect APIs are not a major problem. But for countries in the developing world and Africa, the importation of substandard or falsified APIs can be deadly and often goes unnoticed, said Andreas Seiter, a senior health specialist at the World Bank.

Lack of Resources, Know-How

Regulators in less-developed countries also are more likely to lack the know-how or resources to properly evaluate APIs, Seiter said, adding that often their good manufacturing practice (GMP) verification is limited to the finished product.

“The same is true for manufacturers — the bigger ones can spend more time and resources to verify their API sources, whereas the smaller ones are not able to do that and have to rely on middlemen in procuring their APIs,” he added. Many of these middlemen, brokers and traders have escaped regulatory oversight by operating internationally and selling from countries that don’t regulate exported raw materials, Seiter told IPRM.
Examples of such suspected criminality have already been reported in China. In June, the State Food and Drug Administration found that about 13 percent of all drug capsule makers in the country were producing products with excessive, unsafe levels of chromium. While some companies deviated from GMPs or used substandard materials, others illegally switched out pharmaceutical-grade gelatin for low-cost edible gelatin produced from chrome-tanned leather waste (IPRM, June).

The U.S. Food and Drug Administration (FDA) and its EU and Australian counterparts have developed a blueprint for operating joint good manufacturing practice inspections of API facilities (IPRM, March). And under the recently passed Generic Drug User Fee Amendments of 2012 (GDUFA), the FDA will be required to inspect foreign API makers as frequently as domestic manufacturers, John DiLoreto, executive director of the bulk pharmaceuticals task force of the Society of Chemical Manufacturers and Affiliates, told IPRM.

But a number of factors limit the effectiveness of overseas inspection programs, DiLoreto said. He noted, for instance, that logistical, language and financial barriers prevent the FDA from just going into any Chinese facility it chooses.

GDUFA does, however, give the FDA authority to destroy suspect pharma imports of unknown origin that are discovered during inspections at the border, DiLoreto said. Previously, the agency had to return the packages to their source, where they might be reintroduced into the supply chain. — Zachary Brennan

India Outlines Stepwise Approach to Recalls, Rapid Alerts That Includes Trial Runs

To ensure recall procedures are effective, makers of drugs, biologicals and vaccines must conduct a mock recall of at least one batch of any product and demonstrate the traceability of one of its raw materials, a draft guideline by India’s Central Drugs Standard Control Organization (CDSCO) says.

The mock recall should be performed at least once for the longest distribution chain and whenever distributors or marketing companies are changed, the draft adds. Records of the trial recall should be maintained by the company’s chief quality assurance officer.

The draft guideline, issued Oct. 22, outlines a stepwise recall procedure starting with detailing the problem in a recall log and assigning the recall a unique reference number.

Within 24 hours of deciding to initiate a Class I recall, drugmakers or their local representatives should issue an alert to the entire supply chain stating the severity of the defect, “using the fastest mode of communication,” the draft states. This may include email, telephone, fax, SMS messaging or another form of communication.

Once the distributor receives the recall alert, copies should be forwarded to all depots where the product was actually delivered, with directions to return all unsold stock. The process is repeated down to the warehouse level.

Distributors and retailers are responsible for maintaining the recall notice, stock inventory, procedures for freezing stock and records of returned items for verification by regional drug inspectors, CDSCO said.

Timelines Set

Following the recall, companies should review its effectiveness, investigate the cause of the problem and take remedial action to prevent the problem from recurring.

“If the cause of the recall is established to be [a] quality issue associated with any of the raw material used, then the traceability of that material shall be established in all the product/batches,” the draft states.

Class I recalls should be executed between 24 and 72 hours of the receipt of information concerning a serious health or product quality risk. The timelines for Class II and Class III recalls are 10 days and 30 days, respectively.

View the draft, Guidelines on Recall and Rapid Alert System for Drugs (Including Biologicals & Vaccines), at www.fdanews.com/ext/files/11-12-India-recalls.pdf.
— Meg Bryant

U.S. FDA Lacks Policy to Deal With New EU Directive, Shortage Concern Looms

The U.S. Food and Drug Administration’s (FDA) lack of a policy or guidance to help U.S. active pharmaceutical ingredient (API) manufacturers deal with a new European directive is causing concern among manufacturers about lost sales and drug shortages in Europe, an expert says.

Under the European Commission’s falsified medicines directive, all non-EU API makers must obtain written confirmation from their local regulatory authority to verify APIs were manufactured according to good manufacturing practices equivalent to those in the EU.

But the FDA has yet to issue any guidance on how it will deal with such written confirmation for U.S. manufacturers, and at least four companies have expressed serious concerns about how the issue will be handled in the near term, John DiLoreto, executive director of the bulk pharmaceuticals task force of the Society of Chemical Manufacturers and Affiliates, told IPRM.

The FDA said it is reviewing the directive and importation requirements and will provide industry with directions on fulfilling the mandate once the review is completed.

The written confirmation from third-party regulators comes into effect at the end of the year, although the EU is
allowing a six-month grace period — until July 2, 2013 — for foreign API manufacturers to comply.

