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PAHO Developing Common Vaccine Licensing Requirements

A Pan American Health Organization (PAHO) working group will meet with stakeholders late next month in Washington, D.C., to finalize harmonized requirements for licensing vaccines in the Americas.

The Pan American Network on Drug Regulatory Harmonization (PANDRH) Vaccines Working Group developed a proposal during a series of meetings beginning in 2005. The document is intended to achieve greater harmonization in the information submitted in marketing authorization applications for vaccines.

The draft consists of five modules, based on the International Conference on Harmonisation's common technical dossier format and adapted specifically for authorization of vaccines. It also includes recommendations by the World Health Organization on the production, control and nonclinical and clinical testing of vaccines. The five modules are:

- Administrative and legal information;
- Summaries;
- Quality information (chemical, pharmaceutical and biological);
- Nonclinical information; and
- Clinical information.

A public consultation on the proposal resulted in about 25 comments, mostly favorable, Maria de los Angeles Cortes, PAHO regional advisor on vaccines and biologics, told *IPRM*. The September meeting — which will include representatives from industry, regulatory agencies and independent organizations — will address concerns expressed during the consultation period.

A draft guideline on preparing applications under the harmonized system was prepared in conjunction with the proposal. Cortes hopes to see the two documents approved when the PANDRH meets in Argentina in November and then published by the end of the year.

Having harmonized requirements for vaccine licensure could lead to mutual recognition agreements among countries in Latin America and Canada and "facilitate access to vaccines of quality," she said.

Health Canada co-sponsored the working group's third meeting during which the first drafts of the document and guideline were developed and helped translate the documents into English and French. Alastair Sinclair, a

Health Canada spokesman, said the effort should produce a "faster approval process of vaccines across the Americas" and lead to a more efficient use of technical and financial resources.

The U.S. Food and Drug Administration was invited to participate in the initiative but was prevented from doing so by scheduling conflicts, Cortes said.

"Proposed Harmonized Requirements for Licensing of Vaccines in the Americas" is available at www.paho.org/English/AD/THS/PANDRH_Proposal_01_21_03_2008-Eng.pdf. The draft guideline can be accessed at www.hc-sc.gc.ca/ahc-asc/alt_formats/hpb-dgps/pdf/intactiv/2008-paho-ops-guide-eng.pdf. — Meg Bryant

API Facilities First Target of FDA-EMEA Joint Inspections Program

Regulators worldwide are poised to start a new pilot program for inspecting drug production facilities, beginning with plants that manufacture active pharmaceutical ingredients (API).

The U.S. Food and Drug Administration (FDA), European Medicines Agency (EMEA) and Australia's Therapeutic Goods Administration will jointly plan and conduct inspections of API sites. If successful, the program will be expanded to other types of facilities, such as finished-dose manufacturing plants.

"Through this new collaboration, FDA and these trusted colleagues can spread our inspection net wider by leveraging our respective resources. We will be inspecting some, the Australians others, the European Union still others. We will then share information," U.S. Health and Human Services (HHS) Secretary Michael Leavitt said at the Import Safety Summit.

Leavitt said the program was part of the Bush administration's Interagency Import Safety Action Plan (*IPRM*, December 2007).

"Historically, U.S. authorities have primarily relied on intervening at the border to intercept unsafe goods. The new strategy calls for actively working with trading partners to help ensure they build quality into every step of a product's life cycle, targeting critical points where risk is greatest and focusing attention and resources on these areas," HHS said.

Earlier this year, the EMEA announced the joint inspection initiative (*IPRM*, June 2008). Following a meeting of the Transatlantic Economic Council in May, the EMEA said it and the FDA would exchange inspection schedules and results as well as share information on previously inspected sites to get greater inspection coverage and better identify API production sites in countries outside the U.S. and the EU.
— Christopher Hollis

Chinese Drug Oversight Strong, SFDA Says

The Chinese government has reinforced its efforts to establish a nationwide system for monitoring drug-related adverse events, the State Food and Drug Administration (SFDA) says.

