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Pharmaceutical Care Across the Continuum

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Recent drug counterfeiting cases sound alarm for U.S. pharmacists

The problem is not likely to go away soon

Drug counterfeiting isn't just a problem in other parts of the world. Recent cases in the United States show that pharmacists need to be on alert here, too.

In May and June alone, drug manufacturers GlaxoSmithKline, Eli Lilly, Serono, and Amgen reported counterfeiting of one of their products. The Food and Drug Administration (FDA) is investigating, but cannot yet comment on the recent cases, says a spokesperson for the FDA's Center for Drug Evaluation and Research. **(For more information about the recent cases, see story, p. 50.)** Most of the cases are considered isolated and limited in scope, with no resulting injuries reported.

"Historically, there have been few true domestic cases of counterfeit pharmaceutical products. It is certainly too soon to conclude that these recent reports of counterfeiting represent anything like a new trend," the FDA spokesperson says.

Pharmacists should definitely be concerned about the recent counterfeiting cases, says **Susan C. Winckler**, RPh, Esq., vice president of policy and communications and staff counsel for the American Pharmaceutical Association in Washington, DC. "The number of cases is unique."

Some of the recent cases have been labeled as "tampering" because they involved substitution of a lower-priced drug for a higher-priced one under the higher-priced drug label. Winckler, however, prefers to consider them counterfeits because the reason behind the switching seems to be money, she says. "These are expensive products. It costs some money to make a good counterfeit product, but certainly much less than to make the actual product."

The counterfeiting issue is not likely to go away soon, she says. "Counterfeiting is a significant issue worldwide, not only with pharmaceuticals. We will continue to see people try to corrupt our drug supply system. It will take everyone from the manufacturer down to the patient to figure out how to stop it."

The majority of counterfeits are caught by pharmacists themselves. Here are some tips from the FDA and Winckler on what pharmacists can do to protect their patients from counterfeits:

• Carefully inspect products that come into the pharmacy.

"Look for variations in the label, box, or packaging; cracks in the product; irregular or odd borders; chips; and differences in widths, colors, or dyes," says **Thomas McGinnis**, PharmD, FDA's director of pharmacy affairs.

Pharmacists need to realize that counterfeiters can be sophisticated in their deception, Winckler says. For instance, a different font size on the labeling may be the only way to tell a product is counterfeit.

• Put aside (and don't dispense from) any suspicious product or package.

"We ask pharmacists to contact either FDA or the manufacturer. The manufacturer will send a pharmaceutical representative to the pharmacy to look at the product and compare it to the firm's product," McGinnis says. "If a problem exists, such as a counterfeit, the manufacturer will contact FDA."

• Remember to be vigilant about your source of supply.

"It's time for pharmacists to refocus their efforts on ensuring they are using a quality wholesaler," Winckler says.

• Continue talking to your patients.

Patients need to know that they should report anything unusual about a product. "The counterfeiting of one of the injectable products was discovered because the product burned upon injection," Winckler says.

If consumers have an adverse event from a counterfeit, usually they will contact their physician, who will contact the dispensing pharmacist, McGinnis says. Depending on what was in or not in the product, the physician will have to act accordingly to accommodate the needs of the patient. "Patients should contact their physician if taking a product and not receiving a benefit, especially when they usually benefited from the product. This could be a sign of a counterfeit with no active ingredient."

The patient may not have a noticeable adverse reaction, but no reaction to a product is of great concern as well, and could be another sign that the drug is a counterfeit, he continues. "FDA's advice to patients and consumers is simply to report anything 'funny' or unusual. Many times, the unusual situation is simply due to a defective product or defective batch, but other times, it is a counterfeit."

"These things need to be reported to the manufacturer and to the FDA so we can start to identify some of these issues," Winckler says. "Pharmacists can play a key role in that." ■

A look at the counterfeit drugs

Here is information on some of the recent drug counterfeit cases:

• Olanzapine replaced with tablets marked "aspirin."

On May 4, Eli Lilly notified health care professionals that pharmacists in the United States had found 10 mg and 15 mg bottles of olanzapine (Zyprexa) in which all of the olanzapine tablets had been removed and replaced with white tablets marked "aspirin." Olanzapine is indicated for the treatment of schizophrenia and acute bipolar mania.

The reports have been confined to 60-count 10 mg and 15 mg bottles of olanzapine. Olanzapine 10 mg tablets are round and white, similar to aspirin; however, they are clearly marked in blue with the word "Lilly" and the number "4117" on one side, and no markings on the other side. Olanzapine 15 mg tablets are oval-shaped and blue and are embossed with the word "Lilly" and the number "4415."