DiLoreto said the FDA, which has no current policy on the issue, seems “very resistant” to the idea of issuing certificates. This could in part be due to the additional paperwork burden the requirement would impose, but for API manufacturers this is the “eleventh hour,” he said.

Meanwhile, European customers are telling U.S. manufacturers they may stockpile certain APIs, which could lead to shortages, DiLoreto said. He has written to FDA Commissioner Margaret Hamburg about the matter.

The FDA could file for an exemption from the certification requirement, but has yet to do so. Switzerland, Israel, Singapore, Brazil and Australia all have asked to be exempted, and their requests are pending with the European Commission. — Zachary Brennan

To view the commission’s question and answer document on the Falsified Medicines Directive, click here.

Expert Calls on U.S. FDA to Guide Americans To More Legitimate Foreign Drug Websites

Although the U.S. Food and Drug Administration (FDA) cannot legally endorse foreign websites selling pharmaceuticals to U.S. customers, a leading expert in counterfeit and standard drugs is urging the agency to at least guide Americans to more legitimate sources or website-credentialed agencies.

With more than 5 million Americans currently purchasing drugs online, the FDA’s endorsement of websites certified by the National Association of Boards of Pharmacy does not help low-income citizens purchase drugs at lower costs, says American Enterprise Institute scholar Roger Bate. And while the agency only encourages online pharmacies based in the U.S., it typically turns a blind eye to Americans who purchase personal supplies of up to 90 days worth of drugs from foreign websites, including ones in Canada and the UK, that offer them at a cheaper price. While those websites are certified by legitimate accreditation organizations, they are not acknowledged by the NABP or the FDA.

“We suspect the FDA guideline against any foreign website is most likely based on a lack of jurisdiction and inability to oversee quality outside of the U.S., rather than a careful assessment of drug safety and price savings,” Bate said.

Bate said he understands that it’s beyond the FDA’s jurisdiction and limited resources to assess the quality of foreign websites, but added that a recent survey he and others used to update research published by the National Bureau of Economic Research found more patients are purchasing drugs online using other credentialing associations, such as PharmacyChecker and the Canadian International Pharmacy Association. The study found no authenticity issues related to websites credentialed by either association, though there were failures of drugs purchased from noncertified sites.

Sixty-one percent of the respondents in that survey said they buy drugs online from foreign websites, citing cost savings as the leading cause for the purchases.

More and more patients are expected to turn to foreign websites, as the 2010 Affordable Care Act adds 40 million newly insured but less wealthy prescription drug consumers, said Marc Boutin, executive vice president and chief operating officer of the National Health Council.

“We’ve got to have a robust coverage within the formularies to avoid the creation of this new market of people who are going to look for drugs from sources that are not legitimate or trusted,” he said.

Considering the online pharmacies could be a nearly $1 billion industry, the lack of knowledge about legitimate pharmacies not endorsed by the FDA is disconcerting, Bate said. He called on the Institute of Medicine or National Institutes of Health to conduct a larger study analyzing differences among the various websites. — Zachary Brennan

Global Recall System May be Part Of U.S. FDA International Pivot

SEATTLE — The U.S. Food and Drug Administration’s (FDA) Office of International Programs (OIP) is exploring development of a single, global recall system that would encompass all domestic and international recalls.

The move toward a global system, currently in its early stages, would help address fast-growing gaps in global oversight of international product recalls, said Mark Roh, regional food and drug director for the FDA’s Pacific Region.

The agency can no longer be “the quality control unit at the border that we have been for so long,” he said. Under the global approach being considered, the FDA and its foreign counterparts would jointly determine which country would take the lead in working with a company on a given recall, and the recall would extend to all countries.

The evolution is critical to the safety of medicines supplied in the U.S., Roh said, since U.S. imports of FDA-regulated products could triple by 2015. Roh spoke at the Regulatory Affairs Professionals Society 2012 conference.

The effort — intended to bolster the FDA’s transformation into an explicitly international organization — grew out of the agency’s 2011 supply chain initiative, which fosters partnerships with key foreign counterparts (IPRM, July 2011).

Establishing the new system will likely require revoking or rescinding existing recall procedures and replacing them with new guidance documents. New legislative authorities

November 2012
will also be required to enable use of third-party assistance in global recalls. As a first step, Roh said OIP is assessing the FDA’s own ability to manage the makeover of the recall system and whether all parts of the agency support the change. After that, the agency will evaluate the mechanisms needed to work with foreign partners.

The FDA’s charge to OIP to explore these possibilities comes as the Office of Regulatory Affairs is being restructured to keep up with increasingly global operations. OIP and ORA together make up the larger Office of Global Regulatory Operations and Policy. — Johnathan Rickman

**EU Risk Management Guidance May Aid U.S., Global Risk Management Plans**

Drugmakers developing risk management plans for the EU should synchronize them as much as possible with RMP requirements in the U.S. and elsewhere to facilitate broader acceptance, experts say.

RMP requirements are in effect or being developed in more than 70 countries and typically fall into one of two categories, said John Freeman, head of global pharmacovigilance and risk management programs at Celgene. RMPs in the U.S., Canada, Australia and Japan are based on distribution, while RMPs in the EU and Latin America focus on communication and minimization measures.