Approximately 400 adverse drug incidents per million population were reported last year in China via a network of 200 centers in 31 provinces and more than 97,000 drug safety coordinators. As of June, drug administration departments had issued 13 bulletins detailing events associated with 44 types of drugs, the agency says in a white paper it recently released.

The paper, "Status Quo of Drug Supervision in China," provides an overview of recent improvements in regulatory oversight and the current Chinese market for pharmaceuticals, traditional medicines and medical devices. Available in English on the SFDA website, the report is an effort to reassure foreign companies and regulatory authorities that the SFDA is running a tight ship following the rash of safety issues it confronted a year ago. The document also suggests an increasing transparency in how the SFDA conducts business.

"The state has been steadily increasing its financial investment into drug safety supervision, with the emphasis on improving the drug safety testing level and ability, and providing technical support for the drug safety supervision work," the report says.

The SFDA oversaw sampling of 7,398 batches of chemical drugs and 2,586 batches of antibiotics last year with an acceptance rate of 98 percent and 98.1 percent, respectively, the report says.

It also touts China's increasing commitment to strict regulatory control of pharmaceuticals, citing the promulgation of 17 administrative regulations, 15,000 national drug standards and 54 technical research guidelines. Quality standards for drug research also have been strengthened, the report says.

Since January 2007, all nonclinical drug safety research has been conducted in good laboratory practice-certified laboratories. Good clinical practice (GCP) was initiated in 2004. By the end of last year, 178 institutions doing clinical trials had obtained GCP certification, the report says.

However, the report notes some difficulties and problems remain. It cites the need to improve drug production methods, reform the drug safety administration system, improve R&D capabilities in the industry, and prevent and manage drug risks.

China produces 1,500 types of drug substances and more than 1 billion doses annually of vaccines targeting 26 viruses and pathogenic bacteria, according to the report. Between

1998–2007, pharmaceutical exports increased from $3.4 billion to $24.6 billion, and imports grew from $1.5 billion to $14 billion, the report says.

The white paper is available at eng.sfda.gov.cn/cmsweb/webportal/W43879541/A64028182.html. — Meg Bryant

To view the full text of this document, click here.

MHRA Tightens Scrutiny of Web Advertising of Rx Drugs

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) has issued a draft guidance aimed at discouraging online promotion of prescription medicines to the general public.

The guidance, issued July 11, applies to all consumer websites registered in the UK or aimed at a UK audience that provide services that may result in the prescription and supply of a prescription-only medicine (POM). Examples are sites that offer information on erectile dysfunction and wrinkle treatments.

Prohibitions include icons or other features encouraging consumers to purchase a specific prescription drug, prices and links for specific POMs.

Visitors to the website should be advised they are getting a medical consultation. The person's doctor must decide whether any treatment is prescribed. "Further pages about the condition which the consumer chooses to access may contain information on specific medicines provided this is presented in the context of an overview of the treatment options," the draft says.

While websites are barred from promoting specific POMs, they may include nonpromotional materials such as the UK website of the company marketing the product or a patient information brochure, the MHRA says.

Websites that fail to comply with the agency's advertising regulations risk being shut down, the MHRA warns.

Comments on the draft guidance are due Sept. 30. It can be found at www.mhra.gov.uk/Publications/Regulatoryguidance/Medicines/Guidancenotes/CON020623. — Meg Bryant

Pilot Program May Ease Transition to U.S. FDA Mandatory eRegistration

The U.S. Food and Drug Administration (FDA) is launching a voluntary pilot program for drugmakers to electronically file establishment registration and drug listing information as a step toward requiring electronic submissions next year.

The program is designed to help manufacturers transition from the paper-based system to electronic submissions and to test the FDA's electronic system. The agency said it will end the transition period June 1, 2009, when it will only accept electronic files for the registration and listing information.

The pilot program represents the first time electronic filing will be available for pharmaceutical manufacturers, the FDA said. The FDA Amendments Act, passed last year, required that this data be submitted electronically unless a waiver is granted.

