THE FOOD & DRUG LETTER®

Issue No. 805
Sept. 26, 2008

Abstract: *Awareness of drug safety issues has risen to unprecedented levels in light of some of the drug recalls and adverse events that have occurred in recent years. The result has been new legislation, stricter regulations and revised company strategies in Europe and the U.S. These trends have led to greater regulatory uniformity in the EU, which means greater challenges for the pharmaceutical industry. A company can look forward to improved reporting and an overall enhancement of the quality of the EU regulatory system. If there is a lesson to be learned from recent industry crises, it is that bad things can happen to the best companies. When bad things happen, companies need to have a system in place that will take them through the crisis, including a good communication plan. That includes increasing their understanding of the European Medicines Agency (EMEA) and how the EU system operates. As is often the case when working with governments, education is a key factor, so this issue of* The Food & Drug Letter *focuses on drug safety in the EU.*

European Medicines Agency Regulations Do Not Mirror FDA's

In contrast with the FDA in the U.S., the EU has the EMEA, which has been in existence since 1995. The EMEA is a secretariat for a network of experts, with largely uniform rules on testing, clinical trials, applications, pharmacovigilance and good manufacturing practices (GMPs). Unlike the FDA, however, it does not have the final word on drug approval.

Rules are enforced by the member states with coordination by the EMEA, so there are differences in approach. Each of the 27 members of the EU still has a drug regulatory agency or, in some cases, two. Also, despite the increasing frequency of meetings in London and Brussels to coordinate European work, the review of centrally authorized products occurs chiefly in the national capitals around Europe as the rapporteurs bring back the work from EMEA meetings and assign reviews of applications.

Also, although we constantly talk about EMEA approvals or authorizations, the European Commission has final approval authority. Its key committee — the Committee for Medicinal Products for Human Use (CHMP) — issues an opinion that is nearly always followed, but not followed exclusively.

The EMEA is growing increasingly powerful, controlling some 70 percent of new products entering the market. Nevertheless, most of the products that today are on the market in the EU got there through

(See **Mirror***, Page 2)*

Mirror, *from Page 1*

approval procedures at the member-state level. The EMEA coordinates marketing authorization for the EU nations, but the member states are responsible for enforcement. They also maintain licensing and control sales and promotional activities of drugs. More importantly, there is no sign that they want to relinquish control to the EMEA any time soon.

U.S.-EU Similarities

The FDA has some advantages over the EMEA, particularly in a crisis, because it does not have to coordinate among many states or countries; it is a single approval and enforcement agency. There is a tradition of quasi-independence of the FDA within the executive branch of the government, and it has investigators and relationships with U.S. attorneys nationwide. Because it is the only agency that approves medicinal products for human use in the U.S., it has a good idea of what is on the market.

INSIDE THIS ISSUE

Differences between countries' regulations are principally organizational, not substantive. There are many similarities between the U.S. and EU regulatory agencies, including:

- Common regulatory objectives;
- Conscious effort to eliminate unjustified differences and harmonize;
- Effort toward global submissions and uniform reporting obligations; and
- International Conference on Harmonisation (ICH) guidelines, such as common technical document and pharmacovigilance.

Coordination Between Member States a Challenge

Because many diverse groups comprise the EU, coordination is challenging. The level of transparency that exists in the U.S. does not exist, and it can be difficult to find relevant documents when necessary. However, improvement has occurred and is expected to continue because most of the drug regulatory bodies in the EU can achieve a lot of efficiencies and economies by publishing their documents on the web, often in English, which has emerged as the *lingua franca* of pharmaceutical regulation.

In some cases, the lack of coordination can be traced to cultural differences, prescribing practices or the popularity of a certain product that holds onto market share despite the invasion of generic drugs. Also, prescription drug versus OTC drug classification varies from member state to member state, making regulation difficult.