Kelly Davis, senior vice president of medical and research services at United BioSource, said the U.S. Food and Drug Administration (FDA) typically looks at a manufacturer’s EU RMP and the format is useful for evaluating the need for a risk evaluation and mitigation strategy (REMS) in developing countries. She and Freeman spoke at an Oct. 9 Drug Information Association risk management conference in Silver Spring, Md.

The European Medicines Agency’s (EMA) latest guidance on risk management, Module 5, took effect July 2 (IPRM, March) and requires RMPs for post-authorization efficacy studies in certain instances, Davis said. These include drugs with pediatric indications, advanced therapy medical products, and cases where efficacy concerns can only be resolved after the product is on the market. Davis said the agency could expand the scope of post-authorization efficacy studies in the future and require that companies include post-authorization research plans in their RMPs.

Drugmakers with products authorized in the EU have until Jan. 10 to comply with the guideline.

The EMA has broadened its request for drug utilization studies as part of the RMP review process, especially where off-label use is a concern, Davis said. While a database approach may suffice for some situations, the agency will likely want most manufacturers to perform a chart-review study, possibly in several different countries, which will require advance planning.

The EMA is also asking companies to assess their risk minimization activities more frequently, which can be more challenging and time-consuming than an FDA REMS due to language requirements and data privacy concerns, Davis said.

A new EMA template for RMP submissions, due out this month, is expected to emphasize risk assessment but still include some risk minimization requirements. — Zachary Brennan

**European Commission Lays Out When Trial Results Must Be Posted to Database**

Clinical trial investigators in the EU must post their trial results to a publicly available database within six months for pediatric trials and within a year for all other trials, according to a European Commission guideline.

Data should be posted earlier if available, the final guideline adds.

The guideline will take effect as soon as the relevant trial results databases have been finalized. A detailed technical guideline with the actual data fields should be published by the end of this year or early 2013, and then pilot testing will begin, commission spokeswoman Aikaterini Apostola said. After that, clinical trial data that is not posted within nine

(See EU Trials, Page 5)
EU Trials, from Page 4

months for pediatric trials, or 15 months for other trials, will be flagged as noncompliant.

Investigators whose pediatric trials ended more than a year before the finalization of the database, called EudraCT, will have two years to post their data. For pediatric trials completed before Jan. 26, 2008, a copy of a medical journal article may be posted within two years as a substitute for the results.

The guideline applies to all trials in the EU, trials in a contracting state of the European Economic Area, and those that are part of a pediatric investigation plan that includes trials outside the EU where the sponsor is seeking marketing authorization in the EU.

The commission’s goal is for 60 percent of European publicly funded research articles to be available by 2016 (IPRM, August). The only results that will not be made public are nonpediatric Phase I clinical trial results.

Once results are in the database, the European Medicines Agency (EMA) may remove information, highlight potentially invalid data or add a notice to the public record explaining the possibility of inaccuracies, the guideline notes.

The content of the database will be aligned with the U.S. trials database ClinicalTrials.gov, with some modifications related to EU pediatric investigation plans and harmonization with other evolving international databases, the commission said. Information may be posted to EudraCT via a web interface provided by the EMA, an XML file using that interface or by using a gateway technology.

View the guidance at www.fdanews.com/ext/files/10-12-12-ClinicalTrials.pdf. — Zachary Brennan

UK Patent Revisions Would Remove Legal Uncertainty in Drug Trials

Proposed changes to UK patent law would enable innovative drugmakers to use patented drugs in clinical trials without fear of patent infringement suits — a move designed to expand drug research in the country.

Under the Bolar exemption, generic drugmakers can do limited research using patented medicines in trials aimed at gaining approval of generic drug products, without risking patent infringement. But there is no exemption from patent infringement for trials that compare a novel drug with a patented drug.

“Trials carried out to discover something unknown, to test a hypothesis, or to find out whether something will work in specific conditions can be regarded as an experiment, but trials carried out to demonstrate to a third party that a product works, or to amass information to satisfy a third party that a product works as claimed, are not regarded as acts done for experimental purposes and are therefore not acts which are exempt from infringement,” the Intellectual Property Office (IPO) proposal states.

“This clearly has implications for field and clinical trials where regulatory approval is required in order to obtain marketing authorization,” according to the IPO. Moreover, uncertainty about where the Bolar exemption applies has upped the costs for legal analyses and other measures to assess the risk of patent infringement.

The proposed revisions would clarify the Bolar exemption, which applies to generic drugs and was intended as a UK version of the U.S. Hatch-Waxman Act and add an exemption for the use of patented drugs in novel drug trials. Most European countries currently have such exemptions, in line with international agreements.

Three Options

Specifically, the IPO is seeking input on three proposed options for changing the 35-year-old legislation:

- Exempt from patent infringement all activities required to secure regulatory approval to market innovative drugs in all countries;
- Exempt such activities in the EU and European Economic Area countries only; and
- Exempt such activities and those related to assessment by the National Institute for Health and Clinical Excellence.

The government is also seeking information about the toll on companies — such as licensing negotiations and court costs — that the current legislation exacts and what losses patent holders might experience if the law was changed. The revisions would apply to microbusinesses, as well as larger businesses.

Two non-legislative options are also on the table: Develop guidance clarifying the 1977 law and encourage industry agreements.