A draft guidance and accompanying technical documents explain which registration and listing information to submit and describe how to electronically create and submit structured product labeling (SPL) files.

The FDA is adopting the use of XML files in SPL format as the standard for the registration and listing information. Complete, properly submitted SPL files can be processed in minutes, the guidance notes.

The pilot is a big step in the agency's efforts to transition to an all-electronic environment, Randy Levin, director for health and regulatory data standards, said during a recent FDA conference call.

Electronic filing is expected to help the agency more rapidly identify safety issues and respond to emergencies, such as recalls and drug shortages, the FDA says. It also will improve surveillance for serious adverse drug reactions, inspection of manufacturing facilities and monitoring of imported drug products, according to the guidance.

The information will be used by healthcare practitioners, healthcare payers and patients and will improve public access to product-labeling information, the FDA says.

The agency issued a proposed rule in August 2006 requiring electronic submission of registration and drug listing data. It also made changes to the National Drug Code (NDC) system and required appropriate NDCs on drug labels (*IPRM*, September 2006).

The guidance explaining the new pilot program is one in a series to assist companies making regulatory submissions electronically. The FDA says it will regularly update guidance documents on electronic submissions to reflect evolving technology and user experience.

The draft guidance is available at www.fda.gov/cder/guidance/OC2008145(2).pdf, and related technical documents are available at www.fda.gov/oc/datacouncil/spl.html.
— April Astor

Document Coaches Japanese Reviewers on Evaluating New Drugs

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) has developed a detailed guide for agency reviewers on points to consider in assessing new drug applications.

The PMDA says the document, recently posted in English on the agency website, is intended to "promote an understanding" among the review staff of the basic principles and primary issues to consider during the evaluation process.

The basic principles include the need to facilitate communication with applicants, to grasp domestic and international trends associated with the product's review and to consider earlier studies of similar drugs and the new scientific findings. Review reports are to be written in a manner that promotes greater transparency, the PMDA says.

Decisions to approve or not approve a drug should be based on pharmaceutical law and the following five points:

- Reliability of studies and documents submitted;
- Efficacy in the study population compared with that of the placebo group;
- Clinical significance of the study results;
- Risk-benefit ratio; and
- Quality assurance of the manufacturing process.

A range of additional issues — such as study design, data reliability, efficacy in different ethnic groups, and noninferiority or inferiority of the new drug against an active control — that should be considered also are described in the document.

The PMDA recommends that efficacy be confirmed in two or more randomized controlled studies, including dosing studies. Noninferiority studies may be required to clarify the use of the drug with respect to existing drugs when its clinical significance isn't clear from the studies, the agency says.

The document includes a checklist summarizing the points to consider during a new drug evaluation.

"Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug" can be accessed at www.pmda.go.jp/english/services/reviews/file/points.pdf. — Meg Bryant

To view the full text of this document, click here.

Saudi Arabia Proposes New Framework for Authorizing Drugs

The Saudi Food and Drug Authority (SFDA) is seeking public comment through Oct. 15 on a draft regulatory plan for drug approvals.

The 96-page document describes the requirements for marketing authorization and how to submit a drug application. It also gives the steps required to renew an authorization and approve variations and clinical trials. Application forms are included.

The proposed framework coincides with SFDA plans to require drug manufacturers and importers to obtain marketing approval and a license from the national registry beginning next year.

Performance targets have been set for each type of authorization. For example, the goal for approving a new chemical entity is 295 days, 165 days for a generic drug and 295 days for a biologic agent. An expedited 90-day period has been established for orphan products.

The processing time includes pricing, which is set by the Pricing Committee, according to a formula. The clock will stop if clarification or additional information is required from the company and resume once that is received, the document notes.

The document discusses two types of variations — Type I (notifiable change) and Type II (supplement to the marketing authorization). In both cases, the product file will be assessed ahead of time to ensure the information complies with SFDA requirements and guidelines. For Type I variations, a review staff will evaluate the application and approve or reject it. Type II variations may require additional assessment and testing before a product license is approved, the document says.