Parallel trade offers its own set of complications for companies doing business in the EU. Even though a company might carefully select which markets it wants and offer marketing authorization applications only to those countries' regulatory bodies, its products could turn up elsewhere because of parallel trade and an increasing tolerance by the European Court of Justice in allowing products to be sold anywhere in the EU if

(See **Coordination**, *Page 3)*

Coordination, *from Page 2*

they are approved in one country, or even if a chemical version of that product is approved in one state.

In contrast, the FDA opposes parallel trade with Canada or other countries. Europe also has price controls and formularies and health technology assessments at the member-state level, which can add a lot of complexity. A company is not dealing only with safety, efficacy and quality, but also with cost-effectiveness and other economic factors.

On the other hand, EU regulators have some tools that are not available in the U.S., including:

- A lack of direct-to-consumer advertising;
- Mandatory patient package insert leaflets;
- Unit-of-use packaging;
- More common "behind the counter" OTC drugs;
- A possibility of marketing suspensions while safety concerns are investigated; and
- Trade association advertising code bodies that can regulate members.

In addition, the EMEA and the European Commission have a regulation for penalties for noncompliance with requirements. For example, if companies fail to include required information that results in a decision by the EMEA different from what would have been decided had all the information been required, there can be a penalty. There also could be penalties for refusal or failure to report adverse events and for a failure to do Phase IV studies that are a condition of authorization.

There also could be penalties for violation of marketing practices, including relationships with health professionals.

Article 84(1) of Regulation 726/2004 permits EU members to determine penalties. Article 84(3) of the rule permits the European Commission to impose financial penalties at the EMEA's request on holders of marketing authorizations if they violate certain requirements. Together, these articles could subject companies to fines, proceedings and penalties in EU member states and to infringement proceedings and penalties imposed by the Commission.

The regulation supplements authorities at the member-state level and also supplements the authority that the EMEA has had for some time to recommend the denial of approval of an application or the revocation of an application.

The monetary penalty would be most useful in a case where the EMEA couldn't — or didn't want to — take a product off the market but needed somehow to penalize the company because of some misconduct on its part. This is a way for the EMEA to hurt the company and its standing in the community without depriving patients of a product that they need.

EMEA, CHMP Are Significant Players in EU Pharma

The EMEA and CHMP are significant bodies within the EU. In general, the EMEA acts as a kind of risk assessment body while the European Commission is a risk management body in terms of writing regulations and issuing final decisions, directives and regulations. The European Parliament also is taking an increasing role in formulating policies to manage risk.

The EU member states have the authority to express themselves in a variety of ways on different levels. The most senior level is the European Counsel, which is the chief lawmaking body of the EU. After documents have gone to the Parliament, the European Commission often brokers the compromise. It is a complex legislative system, and it is important to keep in mind that there is not just a single body at work.

The European Court of Justice has become increasingly important for interpreting legislation.

(See **Players**, *Page 4)*

Players, *from Page 3*

It has been the most important determining factor in the area of regulatory exclusivity in generic products and when generics can reach the market. It also is hearing a series of cases on parallel trade that are keenly watched by the industry.

Other important groups include industry associations, companies, law firms and consultants. The FDA also is included because it has a special status in Europe, as does the World Health Organization (WHO). Many direct agreements and relationships exist between the European Commission and the EMEA on one hand and the WHO on the other. The FDA is frequently at the same meetings.

The European Pharmacopoeia is a child of the Counsel of Europe, not to be confused with the European Counsel. It has some 40 countries that are members of the Counsel of Europe and, therefore, have a seat at the European Pharmacopoeia.

The Pharmaceutical Inspection Cooperation Scheme (PIC/S) has served as the principal mechanism for cooperation among European member states in the area of pharmaceutical inspections. The FDA either has joined or is a participant. The European Commission views it as somewhat competitive.

Recent Regulatory Changes

Over the years, landmark laws were enacted in Europe that changed the landscape of pharmaceutical production. In the early 1960s, the enactment of Directive 65/65 was a response to the tragedies created by the drug thalidomide, which was found to cause severe birth defects. It has since been replaced by the Community Code on Medicinal Products.

Mid-2001 began a review process leading to the pharmaceutical package that was published in April 2004, including the Clinical Trials Directive.

