REGULATION

FDA New Drug Review Times Continued to Drop in 2004

In a report about its 2004 accomplishments, the US Food and Drug Administration (Rockville, MD, www.fda.gov) cited a continuing drop in the median approval times for priority and standard new drug applications (NDAs) and biologic license applications (BLAs). Approval times for new molecular entities (NMEs) and new BLAs under priority review also dropped, although approval times for those under standard review increased slightly.

FDA's Center for Drug Evaluation and Research (CDER) approved 29 drugs last year under its priority review program (available for drugs with the potential for significant advances over existing treatments), and approved 90 drugs after standard review. The median approval time for priority-review products was 6.0 months (down from 7.7). The standard approval time was 12.9 months (down from 15.4). Both figures include BLAs for biologic products transferred to CDER from the Center for Biologics Evaluation and Research (CBER) in the fall of 2003. CBER approved two BLAs in 2004, with an average approval time of 19.77 months.

Of the drugs approved by CDER, 36 had novel structures, dassified as NMEs or new BLAs, up from 21 in 2003.

The total number of NDA submissions to CDER was 108, down slightly from 110 in 2003 (see chart). At the same time, the Office of Generic Drugs approved 474 applications in 2004, up from 364 in 2003, also with a faster median approval time (15.7 months compared with 17.0).

–Laura Bush

Number of NDAs received by the Center for Drug Evaluation and Research*

Calendar year	NDAs received
1990	98
1991	112
1992	100
1993	99
1994	114
1995	121
1996	120
1997	128
1998	121
1999	139
2000	115
2001	98
2002	105
2003	110
2004**	108

*Adapted from http://www.fda.gov/cder/rdmt/numofndareccy.htm.
**CY 2004 includes BLAs for therapeutic biologic products transferred from CBER to CDER.

European Applications for New Medicines Rose in 2004

The European Medicines Agency (London, UK, www.emea.eu.int/) received an increased number of applications for new medicines for human use last year, with 51 applications in 2004. This figure is up from 39 in 2003 and 31 in 2002. The agency forecasts small increases to 52 applications in 2005 and 56 applications in 2006. Applications veterinary medicines declined to 8 in 2004, down from 10 in 2003. Increases to 11 and 14 applications are forecasted for 2005 and 2006, respectively. *–LB*

REGULATION

FDA Actions

CFCs banned from inhalers

The US Food and Drug Administration (Rockville, MD, www.fda.gov) issued its final rule prohibiting the use of chlorofluorocarbon (CFC) propellants in albuterol metered-dose inhalers (MDIs) after Dec. 31, 2008. CFC-containing albuterol MDIs were previously exempted from a general ban on CFC production and importation under the Montreal Protocol on Substances that Deplete the Ozone Layer and the US Clean Air Act. FDA now says that sufficient supplies of two approved, environmentally friendly albuterol inhalers will be available by the end of 2008 to allow the CFC-containing inhalers to be phased out.

Drug recalls

FDA logged three drug recalls, all initiated by the manufacturers, since March 11. The three recalls are:

- On April 4, Wyeth's Richmond Division (Richmond, VA) becan recalling 28,727 thousand-tablet bottles of Premarin conjugated estrogen tablets (in 0.625 and 0.3 mg dosages), citing dissolution failures.
- On March 15, McKesson Packaging Services (Concord, NC), started sending out letters recalling 4755 boxes of institutional-use Sky brand blister packs and punch cards of acetaminophen (manufactured by Magno-Humphries Laboratories of Tigard, OR) that might contain metal particles.
- On March 11, Malinckrodt (Berkeley, MO) began its recall of 1194 thousand-tablet bottles of propoxyphene napsylate and acetaminophen tablets because the bottle label referred to pink tablets, while those batches of the product were white.

Magnesium sulfate alert

FDA issued a nationwide alert against the use of PharMEDium Services, (Houston, TX, www.pharmedium.com) magnesium sulfate 1 g in 50-mL D5W (piggyback) IV solution, lot number 100504900049 and expiration date April 4, 2005. This product may be contaminated with *Serratia marcescens* bacteria that can cause serious, life-threatening illness in patients with weakened immune systems.

Warning letters

Palace Pharmacy. FDA's Denver, CO district office sent a warning letter to Palace Pharmacy (Lander, WY) concerning the company's drug-compounding activities.

The agency expressed special concern about Palace Pharmacy's production of domperidone in 10-, 15-, and 20-mg capsules for human use. The letter noted that domperidone (sometimes used to increase prolactin levels and improve breast milk production) is not approved for any human use in the United States, is not approved for enhancing lactation in any country, and has cardiovascular side effects that have forced its witdrawal from the market in several countries where it had been approved to treat gastric stasis and gastropaiesis.