Research-based manufacturers welcomed the proposals. “This will give innovators the freedom to undertake comparative studies so they can provide data on clinical effectiveness,” said Stephen Whitehead, chief executive of the Association of British Pharmaceutical Industries.

John Murphy, chair of the BioIndustry Association’s Intellectual Property Advisory Committee, concurred. “It is important to provide clarity regarding the UK’s interpretation of the Research and Bolar Exceptions so that innovative drug developers operate on a level playing field,” he said.

Comments on the proposal are due by Dec. 19. View the proposals at www.fdanews.com/ext/files/11-08-12-bolar.pdf. — Meg Bryant
EMA Draft Guideline Suggests Primary Efficacy Parameters for MS Drugs

Drugmakers evaluating multiple sclerosis treatments for the EU should use relapse rate as the primary efficacy parameter in clinical trials for relapsing-remitting MS or secondary progressive MS with superimposed relapses, according to a draft European Medicines Agency (EMA) guideline.

The primary efficacy parameter in confirmatory trials for primary and secondary progressive MS should be a clinically measured prevention or delay of disability progression.

The guideline, which focuses on treatments to modify disease progression, is a revision of the agency’s guideline on clinical investigation of drugs to treat MS (CPMP/561/98, Rev.1).

It advises drugmakers on the types of trials to conduct for MS treatments, such as recommending randomized, double-blind, placebo-controlled trials for primary progressive MS. For secondary progressive MS, drugmakers should conduct large-scale, long-term placebo-controlled parallel group trials.

Treatments that modify the natural course of MS require long-term superiority trials, the guideline states. Drugmakers should evaluate progression of disability, and reasonably exclude worsening of disability, via adequately powered long-term studies.

Pediatric Trials

MS products that are expected to have a major effect on the immune system should go through a two-step procedure: comparative superiority studies in patients with insufficient response to first-line treatment, followed by safety studies in a broader population if the safety profile is acceptable.

The EMA expects to see specific data for children. This may come from clinical trials tailored to children, studies incorporating adolescent MS patients into adult trials, or by extrapolating efficacy observed in adult patients, provided that the dose and short-term safety are established and long-term safety is evaluated.

In trials of MS drugs, specific attention should be paid to depression, suicide and other psychiatric symptoms, the guideline states.

The EMA notes that Kurtz’s expanded disability status scale (EDSS) is the most commonly used scale for assessing changes in disability in MS patients. Therefore, even when it may be more appropriate to develop alternative scales, the EDSS should be used to facilitate comparisons with other studies.

Comments on the guideline are due April 9, 2013. The draft guideline is available at www.fdanews.com/ext/files/10-10-12-guideline.pdf. — April Hollis

Acute Heart Failure Drug Trials Should Include Co-Primary Endpoints, EMA Says

Developers of acute heart failure drugs should conduct double-blind, randomized Phase III trials with co-primary endpoints, rather than composite endpoints, according to a European Medicines Agency (EMA) draft guideline.

Co-primary endpoints could include symptom combinations and mortality/morbidity, the draft states. It discourages the use of hemodynamic — or blood movement — measurements as co-primary endpoints.

For secondary endpoints, the EMA recommends using cardiovascular deaths, while overall mortality is acceptable when dyspnoea is the primary endpoint. Other secondary endpoints may include:

- Concomitant medication;
- Oxygen therapy; and
- Intubation/assisted ventilation.

The draft guideline covers aspects of developing acute heart failure treatments that are not covered in the EMA guideline on chronic heart failure, and requires that precise patient selection criteria be tailored for each trial.

Excessive heterogeneity in a clinical trial could result in equivocal or negative results, or lead to post-hoc subgroup analyses that are difficult to interpret, the EMA said. It recommends a more homogenous population, with 25 percent to 30 percent of patients in a multicenter trial coming from Europe. Patients should be selected based on the proposed indication, pathophysiological mechanism and the treatment’s mode of action.

For safety evaluations, databases for each group of patients in a trial should be delineated by indication and be large enough to exclude a detrimental effect on morbidity and mortality. Even if a drugmaker is only filing for symptomatic benefits, the EMA still expects to see mortality data for the hospitalization period, end of 30 days period and a follow-up period after six months. This is to exclude the possibility of any short- or long-term negative effects.

Placebo-controlled studies are required if a new treatment is an add-on therapy, belongs to a new therapeutic class or belongs to a class that has not been considered an acute heart failure treatment. For active comparator trials, the EMA recommends nitroglycerine or Hospira’s Nitropress (nitroprusside) for vasodilators, Sanofi-Aventis’ Lasix (furosemide) for diuretics, and dobutamine — alone or in combination with dopamine — for inotropes.

Comments on the draft guidance will be accepted until April 15, 2013. View the draft at www.fdanews.com/ext/files/10-16-12-EMAHeartFailure.pdf.
— Zachary Brennan
EMA Guideline Recommends Placebo Arms For Short-Term Trials of Schizophrenia Drugs

The European Medicines Agency (EMA) is advising sponsors to use placebo arms, rather than active comparators, in short-term trials of schizophrenia drugs, according to a final guidance. With stringent controls and follow-up safeguards, the benefits of using a placebo should outweigh any ethical concerns — at least for short-term controlled efficacy trials.