A couple of key laws were approved in 2003, including Annex 1 to Directive 2001/83/EC, which dealt with the common technical document. This document also added requirements for biological medicinal products.

There had not been a great deal of distinction at the EU level between chemical drugs and biologic drugs. Some member states have long had such distinctions, but Annex 1 spells out the difference. It also includes a clarification of the coverage of gene therapy and somatic cell therapy, which has had quite an impact on a number of companies.

Key laws include the following:

- EMEA Regulation 2004/726/EC: Authorization and Supervision of Medicinal Products

(See **Players**, *Page 5)*

EDITORIAL ADVISORY BOARD

Mark Barnes
Executive Vice President and Chief Administrative Officer
St. Jude Children's Research Hospital
Memphis, Tenn.

John Hick, M.D.
Assistant Medical Director, EMS
Hennepin County Medical Center
Assistant Professor, Department of Emergency Medicine, University of Minnesota
Minneapolis, Minn.

Kenneth Kaitin
Director
Tufts Center for the Study of Drug Development
Tufts University
Boston, Mass.

Douglas Long
Vice President, Industry Relations
IMS Health
Totowa, N.J.

D. McCarty (Mac) Thornton
Partner, Health Practice Group
Sonnenschein Nath & Rosenthal
Washington, D.C.

Players, *from Page 4*

for Human and Veterinary Use and on the EMEA (replacing Regulation 2309/93/EC);
- Directive 2004/27/EC amending the Community Code on Medicinal Products for Human Use (Directive 2001/83/EC);
- Directive 2004/24/EC on traditional herbal medicinal products; and
- Directive 2004/28/EC amending the Community Code on Medicinal Products for Veterinary Use (Directive 2001/82/ED).

EMEA Offers Centralized or Decentralized Approval

The EU is a conglomeration of laws and regulatory bodies — some of which mesh nicely while others do not. Since the jurisdiction of the EMEA was expanded, approval decisions have become more centralized in the EU.

Whether a company chooses to pursue centralized approval for the EU as a whole or decentralized approval in one or more member states largely depends on the product involved and the company's marketing strategy.

Decentralized approval usually is sought for "me too" drugs or when a company, for whatever reason, wants to limit the markets in which it intends to offer a product. There is a mutual recognition procedure under the decentralized approval process in which member states may recognize a marketing authorization granted by another member state, referred to as the reference member state. If, for some reason, mutual recognition is not granted, companies can use an arbitration process controlled by CHMP, whose decision is legally binding.

Each path to approval also has its own characteristics. The decentralized approach requires several marketing authorizations and several trade names. It also enables a company to choose a reference member state and market. The final marketing authorization may take time, however, and a divergent opinion is possible. A centralized approach has only one marketing authorization, one trade name, one decision, one opinion and one marketing authorization for the entire EU.

Advantages and Disadvantages

The advantages of a decentralized approval process include the ability to pick markets, a familiar procedure and more access and flexibility. The disadvantages of this approach include long review periods, lack of member-state consensus, problems with mutual recognition, industry avoidance of arbitration procedure and lack of a single market.

A centralized approach, on the other hand, provides benefits including a 27-country market, efficiency and a high level of satisfaction. Its disadvantages include a restricted scope, review periods that can be long, a process viewed as heavy and bureaucratic and a risk that authorization may be denied.

The legislation seeks to strengthen the decentralized procedure and make it more difficult for member states to object to mutual recognition of products. It also seeks to make it more difficult for companies to pull their products out of a member state that makes demands the company doesn't want to meet.

The scope of centralized approval versus decentralized approval also is changing. As of November 2005, centralized review became mandatory for biotech drugs and biosimilar products, as well as for orphan drugs and an expanding list of innovative drugs for certain diseases.

Member States Authorize Products And License Production

A number of duties fall to the member states under EU law, including the approval and oversight of clinical trials. Member-state authorities also maintain national authorizations of products and license production of drugs within their territories. So companies

(See **Safety**, *Page 6)*

Safety, *from Page 5*

need to register each facility that produces a drug in each country. Member states also grant licenses for importation, including parallel importation, and this is becoming a very large category in some countries.