Authorizations of clinical trials involve a two-step process: protocol approval and product evaluation. Once the protocol is approved, firms with drugs that haven't been registered in Saudi Arabia must submit the product file for quality and safety reviews. The agency's time frame for protocol approval is 45 days and 140 days for the product assessment.

All applications should be submitted online. Firms also should provide hard copy and CD or DVD versions of the product file, the document says. Both copies should be in the common technical document format.

The SFDA plans to develop guidance documents and standard operating procedures for the various data requirements outlined in the draft framework.

The proposal, "Regulatory Framework for Drug Approvals," is available at www.sfda.gov.sa/NR/rdonlyres/F0897D32-3CEC-4679-BF3F-68CBFBFEFB66/0/RegulatoryFrameworkforDrugApprovalsv7.pdf. — Meg Bryant

Local Expertise Can Smooth the Way For Clinical Trials in India

As more drug companies look to India as a site for clinical trials, the value of local expertise in understanding the regulatory environment and avoiding delays can't be overestimated, an industry expert says.

"Choosing a strong partner with true local knowledge can be the difference between success and failure," Dan McDonald, vice president of business strategy at Excel Life Sciences, told a recent FDAnews audioconference. He advised sponsors to choose a partner with contacts at the Drugs Controller General India (DCGI) and other relevant regulatory agencies.

While recent improvements in its regulatory climate have put India on a par with many mature markets for clinical trials, complexities still exist, requiring a strong understanding of regulations and DCGI expectations to avoid hurdles and delays, McDonald said.

The benefits of conducting trials in India include a large patient pool, a well-respected physician base, a cost-effective climate, an increasing market for patent-protected therapies and a strong market and supply chain infrastructure, he said. In overall attractiveness as a destination for clinical trials, using the U.S. as the benchmark, India ranked second behind China in 2006.

Before beginning clinical trials in India, sponsors are required to complete a Form 44 to get clinical trial approval. This form summarizes the trial and includes both the sponsor's information and clinical protocol. It is submitted to the DCGI and the Directorate General of Foreign Trade. Sponsors also must assure both agencies that the institutional review board (IRB) is current and belongs to the institution conducting the study. They must agree to immediately report any changes to the trial to the DCGI, Vijai Kumar, Excel Life's president and chief medical officer, said.

Clinical studies cannot begin until the sponsor receives a letter from the DCGI approving the trial and permitting importation of the drug study substance.

Indian trials fall into two categories: Category A and Category B. Category A trials are global studies with India as a location; they must first be approved by the U.S. Food and Drug Administration (FDA), the European Medicines Agency or another International Conference on Harmonisation region such as Japan. Trials in this category typically take four to six weeks to approve, Kumar said.

For Category B trials, India is the sole site for a proof-of-concept study of a drug discovered elsewhere with the intention of marketing it in India and developing countries, he said, adding the time frame for approval is 12–16 weeks. By contrast, the average time to get approval for a clinical trial in China is 12 months, he noted.

For either category, the study document should include the proposed protocol, case report forms, the investigator's brochure, informed consent forms in English, dosing information, ethics committee approval, and previous safety and efficacy data for the product, Kumar said. In addition, sponsors should note the total number of patients to be enrolled globally, number of patients and sites in India, names of other countries and investigator sites and details of biological samples to be exported to control laboratories.

The FDA historically has accepted "up to 40 percent of patients coming from India" for a new drug approval on a global study, Kumar said.

Sponsors must get approval from both the IRB and DCGI for changes in the study protocol, the number of patients recruited, and inclusion and exclusion criteria. Other changes, such as adding trial sites or switching investigators, require simple notification to the DCGI, he said.

Most IRBs in India are site-specific, but central IRBs do exist to support institutions that don't have their own review board. About 80 percent of the IRBs are affiliated with teaching hospitals.