FDA warned Palace that the current domperidone label "fails to bear adequate direction for their use" and that the products themselves are unapproved drugs under 21 CFR § 201.115.

Germiphene. In April, FDA released a warning letter to Germiphene Corp. (Brantford, Ontario, Canada, www.germiphene.com), citing significant deviations from US Current Good Manufacturing Practice regulations.

The five-page letter, dated Feb. 15, stated that employees at the inspected manufacturing facility lacked the education and training required to perform their assigned functions, and that the laboratory facilities and equipment used for testing and approval or rejection of components and drug products were found to be inadequate. Other violations included the use of instruments/apparatus not meeting established specifications, and an inadequate stability testing program.

In addition, Germiphene's labeling was found to be "seriously deficient for marketing the products in the United States." The products were therefore misbranded, and in some cases unapproved new drugs, including the company's fluoride products, "Denti-Care" oral rinse products, and over-the-counter healthcare products, whichwere found to contain an non-FDA approved combination of tetracaine and benzocaine.

In the letter, FDA recommended the disapproval of any new applications listing Germiphene as manufacturer until the deficiencies observed have been corrected.

In a statement to *Pharmaceutical Technology* the drug manufacturer said, "Germiphene Corp. takes the FDA comments very seriouslyand is addressing their concerns. We believe the issue will be concluded shortly."

Drug shortages resolved

Also last month, FDA announced resolution of drug shortages for Avonex (interferon Beta 1a), "Solu-Cortef" (Hydrocortisone sodium succinate) for injection, "Trecator SC" (ethionamide 250-mg tablets), and Penicillin G Potassium and Penicillin G Sodium Injectables have been resolved.

R&D

HHS Awards $97-Million Vaccine Contract

The US Health and Human Services Department (HHS) has awarded Sanofi Pasteur, the vaccines business of the Sanofi-Aventis Group (Lyon, France and Swiftwater, PA, en.sanofi-aventis.com/), a $97-million contract to accelerate the development of new cell-culture influenza vaccines in the United States.

The company's cell-culture influenza vaccine program is based on the "Per.C6" cell-line technology of Crucell N.V., a Dutch biotechnology company. Cell culture is an emerging technology that eliminates the need to use chicken eggs for the production of influenza vaccine. Instead of eggs, the virus is grown on specially selected cell lines, a process that may cut the manufacturing time from four weeks to two or three weeks after the virus strain has been identified and could potentially lead to a more-predictable process.

The five-year agreement also will fund the design of a US-based licensed cell-culture vaccine manufacturing facility. Pasteur will deliver to HHS a feasibility plan for a production plant designed to supply as many as 300 million monovalent influenza vaccine doses per year. The award will not fund the construction of the facility.

–Maribel Rios

STANDARDS

USP to Publish Spanish Translation of *USP–NF*

The United States Pharmacopeia (USP, Rockville, MD, www.usp.org) will begin publishing the *US Pharmacopeia–National Formulary* (*USP–NF*) in Spanish beginning in November 2005. The Spanish version (*Farmacopea de los Estados Unidos de America–Formulario Nacional*) will be a scientifically exact translation of the English *USP 29–NF 24* and will become official in January 2006.

"The *USP–NF* Spanish version makes it easier for non-English speakers to understand and meet USP standards while also helping to fulfill our mission of providing standards for quality medicines worldwide," commented USP Executive Vice-President and CEO Roger L. Williams, MD, in an official statement. The *USP–NF* provides standards of identify, strength, quality, and purity for prescription and nonprescription drug ingredients and dosage forms, dietary supplements, medical devices, and other healthcare products. Those standards are enforceable in the United States by the US Food and Drug Administration and are followed in many other countries around the world.

Linguistic Systems, Inc. (LSI, Cambridge, MA, www.linguist.com) translated the *USP 29–NF 24* with help from Spanish-speaking USP staff and numerous translators in Spanish-speaking countries. LSI started from a Spanish-language glossary developed by the USP Implementation Group, which consists of volunteers representing various public health organizations, the pharmaceutical industry, and pharmacy schools in Spanish-speaking countries.

USP appointed members to the Implementation Group based on their scientific expertise, understanding of the standards, and fluency in Spanish.

Enrique Fefer, PhD, chair of the Implementation Group, noted that the group played a vital role in ensuring the accuracy of the translation. "By working together, this group ensured that the *USP–NF* Spanish version was a mirror image of the English version and retained the stringent scientific standards established by USP," he said in a prepared statement. The announcement of the Spanish translation was made following USP's 2005 convention, held March 9–13 in Washington, DC.

–Laura Bush

PROTEIN PRODUCTION

Cardinal Health Gains Patent for Gene Expression Technology

Cardinal Health (Somerset, NJ, www.cardinal.com) has been awarded its first patent for its innovative mammalian-cell genetic engineering technology. Titled, "Host Cells Containing Multiple Integrating Vectors," the patent covers the company's "GPEx" gene product expression technology platform, which enables rapid genetic engineering of stable mammalian cell lines to produce recombinant human proteins and antibodies.