Under the EU's law governing drug approvals, commonly referred to as the Community Code, member states must license wholesalers and distributors. They also maintain overall surveillance and conduct inspections and enforcement. They regulate sales and promotional activities.

EU Laws in Each Phase of Development

Many other changes are taking place in an effort to help the EU keep a closer watch on safety during the drug development and trial stages.

In the preclinical development phase, the Good Laboratory Practice Directive is applicable. The Good Laboratory Practice Directive has been in place for a number of years, and the Organization for Economic Cooperation and Development is instrumental in organizing mutual joint visits among different European and non-European advanced economies, looking at animal testing principally.

During clinical development, the Clinical Trials Directive and ICH good clinical practices (GCPs) apply. The Clinical Trials Directive clearly is important at the clinical trial stage. Depending on what kinds of studies are needed and what the protocol should be to provide proof of concept, it often is necessary to look to the Community, regulations of the European Medicines Agency or guidelines coming out of ICH and other sources.

For marketing authorizations, manufacturers dealing with an EMEA situation need to review both the Community Code and the EMEA regulation to determine all rules with which they must

(See **Safety**, *Page 7)*

Risk Management and Drug Safety Summit

Building An Effective Global Risk Management and Drug Safety Program

Oct. 28–29, 2008 • National Press Club • Washington, DC

In this two-day event, you'll drill down to the core of what the global regulatory bodies expect now and in the future from top officials and industry leaders responsible for drug safety regulation and legislation. It's the one opportunity you'll have this year to come to the nation's capital and hear — straight from the source — how you can create world-class programs of your own.

Presented by **FDAnews** in conjunction with United BioSource Corporation and the Center for Medicine in the Public Interest, **Risk Management and Drug Safety Summit:** ***Building An Effective Global Risk Management and Drug Safety Program*** takes place Oct. 28–29, 2008, at the prestigious National Press Club in Washington, DC.

You'll be hearing presentations and interacting with Dr. Janet Woodcock, director of CDER; Rear Admiral Steven Galson, acting surgeon general of the U.S.; Claudia Karwoski, acting director, Division of Risk Management Team, Office of Surveillance and Epidemiology, CDER; and other outstanding industry leaders to dissect and debate how to create world-class risk management and drug safety programs.

Register online at: www.drugsafetysummit08.com

Or call toll free: (888) 838-5578 (inside the U.S.) or +1 (703) 538-7600

FDANEWS

Safety, *from Page 6*

comply. In some cases, there is explicit incorporation by reference, while in other cases, the EMEA rules are not clear about whether a requirement in the Community Code is applicable. There are a number of ambiguities that will have to be sorted out over the next few years.

GCPs Harmonized, Ethics Committee Role Expanded in Clinical Trials

A number of legal instruments, including a Good Clinical Practice Directive issued in March 2005, member-state laws and ICH's GCPs, have harmonized and tightened requirements for clinical trials in the EU. To complement this, the role of ethics committees has expanded, not just for reviewing informed consent documents but also for looking at risks and benefits.

There is now a database for clinical trials in Europe, partly due to drug safety concerns about forum shopping. European authorities didn't like the idea that a disappointed sponsor could pack up from one European member state and go to another and possibly get a clinical trial going.

As is true in the U.S., adverse events are of great concern. Whether suspected, unexpected or serious, adverse reactions must now be reported to the European Commission as well as the EMEA. This reporting provides a signal that a serious safety problem might exist with an investigational product so clinical trials can be terminated before people get hurt.

Member states have been implementing GCP audits, which is a new process for many European member states. The EMEA is playing a coordinating role between the GCP audit and the EU direct clinical trial database.

EU Market Authorization

The FDA and the EMEA deny that they are looking at drugs any differently than they did in the past, but there is a general feeling in the industry that after the crisis with Cox-2 inhibitors and other incidents, the agencies are taking a tougher stance on new applications. They are more likely to demand new data or put off a Prescription Drug User Fee Act review period or just take longer to make a decision. In Europe, conditional approvals are possible, but they are linked to additional requirements for safety testing. In addition, new penalty regulations will add teeth to present laws.