McDonald advised firms to know their IRB meeting schedules, noting that some may go three months between meetings. "IRBs in India don't meet as frequently as IRBs in the U.S., and this requires some advance planning" to avoid disruptions and other problems, he said.
— Meg Bryant

Czechs Outline Import of Controlled Substances for Clinical Trials

Manufacturers who plan to conduct clinical trials of narcotic or psychotropic drugs in the Czech Republic must first obtain an import authorization, according to rules posted last month on the website of the State Institute for Drug Control (SUKL).

Applications for import authorization can be made through a wholesaler who already has permission to handle the drugs or by a Czech-based representative of the foreign sponsor. A fee of CZK 1,000 (U.S. $60) is assessed on all such transactions.

The application must include the following information:

- Pharmaceutical form;
- Strength;
- Package size;

- Full name of the narcotic or psychotropic substance; and
- Number of packages of placebo, if applicable.

Import authorizations are granted for six months but may be issued for a shorter period at the sponsor's request, the agency says. Firms must submit monthly reports to the Inspectorate of Narcotic Drugs and Psychotropic Substances on the status of the imported products.

In order to return unused products or redistribute drugs from the Czech Republic to other foreign trial sites, an export authorization must be obtained, SUKL says. For redistributions, sponsors must have permission from the competent authority of the third country before an export authorization will be granted.

"Without these documents, the narcotic drugs and psychotropic substances cannot move between countries, even within the EU," SUKL says. Monthly reports are required for exports as well. — Meg Bryant

Some Phase I Drugs May Be Exempt From GMP Requirements

After withdrawing a final rule more than two years ago to exempt investigational drugs in Phase I testing from certain good manufacturing practice (GMP) regulations, the U.S. Food and Drug Administration (FDA) is issuing another final rule that will do just that.

The new rule, which amends the GMP regulation with the same language as the withdrawn rule, was published recently in the *Federal Register*. Slated to take effect Sept. 15, it will apply to small-molecule drugs and biologics, including vaccines and gene therapy products.

"FDA's position is that the United States' [GMP] regulations were written primarily to address commercial manufacturing and do not consider the differences between early clinical supply manufacture and commercial manufacture," the agency says.

For example, the requirements for a fully validated manufacturing process, rotation of stock for drug product containers, repackaging and relabeling of drugs, and separate packaging and production areas need not apply to investigational drug products made for use in Phase I trials, the agency says.

The original final rule exempted Phase I investigational drugs from GMP regulations covered under 21 CFR 211, but the agency withdrew it under pressure from groups as varied as Public Citizen, the Biotechnology Industry Organization and the Parenteral Drug Association.

Under the new regulations, drugs manufactured for Phase I clinical study are exempt from the GMP requirements under 21 CFR 211 if such products are not marketed or are not being studied in Phase II or III testing.

However, the rule would require such products to be made under conditions that meet "statutory GMP" rules, the FDA says. To ensure Phase I drugs are suitable for human use, the agency stresses its authority to regulate them under INDs, which contain sections on chemistry, manufacturing and controls.

"In addition to the authority to put an IND on clinical hold or terminate an IND, FDA may initiate an action to seize an investigational drug or enjoin its production if its production does not occur under conditions sufficient to ensure the identity, strength, quality and purity of the drug, which may adversely affect its safety," the agency says.

While noting this rule is intended to streamline the drug development process, the agency says it will help promote simple, innovative and less expensive approaches to complying with statutory GMP requirements.

The FDA estimates sponsors that make their own drugs for Phase I study could realize substantial savings in areas such as testing and analysis of components and in-process materials, which range from $50–$1,200 per component tested.

Another benefit for sponsors is that use of standard operating procedures and methods validation might be greatly reduced. "We estimate that large drug manufacturers that manufacture in-house investigational drugs used in Phase I clinical trials could potentially save between 24 to 40 hours per IND," the agency says.

In connection with the final rule on Phase I drug GMPs, the FDA issued a guidance recommending approaches to satisfy statutory GMP requirements for such drugs.