GPEx will be made available to the company's customers for the development of their proprietary biomolecules. In addition to enabling rapid cell line development and availability of candidate gene products, the GPEx technology is well suited for both efficient pilot and large-scale production of antibodies and other therapeutic recombinant proteins.

According to the company, GPEx–through insertion of multiple copies of the gene (or genes)—can generate stable

Multiple gene copies in stable mammalian cell lines

cell lines that exhibit significantly higher levels of expression than cell lines generated by other methods. For example, the company reportedly can take the gene for a protein that is believed to treat various cancers and generate a cell line that expresses that protein. This protein is then isolated from the cell culture media after the cell line is grown and has expressed and secreted the protein.

In a company statement, Paul Weiss, PhD, head of Cardinal Health's Biopharmaceutical Development Services center, said, "We are excited to have our first GPEx patent issued, and look forward to several more as we continue to develop the technology and expand the applications of it. This is a credit to our dedicated scientific staff who have developed this technology over the last 3-4 years."

–Maribel Rios

R&D

Crucell and NIH Sign Ebola Vaccine Manufacturing Contract

The National Institutes of Health (NIH, Bethesda, MD, www.nih.gov) has awarded a $27.6-million contract to the Dutch biotech company Crucell NV (Leiden, The Netherlands, www.crucell.com) for the manufacture of a recombinant Ebola vaccine for Phase I and early Phase II clinical trials.

Under the contract with the Vaccine Research Center, part of the National Institute of Allergy and Infectious Diseases (NIAID), Crucell will manufacture up to ten batches of clinical material for an Ebola vaccine in its own manufacturing facility, using the company's PER.C6 technology.

PER.C6 is a recombinant production technology for manufacturing inactivated-whole-virus, live-attenuated, live-vector, and subunit vaccines. Using the PER.C6 cell lines, which are derived from a human retinal cell, viruses can be cultured under serum-free conditions in formats ranging from roller bottles to bioreactors. Crucell currently is expanding its GMP-production capacity to 100-L working volumes.

The NIH production contract follows a deal last month in which NIH granted Crucell an exclusive patent license to commercialize Ebola vaccines. In addition to the NIH, Crucell has partnered with Aventis Pasteur, GlaxoSmithKline (GSK), the Walter Reed Army Institute of Research, and New York University to develop vaccines for influenza and malaria. The company also has licensed its cell line technology to pharmaceutical companies such as DSM Biologics, GSK, Johnson & Johnson's Centocor, and Merck.

–Laura Bush

STRATEGY

Pfizer to Cut Back $4B per Year

The $4-billion-a-year cost-reduction program Pfizer (New York, NY, www.pfizer.com) announced last month will be realized by "realigning individual business lines for productivity and organizational efficiency in R&D, manufacturing, licensing, and in the commercial group," according to a company statement.

The company is cutting back to compensate for patent expirations, falling COX-2 sales, and new Medicare rules, which will whittle last year's $11.4 billion in revenue to a predicted $8.6 billion for the current year.

In their April 5 presentation to analysts, Pfizer Chairman David L. Shedlarz and Pfizer Human Health President Karen Katen indicated that the company will compensate for the drop in current revenue sources through:

- acquisition of new products and technologies;
- R&D productivity;
- field force optimization;
- manufacturing plant rationalization;
- procurement;
- shared services;
- systems standardization;
- governance speed/focus.

The manufacturing plant rationalization and procurement reforms have not yet been specified.

–Douglas McCormick

STRATEGY

The Empire Strikes Back: Innovators Releasing Generic Drugs

A new study confirms the trend toward innovator pharmaceutical companies switching their brand names to generics as they come off patent.

The report, "Combating Generics: Pharmaceutical Brand Defense" released last week by Cutting Edge Information (Durham, NC, www.cuttingedgeinfo.com), notes that most innovator companies hold off making the move until a generic company announces its intentions to enter the market. The innovator then switches into high gear to reach the market first, taking advantage of its existing resources to fix the generic drug's price and claim a portion of generic revenues. According to the report, generic drug prescriptions constitute 50% of all US drug prescriptions.

Cutting Edge reports that "in the next five years, participating companies will expose an average $541.7 million in aggregate revenue to generics competitors."

"If a pharmaceutical company's generic subsidiary can be first-to-market, the company essentially retains devalued market share for its off-patent drug," states Jon Hess, senior analyst for Cutting Edge Information in the company's statement. "With patents for drugs such as Prevacid and Zoloft set to expire in July and December 2005, respectively, generic drug makers stand poised to enter the market with competitive generic products. It will be interesting to see which generic defense strategies these brands utilize."