Like the FDA, the EMEA and member-state agencies are moving to a quality risk management process in the GMP area.

This is a dynamic area. Laws relating to marketing authorization contain some key elements: access, greater transparency and patient information. New provisions on transparency/patient information — this is a breakthrough in Europe, which had a tradition of secrecy in the past — include the following:

- Reason for withdrawal of a drug;
- Refusals of drugs;
- European Product Evaluation Reports;
- Rules of procedure;
- Database on drugs is being created;
- Database on clinical trials; and
- Pharmacovigilance opinions of CHMP.

The European authorities declined to adopt direct-to-consumer advertising for now. The issue is likely to come up again soon. Widespread access to the internet makes it unrealistic to think that consumers don't have access to information about prescription products.

Industry Invited to Comment on Amendments to Licensing Regulation

To cut through the red tape of what industry considers a burdensome regulation, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) asked for public comment on the European Commission's proposed changes to its centralized medicines legislation that deals with variations to licensed drugs.

(See **Licensing**, *Page 9)*

BARNETT EDUCATIONAL SERVICES

Data…Analysis…Trends…Industry Insights

Hot Off the Press…New Edition!

PAREXEL's Bio/ Pharmaceutical R&D Statistical Sourcebook 2008/2009

PAREXEL's Bio/Pharmaceutical R&D Statistical Sourcebook, 2008/2009 is a leading compendium providing new insights into trends that are reshaping the biopharmaceutical industry. Supported by thousands of graphs, illustrations, and analysis, the compendium provides the latest intelligence on every aspect of biopharmaceutical development—from product discovery to R&D performance and productivity to time-to-market trends.

Copyright 2008., 400+ pp., ISBN# 1-882615-87-5. Price: $425 (hardcopy) or $1,200 (single-user web access plus hardcopy)

With key analysis and contributions from leading consultancies and experts, the compendium provides real-world data and analysis, including:

- Emerging data on worldwide and company-specific R&D pipelines and product launch trends
- Drug approval statistics compiled from FDA, EMEA, and other regulatory agencies
- New and comprehensive analysis of the countries in which biopharmaceutical companies are locating clinical studies
- New global R&D spending trends and other international R&D data from key markets
- International statistics on drug development output
- And much more!

> "This is an incredibly useful and reliable resource for anyone connected to the pharmaceutical and biotech industries: marketers, financial planners, investors, or researchers."
>
> ***—Judy Blaine, Librarian***
> ***ArQule, Inc., Business Information Alert***

In response to customer demand, the 2008/2009 edition is once again available in electronic format. Gain instant access to the data, analyses, and insights provided in the hardcopy compendium on a fully searchable, hyperlinked and printable web-based edition!

The Largest Compendium of Drug Approval Performance Metrics Ever Compiled!

The US Drug Approval Trends and Yearbook 2008/2009

Finally a comprehensive source for the very latest performance metrics and trend analysis on every key aspect of the new drug approval process—**The US Drug Approval Trends and Yearbook 2008/2009**!

Copyright 2008, Approx 200 pp., ISBN# 1-882615-88-3. Price: $295 (Softcover)

Building on last year's widely read edition, the new 2008/2009 edition examines hundreds of key trends and metrics to provide industry with all-new benchmarks and metrics on which to assess their own performance, to plan their own R&D projects, and to assess the various drug approval options and strategies available to them.

The US Drug Approval Trends and Yearbook 2008/2009 provides an unprecedented number of in-depth analyses and benchmarks, including the following:

- NDA and NME first-cycle success rates, review outcomes, and trends
- Complete review and approval profiles for each NME and NDA, including cycles to approval, review times, and review outcomes
- Analysis of drug review times, review cycle outcomes and success rates by therapeutic category and standard vs. priority classification
- NDA and NME cycles to approval and review times
- The impact of priority review, fast track, accelerated approval, orphan drug status and related programs on review times and review outcomes
- Review outcomes, review times, and success rates for other key new drug submissions, including NDA resubmissions, efficacy supplements, and manufacturing supplements

Based on data compiled through internal studies, Freedom of Information requests to the FDA, and other public and private sources, our proprietary analyses will provide you with unique insights, benchmarks, and performance metrics in areas critical to the success of your R&D projects. We guarantee it!