"During product development, the quality and safety of Phase I investigational drugs are maintained, in part, by having appropriate [quality control (QC)] procedures in effect," the guidance states. "Using established or standardized QC procedures and following appropriate cGMP will also facilitate the manufacture of equivalent or comparable IND product for future clinical trials as needed."

Having well-defined written procedures, adequately controlled equipment and production environments, and accurate and consistent manufacturing data are ways sponsors can comply with GMPs for Phase I drugs, the guidance says.

The FDA recommends a systematic evaluation of the manufacturing setting that includes an assessment of the product environment, equipment, process, personnel and materials. It also encourages actions to mitigate potential hazards to ensure the quality of the drug.

More information on the final rule is available at www.fda.gov/OHRMS/DOCKETS/98fr/oc07114.pdf. The guidance, "CGMP for Phase I Investigational Drugs," can be found at www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2005-D-0157-gdl.pdf. — Christopher Hollis

To view the full text of these documents, click here.

U.S. FDA Offers Guidance on Trial Design for IGIV Products

A statistical demonstration of a serious infection rate of less than one per person-year is adequate to provide substantial evidence of efficacy in clinical trials of investigational human immune globulin intravenous (IGIV) products, the U.S. Food and Drug Administration's (FDA) Center for Biological Evaluation and Research (CBER) says.

According to a new guidance, which finalizes a draft guidance released in November 2005, sponsors of IGIV products may be able to run pivotal clinical trials using various types of designs.

IGIV products are used as replacement therapy for primary humoral immunodeficiency. They are prepared from large pools of plasma collected from numerous individual healthy donors, so they contain antibodies against many infectious agents.

At an FDA Blood Products Advisory Committee meeting in 1999, the agency suggested a pivotal trial design using a prospective, randomized, double-blind, parallel, positive control, noninferiority study in 80 subjects with a documented history of primary humoral immunodeficiency in which the safety and efficacy of the test product would be compared with that of a U.S.-licensed IGIV product. Sponsors were advised to evaluate efficacy by comparing the serious infection rate in each group over a year's time.

Since then, CBER has determined that other approaches may work. For example, it suggested alternative clinical trial design proposals involving testing in fewer subjects in an open-label, single-arm trial compared with a statistically modeled historical control might be sufficient to provide evidence of safety and efficacy.

The guidance outlines how sponsors are to conduct pharmacokinetic studies to describe the distribution, metabolism and elimination of IGIV products for a biologic license application (BLA). Data from the studies would help determine the optimum dosing schedule and provide a basis for historical comparison between the investigational IGIV product and licensed IGIVs.

CBER recommends that sponsors obtain pharmacokinetic data from at least 18–20 adult subjects with primary humoral immunodeficiency, regardless of prior treatment. The guidance also details how to conduct pharmacokinetic studies in children.

To capture adverse events that occur with a frequency of 10 percent or more, CBER advises sponsors of IGIV trials to study a minimum of 30 subjects at the highest dose to be recommended in the product's labeling.

The guidance stresses the need for protocols to define and capture all adverse events associated with the use of the product regardless of whether the investigator thinks the event is product-related. The protocol should define criteria for determining whether an adverse event is temporally linked with an infusion. Adverse events should be listed individually by body system with subject identification numbers. The numbers of events that occur within one hour, 24 hours and 72 hours following infusion of the test product should be tallied separately.

For safety reasons, the protocol should provide explicit directions for starting and adjusting infusion rates, including the time frames for incremental changes and the size of infusion rate increments.

CBER considers real-time subject diaries to be important source documents for complete adverse event data. Sponsors are advised to provide an explanation for discrepancies between diary entries and case report form entries made by the clinical investigator, subinvestigators or other staff.

CBER discourages premedication in clinical trials designed to evaluate the safety of biologic products, except when subject safety is at stake. In such instances, sponsors should keep records of the use of any premedications and their possible impact on the study data, and evaluate their possible impact in the final study report, the guidance says.