Long-term placebo-controlled studies can be “ethically problematic” and are associated with a high rate of premature withdrawals that can add to difficulties interpreting trial data, the guideline notes. However, these trials are possible using a randomized withdrawal study where patients are stabilized on open-label treatment for at least 12 weeks and then randomized to either active treatment or placebo. Patients who relapse can be started on active treatment immediately, the guideline states.

In addition to highlighting the use of placebo in schizophrenia studies, the guideline focuses on study design, treatment-resistant populations and alternative treatment options.

For demonstrating efficacy to support a treatment-resistant indication, the EMA recommends two possible approaches:

- A primary trial objective demonstrating superiority to an active comparator, which should be a drug with which treatment failure has previously been identified; or
- A primary trial objective demonstrating noninferiority to clozapine, which is the only drug approved in the EU for treatment-resistant schizophrenia.

In other respects, the study designs and endpoints for treatment-resistant patients are essentially the same as for other trials.

For trials assessing alternative treatment options, such as add-on, augmentation or combination treatments, patient populations should be clearly defined in terms of number and degree of treatment failures, as well as the domains of their insufficient responses.

The agency also recommends the development of improved scales for measuring negative symptoms and tools to assess treatment effects on cognition. Specific adverse events that should be monitored in all trials include:

- Extrapyramidal symptoms;
- Withdrawal and dependence;
- Psychiatric adverse events;
- Adverse effects on cognitive functioning;
- Suicide;
- Metabolic risk factors;
- Neuroleptic malignant syndrome; and
- Hematological, endocrinological and cardiovascular adverse events.

An appendix provides guidance on the development of depot preparations and focuses on the methodology of clinical trials for their development. The guideline comes into effect April 1, 2013, and can be viewed at www.fdanews.com/ext/files/10-11-12-EMASchizophrenia.pdf. — Zachary Brennan

Roche May Face Fine in EU Over Alleged Pharmacovigilance Shortfalls

The European Medicines Agency (EMA) has initiated its first-ever infringement procedure against a drugmaker, alleging Roche did not report potential adverse events for 19 of its U.S. drugs.

If Roche is found to have infringed on its pharmacovigilance obligations, it could be fined up to 5 percent of its EU revenue from last year. And if the infringement is not settled following the initial fine, the European Commission could impose daily penalties of up to 2.5 percent of Roche’s average daily EU revenue from last year.

The EMA’s Pharmacovigilance Risk Assessment Committee is currently reviewing the data provided on previously missing case reports and corrections to previously submitted data. The committee is expected to finalize its review by March 2013 and submit it to the commission, which will ultimately decide on the fine.

In June, the EMA called on Roche to immediately report any possible adverse events from marketed drugs or those in clinical trials to EU authorities.

The alleged deficiencies were identified in May in the course of an inspection of Roche subsidiary Genentech by the UK’s Medicines and Healthcare products Regulatory Agency (MHRA). During the inspection, the company identified about 80,000 case reports from a patient support program that had not been evaluated for adverse events or reported to EU authorities.

The investigation did not reveal any evidence of a patient safety risk, although the reports included 15,161 deaths, the MHRA said.

The company also must submit a revised action plan to ensure it submits and processes the correct adverse drug reactions in the future, the EMA said. — Zachary Brennan

French Pathway for Off-Label Prescribing Increases Scrutiny, While Allowing Access

Recent measures in France will broaden risk-benefit scrutiny and expand off-label drugs use in justifiable situations, according to an opinion piece in the Oct. 4 issue of The New England Journal of Medicine. The authors urge other countries to adopt a similar approach.

According to the authors, all employees of France’s National Agency of Medicine and Health Product Safety (ANSM), last
year’s drug safety legislation and a May 2012 decree establish a regulatory pathway for off-label indications by allowing temporary indication for uses (TRU) for drugs when no alternative treatment exists. The TRU is good for three years and sets the stage for the off-label indication to be reimbursed.

Before ANSM can issue a TRU, an expert panel must evaluate the following:

- Quality of the scientific evidence surrounding the drug and the proposed indication;
- Drug safety;
- Prognosis associated with a given disease; and
- Frequency of the disease’s occurrence.

**Drugmaker Requirements**

Companies whose drugs receive a TRU must sign a formal contract with ANSM defining patient follow-up; evaluate the safety and efficacy information to be collected; investigate the actual — as opposed to indicated — conditions of use; and create a schedule for reporting data to the agency.

They also must monitor the extent to which physicians are prescribing the drug according to its approved indication and cannot promote the product for any of its off-label uses, even those covered by the TRU. And they must inform ANSM if unconventional prescribing patterns are detected and take steps to reverse them.

But companies may not request a TRU. Instead, other government agencies, rare disease organizations and patient advocacy groups will alert ANSM to situations where off-label uses may be recommended, the authors note.

Once a TRU is granted, the Medicines Evaluation Commission has three months to render an opinion on the treatment’s reimbursement, author Annie Lorence told IPRM. She said no TRUs have as yet been granted. — Zachary Brennan

**Canada Expects Minimal Industry Burden from New API GMP Regs**

Proposed good manufacturing practice (GMP) regulations will cost active pharmaceutical ingredient makers in Canada nearly $1 million dollars in initial costs and $100,000 in annual compliance, according to an analysis by Health Canada.