Barnett International: A division of Cambridge Healthtech Institute, www.barnettinternational.com.
250 First Avenue • Suite 300 • Needham, MA 02494 USA • Phone: (800) 856-2556

CHI

www.barnettinternational.com

Licensing, *from Page 7*

The MHRA launched its public consultation following a vote by CHMP that favored amendments to streamline procedures and expand the scope of the Variations Regulation. The amendments must be reviewed and adopted by the European Parliament.

Directive 2001/83/EC, the human medicines legislation, provides detailed instructions on dealing with variations to the license of a drug product. Minor variations, such as a change of address, are classified as Type IA or IB. Changes in dosage or safety warnings are considered major variations, or Type II.

As written, the Variations Regulation (1084/2003/EC) applies only to marketing authorizations granted under EU harmonizing provisions — e.g., mutual recognition and decentralized and centralized procedures. It does not cover variations granted by EU member states as part of a national procedure. Thus, drug firms wanting to alter an aspect of a medicine authorized nationally in multiple member states can face an array of procedures.

Where it does apply, the regulation is considered by regulators and industry to be overly burdensome, the MHRA says.

The proposed revisions — part of the Commission's Better Regulation of Medicines Initiative — are intended to streamline existing variations procedures and expand the scope of the regulation to include national variations. "This would ensure that all medicinal products, regardless of the procedure under which they have been authorized, are subject to the same criteria for the evaluation, approval and administrative treatment of variations to licenses," the MHRA says.

Weighing in on the standing committee's approval of the amendments, the European Federation of Pharmaceutical Industries and Associations said, "Cutting the red tape will encourage industry to make continual improvements to existing medicinal products … [and] facilitate the submission and management of new data concerning authorized medicinal products."

Specific questions the MHRA wants to address through its consultation are:

- How extensive is public support for the commission's initiative?
- Will the scope of the proposed changes lessen the administrative burden on firms applying for national marketing authorizations?
- What are the potential savings and short-term or capital costs resulting from the new system?
- Assuming the revisions will result in cost and time savings, should the scope of the Variations Regulation be extended to purely national marketing authorizations?

EMEA Seeking Cooperation With FDA on Clinical Trial Oversight

The EMEA wants to improve coordination with the FDA and the WHO on supervising international clinical trials, the agency says in a summary of its 2008 work program.

Such coordination, the European agency says, "will result in reduced duplication of international inspections and contribute to the efficient use of inspection resources."

Ensuring that trials conducted outside the EU are conducted ethically will continue to be part of the agency's review process for initial marketing authorizations and will be reflected in its public assessment reports.

To further implement the EU Clinical Trials Directive, which was first imposed in 2004, the EMEA plans to:

(See **Oversight**, *Page 10)*

Oversight, *from Page 9*

- Develop and support clinical trial guidelines for the European Commission as a follow-up to the 2007 conference on the implementation of legislation in this field;
- Upgrade the European Clinical Trials database through the EU telematics project as the Clinical Trials Facilitation Group has called for;
- Make public more information on clinical trials, especially pediatric studies; and
- Establish a new procedure to provide advice on biomarkers.

The number of requests the agency receives for scientific advice and protocol assistance is likely to keep rising this year, as will appeals for advice on alternative clinical trial designs. The agency says it also expects to conduct more routine GCP inspections and special pharmacovigilance inspections than in previous years.

Eco-Risk Assessments Will Increase Time, Costs of Authorization in EU

Getting market authorization in the EU could take up to a year longer due to environmental risk assessment (ERA) requirements, an industry expert says.