To evaluate the efficacy of an investigational IGIV, CBER recommends that clinical trials compare the frequency of serious bacterial infections among patients taking the test product regularly with a historical standard or a control group over a year's time to avoid seasonal biases. Sponsors also are advised to:

- Discuss plans for pediatric studies with the reviewing division at the investigational new drug (IND) stage;
- Prospectively provide specific diagnostic criteria for each type of serious infection to be included in the primary efficacy analysis in the protocol. "Diagnostic criteria should not be overly restrictive so that you capture all infections of interest. Clinical investigators at different sites should use uniform diagnostic criteria," CBER says;
- Prospectively define the study analyses in the protocol. CBER expects the data analyses presented in the BLA to be consistent with the analytical plan submitted in the IND;

- Enroll about 40–50 subjects;
- Provide in the BLA descriptive statistics for the number of serious infection episodes per person-year during the period of study observation, a frequency table giving the number of subjects with serious infections, a description of each serious infection and summary statistics for the length of observation of each subject; and
- Obtain and analyze secondary endpoints, including candidate surrogate efficacy endpoints.

The guidance can be accessed at www.fda.gov/cber/gdlns/igivimmuno.htm. — Martin Gidron

To view the full text of this document, click here.

Global Clinical Data Interchange Should Improve With Launch of CDASH

The first version of the Clinical Data Acquisition Standards Harmonization (CDASH) initiative will be available for clinical research by early next month, enabling trial sites to follow incompatible standards used by different sponsors.

CDASH is an initiative of the Clinical Data Interchange Standards Consortium (CDISC), a global nonprofit organization whose goal is to promote interoperability. The organization's Study Data Tabulation Model (SDTM), a standard used for regulatory submissions, has been adopted by industry, Bron Kisler, CDISC's director of terminology and strategic alliances, said at the Drug Information Association's annual meeting.

The U.S. Food and Drug Administration (FDA) requests that drug companies use SDTM for esubmissions; that standard will be aligned with CDASH, Kisler added.

After finalizing CDASH Version 1.0, CDISC plans to develop training programs, deliver presentations at industry meetings and seminars, collect feedback and add and update SDTM domains as needed, he said.

CDASH is intended to resolve what project director Rhonda Facile called "the investigators' plight: a plethora of data formats and conventions, which are inefficient, multiply the potential for error and make data sharing and mining impossible." The goal is a single set of standards for such information as element names, definitions and metadata, starting with safety standards.

CDASH was developed in response to the FDA's Critical Path Opportunity No. 45 as a way to streamline data collection at investigative sites. The first version is available at www.cdisc.org/standards/cdash/cdraft.html.

"In the past few years, FDA has become a standards-based organization," Armando Oliva, deputy director for bioinformatics at the FDA's Office of Critical Path Programs, said at the conference. "There are tremendous benefits for everybody."

For the FDA, the advantages include higher-quality submission specifications and harmonization across divisions and centers. For industry, the advantage is that "everyone can influence the final outcome to make sure it meets business needs," Oliva said.

The agency also supports Health Level 7 standards for structured product labeling, individual case safety reports and regulated product submissions, he noted.

The CDASH initiative started with SDTM and focused on the content of case report forms (CRFs), Paul Bukowiec, director of statistical programming at Millennium Pharmaceuticals, said. Volunteers were asked to collect sample CRFs from their companies and evaluate their similarities and differences. The aim was not to develop actual CRFs but to create metadata tables to standardize content.

While the FDA does not design or use CRFs, it is interested in seeing them improved because it audits them and uses the data contained in them, Oliva said. For eCRFs, the FDA standard is Adobe PDF files, but these are not ideal because of variability in the way they format information, especially audit trail data. CDISC's Operational Data Model would fit the bill, but it is still in development, Oliva said.

The FDA will continue to support efforts to standardize clinical data, especially esubmissions, Oliva said. Down the road, clinical research could be done through electronic health records, which could contribute to postmarketing safety data, he added.