This represents a minimal burden on companies, while the new rules could save nearly $35 million over 10 years from reduced foreign inspections for Canadian manufacturers selling abroad, according to the draft proposal released Oct. 22. Canada is one of the last industrialized countries to adopt GMPs for APIs.

GMPs should also decrease waste and recalls because API problems will be detected earlier, the draft states. If the proposal can prevent 2 to 8 percent of API-related recalls, the savings would amount to $3.8 million to $15.4 million annually.

Companies — in particular, API packagers, labelers and drug identification number distributors — should anticipate one-time employee training costs of about $966,000 related to filing the new GMP applications. The cost assumes use of ISO 9001 and the FDA’s cGMP trainings as proxies.

In addition to extending GMP requirements to APIs, Health Canada’s proposal would:

- Add new drug establishment licensing requirements;
- Create a new recordkeeping requirement to increase traceability; and
- Align Canada with the International Conference on Harmonisation’s Q7 document on GMPs, to establish regulatory equivalence with the U.S., EU, Japan and other countries.

The proposal is expected to affect about 40 Canadian API manufacturers; 10 API testers; between 30 and 40 packagers, labelers and distributors; and 250 to 300 importers.

Stakeholders can comment on the draft until Jan. 5, 2013. It is available at www.fdanews.com/ext/files/10-23-12-Canada.pdf. — Zachary Brennan

**Canada Looks to Boost Rare Disease Research Via Orphan Drug Pathway**

Health Canada is developing a new approval pathway for orphan drugs as part of an effort to spur development of drugs for conditions that affect less than five in 10,000 patients.

The proposed framework — which is in the final stages of development before being released for comment — will be supported by increased information-sharing among international partners, the agency said.

Canadian drugmakers and patient groups have long pressed the government to create a special pathway and incentives for orphan drug development. BIOTECanada praised the proposal, noting that 21 Canadian companies have received orphan drug designations by the U.S. Food and Drug Administration (FDA), and four drugs have been approved.

According to the Canadian Organization for Rare Disorders (CORD), Canadians have access to about half the more than 300 new drugs approved under the FDA’s orphan drug pathway. Most of those drugs were approved in Canada several years after they became available in the U.S., the group said.

And while Ontario, British Columbia and Alberta have special pathways for such approvals, they rarely approve them with any consistency, the group added. Under the common drug review, most Canadian provinces routinely deny funding for rare diseases, CORD said.

Over the years, CORD has urged Health Canada to establish an orphan drug pathway, waive market authorization application
fees, recognize FDA and European Medicines Agency approvals, and grant 10-year market exclusivity for orphan drugs.

Separately, Health Canada launched an online reference portal for information on rare diseases. Orphanet will enable Canadian scientists to access the world’s largest online portal for information on the diagnosis, care and treatment of patients with rare diseases, the agency said. The EU-based reference portal is not currently available in the U.S. or Latin America. — Zachary Brennan

**Safety Risks Seen in Health Canada Priority Approvals Could Signal System Flaws**

A new study finds one-third of drugs approved using Health Canada’s priority approval process eventually develop safety problems. The study’s author attributes the findings to deficiencies in the agency’s fast-track approvals process.

Health Canada granted priority review to 112 drugs between 1995 and 2010. About 34 percent of those were later associated with a serious safety issue, a review by York University professor Joel Lexchin revealed. That compares with a considerably lower 20 percent estimate for new active substances (NAS) that underwent a standard review.

According to the study in the Oct. 8 *Archives of Internal Medicine*, the shorter review period may be to blame for the increase.

Health Canada disputed that conclusion Oct. 11, saying the same regulatory framework supports both review tracks. “The level of scrutiny and the rules applied remain identical,” the agency said.

But Lexchin notes that alternative “explanations for the difference between standard and review NASs are less likely” because priority review “drugs that were not major therapeutic advances were still more likely to acquire serious safety issues than standard review NASs.”

In Canada, the target review time for a priority review decision is 215 days, compared with 355 days for standard reviews.

Regulators in the U.S. and Canada face increasing pressure from drugmakers, lawmakers and patients to speed the drug review process, said Thomas Moore, senior scientist for drug safety and policy at the Institute for Safe Medication Practices. He noted a recent report on the U.S. bioeconomy by the White House Office of Science and Technology Policy, which cites concern about slow drug reviews and approval processes. — Johnathan Rickman

**Global Dragnet Nabs $10.5 Million in Online Counterfeit, Unapproved Drugs**

An international offensive against thousands of online peddlers of counterfeit and illicit drugs has resulted in the seizure of some 3.75 million units with an estimated value of $10.5 million.

Code-named Operation Pangea V to signify the global nature, the Sept. 25 to Oct. 2 initiative involved 100 countries and is the largest internet-based enforcement action of its kind to date. The U.S. Food and Drug Administration (FDA) zeroed in on websites selling unapproved drugs, including drugs containing acne treatment isotretinoin. It also seized unapproved Tamiflu (oseltamivir phosphate), misleadingly marketed on the sites as a generic, and Viagra (sildenafil citrate), sold without requiring a valid prescription.