The requirements, detailed in a December 2006 EMEA guideline, require firms to conduct an ERA as part of the process of registering new active pharmaceutical ingredients (APIs) or new uses of APIs that could increase environmental exposure to the compound.

The guideline targets APIs because they're designed to elicit a biological response at low concentrations. Amino acids, peptides, proteins and herbal medicines are exempt from the guideline.

The goal of the guideline is to reveal potential risks to wildlife from society's use of human medicines, Jennifer Saxe, founder of EcoSafety Sciences, an ecological risk and safety evaluation consulting firm, said at an FDAnews audioconference.

The EMEA "is concerned about low levels of pharmaceutical ingredients that go through the human body, through the sewer treatment plants and come out still active" in the environment. The guideline is not aimed at manufacturing plant effluence, Saxe said.

While ERA results may trigger a requirement for a special label or a risk-mitigation plan, they will not be used to deny approval of a drug. "It's a data collection method more than anything else," Saxe said. The intent is to collect data and make it available to regulators as they are considering what issues a particular drug may present.

(See **Eco-Risk**, *Page 11)*

Take the FDAnews Brand Awareness Survey and receive a complimentary report!

We know your time is precious. That's why, for just 5 minutes of yours, **FDAnews** will provide you with our best-selling ***Managing SAS Validation: Mastering the Five Critical Programming Obstacles*** management report as a way of saying thank you for your participation. And rest assured — all participant responses will be aggregated and kept completely confidential.

We appreciate your time and input. Please feel free to share this survey invitation with any of your colleagues whose you value.

Visit www.BrandAwarenessSurvey.com now to begin! Hurry — response intake ends on Oct. 15, 2008!

FDANEWS

Eco-Risk, *from Page 10*

Under the guideline, all APIs must complete a Phase I risk assessment. For APIs with an octanol-water partition coefficient greater than 4.5, a persistent, bioaccumulative, toxic (PBT) assessment must be done to evaluate long-term effects on ecosystems. If the API is a PBT, the firm must develop a mitigation proposal, Saxe said.

Firms also must test APIs to determine their predicted environmental concentration (PEC). If the PEC to predicted no environmental concentration (PNEC) ratio is less than one, no further environmental risk assessment is required, she said. A ratio of more than one will trigger a Phase II Tier A and possibly a Tier B assessment.

The 1 percent market penetration factor can be recalculated for APIs used for rare conditions, but any such request must be supported by published epidemiological data about the prevalence of the condition. "This modification will reduce the PEC in Phase I and Phase II and can be worthwhile even if a Phase II ERA is triggered," Saxe said.

To date, officials have been "pushing for nearly all compounds to go through a Phase II Tier A assessment," Saxe said.

The EMEA guideline lists seven recommended studies for Phase II Tier A evaluation: adsorption-desorption study, ready biodegradability, transformation in aquatic sediments, algae growth inhibition, water flea reproduction, fish early life-stage toxicity and activated sludge respiration inhibition. It also allows for the use of relevant data to demonstrate that the environmental risk is negligible. Saxe said officials generally have required firms to conduct all the studies and have not permitted them to offer relevant data.

For Phase II Tier B, firms must complete only the tests that correspond to criteria failed in Tier A, she said. Possible pathways are PEC refinement, a microbial effects study, PNEC refinement, sediment-risk assessment, bioaccumulation-risk assessment or terrestrial-risk assessment.

These tests can be time-consuming and expensive. The cost of studies required as part of a terrestrial-risk assessment, for example, can range from $7,000–$30,000 for a soil microorganism nitrogen transformation test to $80,000–$100,000 for a study of API transformation in soil.

Saxe advised firms to plan well ahead and to look for red flags that may indicate the need to begin the process even earlier. "My experience lately has been that a lot of the contract laboratories that do this are bogged down with work because of the new EMEA requirements, and sometimes it will take several months before your study is queued up and done," she said.

For a study that takes 100 days, the countdown can't begin until the study has queued up, she said, which means the turnaround time on a big study can be six months. There also is the possibility that test results may trigger additional tests.