The agency discusses esubmissions in its Study Data Specification guidelines, which were updated last year and are available at www.fda.gov/CDER/regulatory/ersr/Studydata.pdf. — Martin Gidron

MHRA Seeks Input on ATMP Exemption Plan

The Medicines and Healthcare products Regulatory Agency (MHRA) wants industry input on the UK's proposed exemption plan for advanced therapy medicinal products (ATMP) that are prepared on a case-by-case basis and used in a hospital according to a prescription for a specific patient.

The European Council adopted its regulation of new medical products based on genes, cells and tissues May 31, 2007, following approval by the European Parliament (*IPRM*, June 2007). The ATMP regulation, which takes effect Dec. 30, lays the groundwork for a single, harmonized regulatory framework for those products in the EU.

Under the UK's exemption scheme, traceability, quality and pharmacovigilance of ATMPs must be equal to those requirements

authorized under the centralized procedure. The MHRA says the hospital exemption proposals concerning those issues, as well as patient information and ethics, also should apply to ATMPs prepared as "specials." Specials are national arrangements set up under a derogation in Article 5.1 of Directive 2001/83/EC.

The UK proposal would require reporting of adverse events but not periodic safety update reports as they would be hard to conduct on products manufactured on a nonroutine basis, the MHRA says in a consultation released last month.

The agency would retain the right to request a risk management plan for an ATMP. "Initial consideration of the need for such a plan would be instigated at the point that a manufacturer's license is sought to operate under the exemption and would reflect the nature of the proposed activity," the MHRA says.

The agency proposes that the manufacturer would be responsible for traceability of ATMPs under the hospital exemption. When the manufacturer is not the hospital, defined responsibilities for the hospital administering the product should be in place, the MHRA says.

Firms seeking a license to manufacture ATMPs would be encouraged to consult with the MHRA to ensure they apply under the appropriate scheme.

The MHRA also suggests amending the advertising provisions relating to "specials" to permit circulation of price lists but not advertisements of specific products. The change is in line with proposed requirements for advertising under the UK's hospital exemption for ATMPs.

The consultation on ATMPs can be accessed online at www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON020714. — Meg Bryant

Application Fees to Increase For Fiscal 2009

The U.S. Food and Drug Administration (FDA) has increased its user fees for drug applications by about 6 percent for fiscal 2009 under the Prescription Drug User Fee Act (PDUFA).

The new rates will be in effect Oct. 1 through Sept. 30, 2009.

Applications requiring clinical data will have a fee of $1,247,200, according to the FDA notice published in the Aug. 1 *Federal Register*. Applications not requiring clinical data and supplements requiring clinical data will have fees of $623,600.

The establishment fee for fiscal 2009 will be $425,600. The FDA estimates that 35 establishment fee waivers will be made — the same as this year — with 10 waivers coming from the orphan drug exemption in the FDA Amendments Act, which reauthorized PDUFA. Establishment fees are assessed annually for each establishment that manufactures a prescription drug.

The product fee for fiscal 2009 will be $71,520. The FDA estimates that 2,450 products will be billed for product fees. Just as for fiscal 2008, the FDA estimates that 70 products will receive waivers or reductions next year, including 30 exemptions from fees for orphan drugs.

As in previous years, revenue from each of the three fee categories will provide one-third of all fee revenue, according to the FDA. The total drug fee revenue for fiscal 2009 is projected to be $510.67 million after adjustments for inflation and workload charges — an 11 percent increase from the $459.41 million the agency expected to collect this fiscal year (*IPRM*, November 2007).

Congressional criticism of PDUFA has been growing. Rep. Maurice Hinchey (D-N.Y.) called it "a big fat mistake that needs to be corrected" and "an open invitation to corruption" during February hearings before the House Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, which funds the FDA.

The PDUFA budget includes $35 million in user fees for drug safety in fiscal 2009 compared with $25 million in the current fiscal year.

The FDA's notice on prescription drug user fee rates can be seen at www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-N-0427-n.pdf. — Martin Gidron

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