In the UK, enforcement officers from the Medicines and Healthcare products Regulatory Agency (MHRA) seized more than 2.3 million doses of unlicensed drugs worth about US $6.1 million. Similarly, New Zealand’s Medicines and Medical Devices Safety Authority seized more than 100 parcels from 21 countries that were suspected of containing illegal prescription drugs.

An estimated 18,000 websites were closed down as a result of the crackdown, according to INTERPOL. Additionally, some 133,000 packages were inspected, of which about 6,700 were confiscated. To date, 79 individuals are under investigation or under arrest for illegally manufacturing, selling and supplying unapproved or prescription-only drug products, and operators of more than 4,100 internet pharmacies have received warning letters from the FDA.

The recent action was coordinated by INTERPOL, the World Customs Organization, the Permanent Forum on International Pharmaceutical Crime, the Heads of Medicines Agencies’ Working Group of Enforcement Officers, the Pharmaceutical Security Institute, Europol and the Center for Safe Internet Pharmacies. Drug security and electronic payment companies also participated in the international sting.

The size of the sting and the amount of drugs seized dwarfs last year’s Operation Pangea IV, which involved 81 countries and nabbed some 2.1 million pills worth about $6.3 million (*IPRM, October 2011*). — Johnathan Rickman

**Policing Internet Pharmacies Has Limited Impact, Public Education Is Key: ICE Official**

Despite the success of the annual Pangea sting and steady casework by FDA gumshoes, the only way to stop the spread of unlicensed internet pharmacies and pharmaceutical fakes is to educate consumers about their dangers, U.S. Immigration and Customs Enforcement (ICE) officials say.

“We can't police our way out of this problem,” James Dinkins, ICE’s executive associate director for Homeland Security investigations, said at the Partnership for Safe Medicines Interchange in Washington, D.C. While ICE has 72 offices in 50 countries working on this issue, criminal networks that traffic in fake drugs still find ways to fly under the radar, he added.

And a better means of helping U.S.-accredited internet domain name registrars (DNRs) weed out shady website operators remains elusive. The government and the
nonprofit Internet Corporation for Assigned Names and Numbers (ICANN), the U.S. accreditor, continue to look for a mutually agreeable solution that builds on internet service codes of conduct for DNR clients, Dinkins said.

An international coalition of pharma supply chain stakeholders has called on ICANN to do more to combat illicit online sales of prescription drugs (IPRM, August).

Meanwhile, more efforts to raise public awareness of the dangers of rogue internet pharmacies, such as the FDA’s new BeSafeRx campaign, are needed to help shutter fake shops, Dinkins said.

The campaign, launched Sept. 28 to coincide with the interchange, provides consumers with fact sheets and other tools to guide decisions about buying drugs online.

— Johnathan Rickman

IN BRIEF

EU Seeks to Extend Brand Patents in Canada

The European Commission is negotiating with Canada over changes it would like Canada to make to its intellectual property (IP) protections for pharmaceuticals. The proposed changes would add more data protection for brand drugs and extend and increase the scope of Canada’s patent linkage system, Jody Cox, director of federal government relations at the Canadian Generic Pharmaceuticals Association, told IPRM. Both CGPA and the European Generic Medicines Association oppose the Comprehensive Economic and Trade Agreement, which is favored by research-based companies. Generic drugmakers cite a study that found the proposals could delay introduction of Canadian generics by 3.5 years and increase costs by more than $2.8 billion annually. The negotiations are expected to wrap up by early 2013, Cox said.

Italy Looks to Stimulate Clinical Research

The Italian Agency of Drugs, Superior Institute of Health and Italian Association for the Development of Biotechnology have signed an agreement to encourage clinical trials in the country. The goals are to increase the number of early-stage trials by at least 30 percent in the next three years, ensure a faster decision on reimbursement prices for companies in early-stage trials, and reduce inspection times.

Indonesia Issues Compulsory Licenses

Indonesian President H. Susilo Bambang Yudhoyono signed a decree authorizing domestic generic drugmakers to begin producing seven patented HIV and hepatitis B drugs, including Gilead’s Viread (tenofovir), Merck’s Sustiva (efavirenz) and Glaxo-SmithKline’s Ziagen (abacavir). The proposal replaces decrees from 2004 and 2007, and has the potential to supplement other licenses negotiated between Gilead and the Medicines Patent Pool. Patent holders affected by the compulsory licenses will receive a 0.5 percent royalty. Indonesia joins others in the region, including China, Japan and India, in issuing such patents (IPRM, July).

Zimbabwe Updates Guidance on Generics

The Medicines Control Authority of Zimbabwe (MCAZ) has updated its guidance on the submission of quality information related to active pharmaceutical ingredients and finished generic drugs that should be submitted in support of multisource generic drugs applications. MCAZ’s guidance focuses on common technical document summaries, quality data and nonclinical and clinical study reports. The guidance, which comes into effect in March 2013, is available at www.mcaz.co.zw.