For firms that began ERA studies too late, Saxe suggested running studies simultaneously — at the risk that some unnecessary tests may be conducted — or submitting an ERA with modeled results and providing the EMEA with full studies post-approval.

EMEA Sets Parameters for Bioequivalence Studies

Manufacturers may use a two-stage approach to demonstrate the bioequivalence of a drug and a reference product, provided the strategy is prespecified in the study protocol, a draft guideline by CHMP says.

(See **Bioequivalence**, *Page 12)*

Bioequivalence, *from Page 11*

Under the two-stage approach, an initial patient group is treated and the data is analyzed. If the first trial fails to demonstrate bioequivalence, a second group of subjects may be tested and the results of the two groups combined in a final analysis, the guideline says. The protocol must specify the adjusted significance levels to be applied to each of the analyses and appropriate steps taken to maintain the overall error rate of the study.

The guideline is aimed at bioequivalence for immediate-release dosage forms with systemic action and details when studies are needed and how they should be designed, conducted and assessed.

While bioequivalence is crucial to approval of generic drug applications, it also can be useful in evaluating hybrid applications, extensions and varying formulations used in development of a drug containing a new chemical entity, CHMP says.

According to the draft, the number and design of the studies is determined by the pharmacokinetic and physiochemical properties of the drug and should take into consideration "linearity in pharmacokinetics, activity of metabolites, contribution of metabolites to the effect, the need for a type of chemical analysis called enantioselective, and solubility of the active substance." All bioequivalence studies conducted must be included in the application for marketing authorization, regardless of outcome, the guideline adds.

The guideline also recommends acceptance limits for demonstrating bioequivalence. A 90 percent confidence interval for the ratio of test and reference products should kept within the acceptance interval of 80 percent to 125 percent, the draft says.

Equivalence for substances in which rapid absorption is important should be demonstrated by bioequivalence for partial AUC as a measure of early exposure, with the same acceptance interval as for Cmax, the guideline says. In cases of drugs with a narrow therapeutic range and for highly variable drugs, the acceptance interval may require tightening or widening, respectively, it adds.

The guideline also discusses the possibility of using in vitro tests instead of in vivo studies for quality control purposes. The parameters for the in vitro dissolution should be based on the dissolution profile of the test product batch that was shown to be bioequivalent to the reference product, the guideline says.

"Appropriate in vitro dissolution should confirm the adequacy of waiving additional in vivo bioequivalence testing" the guideline says, noting that dissolution should be analyzed at different pH levels and dosage form taken into consideration in determining how to conduct the study. Manufacturers should demonstrate the similarity of the in vitro dissolution in all situations within the applied product series and between additional strengths of the test substance and reference product, the guideline says.

The deadline for comments on the draft guideline is Jan. 31, 2009. It can be accessed at www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf.

FDANEWS

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

Editor: Lauren Lentini
(703) 538-7663
llentini@fdanews.com

Ad Sales: Andrew McSherry
(703) 538-7643
amcsherry@fdanews.com

Content Sales: Alka Desai
(703) 538-7669
adesai@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.fdanews.com

Reporters: Martin Gidron, Christopher Hollis, Elizabeth Jones

President: Cynthia Carter; **Publisher:** Matt Salt; **Editorial Director:** David Grant; **Executive Editor:** Theresa Barry

Copyright © 2008 by Washington Business Information Inc. All rights reserved. **The Food & Drug Letter** *(ISSN 0362-6466), an in-depth analysis of regulations and issues affecting the pharmaceutical and biologics industries, is published biweekly, 24 issues, for $1,245. Photocopying or reproducing in any form, including electronic or facsimile transmission, scanning or electronic storage is a violation of federal copyright law and is strictly prohibited without the publisher's express written permission. Subscribers registered with the Copyright Clearance Center (CCC) may reproduce articles for internal use only. For more information, contact CCC at www.copyright.com or call (978) 750-8400. For site licenses for multiple users or to purchase multiple copies, contact Content Sales Manager Alka Desai at (703) 538-7669.*