Brazil Eyes Speedier Drug Registration Process

Brazil’s Anvisa is adopting three initiatives aimed at speeding drug registrations and reducing a growing backlog of applications. An electronic registration system to be operational later this year will eliminate the agency’s paper-based system. Anvisa is also restructuring its regulatory framework to better address high-priority drugs and is reducing some of the registration burden by allowing reference countries’ regulators to perform foreign inspections.

EFPIA Selects Viehbacher as New President

The European Federation of Pharmaceutical Industries and Associations has selected Sanofi CEO Christopher Viehbacher as its new president, effective in June 2013. Viehbacher also chairs the CEO Roundtable on Cancer and was previously chairman of U.S. industry group PhRMA. The position is for two years.
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Nathan Basken, Senior Scientist, Ventana Medical

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“[Barbara’s] anecdotal stories brought the
course material to life.”

Steve Henderson, Quality
Assurance, Shared Capabilities,
Procter & Gamble
Pharmaceuticals

WORKSHOP AGENDA

DAYS ONE

8:00 a.m. – 8:30 a.m. REGISTRATION/ CONTINENTAL BREAKFAST
8:30 a.m. – 10:00 a.m. REGULATORY REQUIREMENTS AND EXPECTATIONS
• Review of FDA requirements
• CAPA definitions and terms
• Consequences of noncompliance
• How the FDA trains its investigators to review investigations and CAPA

✓ INTERACTIVE EXERCISE! What’s Driving Us Crazy?
✓ INTERACTIVE EXERCISE! Review and discuss recent pertinent FDA warning letters

10:00 a.m. – 10:15 a.m. BREAK

10:15 a.m. – 12:00 p.m. PROBLEM INVESTIGATION TECHNIQUES
• Identifying the need for an investigation
• Setting priorities — determining risk and severity of issue
• 22 investigation tips
• Crafting a clear, complete problem statement

12:00 p.m. – 1:00 p.m. LUNCH

1:00 p.m. – 2:00 p.m. ROOT CAUSE ANALYSIS
• How to conduct and document a root cause analysis
• Six solution criteria
• Root cause analysis guide
• Problem solving worksheet

✓ INTERACTIVE EXERCISE! Analyze real industry cases and prepare fishbone diagram
✓ INTERACTIVE EXERCISE! Practice brainstorming root causes for a real investigation

2:00 p.m. – 3:00 p.m. REPORT WRITING
• Using critical thinking when evaluating reports
• Typical content and structure
• Tips on crafting the executive summary
• Purpose of a report: to allow others to make a decision
• Designing a report to be easily skimmed and used

8:00 a.m. – 8:30 a.m. REGISTRATION/ CONTINENTAL BREAKFAST
8:30 a.m. – 10:00 a.m. MANAGING CAPA
• Tips from law enforcement
• CAPA systems and SOPs
• Data sources, trending, effectiveness checks
• Selecting, training and coaching employees

WHO SHOULD ATTEND
• CAPA managers
• QA/QC managers and directors
• Compliance officers
• Training managers
• GCP, GLP or GMP professionals
• Regulatory affairs managers
• Quality engineers
• Anyone wishing to improve an organization’s CAPA activities and investigations

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David Flemming
QA Manager
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Congratulations — ADVANCED

Barbara K. Immel, a published author and nationally known speaker, is president of Immel Resources LLC and editor of the Immel Report. She has 30 years of industry experience working in corporate quality assurance, compliance, training, documentation and labeling. Barb’s experience includes more than 12 years with Syva Company, Chiron Corporation and Syntex Corporation. Barb is the chairperson of the Annual FDA Inspections Summit hosted by FDAnews and a member of the steering committee for FDA MedCon 2010, Xavier University’s new medical device conference.

Barb has been teaching well-respected courses on writing reports for deviations and failure investigations, and on conducting CAPA investigations, for the past 11 years (2000–2011).

YOUR EXPERT INSTRUCTOR

10:00 a.m. – 10:15 a.m. BREAK

10:15 a.m. – 12:00 p.m. RISK MANAGEMENT AS IT APPLIES TO CAPA

• Patient safety: number one concern
• Risk analysis refresher
• ☑️ INTERACTIVE EXERCISE! Practice using FMEA to analyze the risk of different scenarios

12:00 p.m. – 1:00 p.m. LUNCH

1:00 p.m. – 2:00 p.m. PREVENTIVE ACTION AND CRISIS MANAGEMENT

• Encouraging preventive action
• Key crises to prepare for (and how)
• ☑️ INTERACTIVE EXERCISE! Developing a preventive action plan for a real scenario, working with a team

2:00 p.m. – 3:00 p.m. REQUIRED FDA NOTIFICATIONS

• Refresher on requirements and timelines
• Recalls, corrections and removals

3:00 p.m. – 3:15 p.m. BREAK

3:15 p.m. – 4:00 p.m. RESPONDING TO THE FDA

• Timeliness requirements and key elements in written responses to FDA Form 483s
• ☑️ INTERACTIVE EXERCISE! Practice responding to real observations
• ☑️ INTERACTIVE EXERCISE! Review and discuss pertinent FDA Form 483 observations

4:00 p.m. – 5:00 p.m. CLASS PROJECT

• Conduct a mock investigation working with your team
• Present your findings to the overall class
• Review and complete brief quiz on key points of class exercises

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