• The incorrect labeling of abacavir sulfate (Ziagen) tablets as lamivudine plus zidovudine (Combivir) tablets.

On May 10, GlaxoSmithKline (GSK) announced that it had received four reports of suspect bottles with 60-count lamivudine plus zidovudine tablet labeling that actually contained abacavir sulfate

tablets. GSK has determined that counterfeit labels for lamivudine plus zidovudine tablets were placed on two bottles of abacavir sulfate and that labels on another two bottles are suspect. Both medicines are used as part of combination regimens to treat HIV infection.

Involved in the counterfeit labeling cases were 60-count bottles of lamivudine plus zidovudine tablets, which contain 150 mg of lamivudine and 300 mg of zidovudine, and 60-count bottles of 300 mg tablets of abacavir sulfate.

This instance of counterfeiting imparts a complex risk profile since approximately 5% of individuals who receive abacavir sulfate develop a potentially life-threatening hypersensitivity reaction. In addition, the replacement of lamivudine plus zidovudine, which contains two antiviral drugs, with abacavir sulfate, a single antiviral, may decrease the effectiveness of a patient's treatment regimen.

GSK says pharmacists can easily distinguish the two medications. The lamivudine plus zidovudine tablet is a white capsule-shaped tablet engraved with "GX FC3" on one side; the other side is plain. Abacavir sulfate is a yellow capsule-shaped tablet engraved with "GX 623" on one face; the other side is plain. The Combivir label shows a color photo of the tablet.

• A counterfeit lot of somatropin (rDNA origin) for injection (Serostim).

On May 16, Serono announced the discovery of a counterfeit lot of somatropin (rDNA origin) for injection (Serostim). The counterfeit material had been packaged to appear as drug product lot number S810-1A1, which is not a legitimate somatropin lot number. Preliminary information appears to indicate that the counterfeit material may have been distributed via the Internet.

Somatropin (rDNA origin) for injection is approved in the United States for the treatment of AIDS wasting.

• Counterfeit epoetin alfa product.

On May 8, Amgen announced the existence of a counterfeit drug product labeled as epoetin alfa (Epogen) 40,000 U/mL vials in 10-pack boxes, lot number P002970 and expiration 07/03. The counterfeit vials examined by Amgen held a clear liquid that contained the drug's active ingredient. However, the concentration of the active ingredient was approximately 20 times lower than expected for epoetin alfa's 40,000 U/mL vials.

On the counterfeit product, the Amgen logo on the carton closure label on the exterior of the box remained blue when viewed at different heights. The authentic logo shifts from blue to purple. Also, the degree sign is missing from the storage temperature on the counterfeit vial label.

On June 5, Amgen identified two additional counterfeit lots of epoetin alfa. The affected lots are P001091, with an expiration date of 09/02, and P001486, with an expiration date of 12/02.

Epoetin alfa is primarily used for the treatment of anemia associated with chronic renal failure in patients on dialysis. ■

Bowel drug to go back on market

FDA allows restricted marketing only

In an unprecedented move, the Food and Drug Administration (FDA) announced that it would allow the restricted sale of a drug that had been pulled off the market because of severe side effects — including several patient deaths.

The indication for alosetron hydrochloride (Lotronex) has been narrowed to only women with severe, diarrhea-predominant irritable bowel syndrome (IBS) who have failed to respond to conventional IBS therapy. Less than 5% of IBS cases are considered severe, and even fewer of these cases are diarrhea-predominant IBS. The drug's manufacturer, GlaxoSmithKline (GSK), is implementing a risk management program, which includes an enrollment program for physicians who want to prescribe the drug.

The FDA first approved alosetron HCl in February 2000. GSK voluntarily pulled the drug off the market nine months later after reports of serious complications of constipation and ischemic colitis.

IBS patients upset over alosetron HCl's removal pleaded their case through letters, e-mail, telephone calls, and public testimony. GSK then resumed negotiations with the FDA about the drug, and submitted a Supplemental New Drug Application in December 2001. The FDA's final June 7 decision follows an April 23 recommendation by the FDA's Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Subcommittee of the Advisory Committee for Pharmaceutical Science to restore access to alosetron HCl through a restricted distribution and use program.

Risk management program requires teamwork

GSK's Lotronex Risk Management Program emphasizes the need for physicians, patients, and pharmacists to work together to maximize the benefit of alosetron HCl and minimize the risk, the FDA says. The program includes the following components:

- For safety reasons, alosetron HCl should be started at a dosage of 1 mg orally once a day for four weeks. If, after four weeks, the 1 mg once-a-day dosage is well-tolerated but does not adequately control IBS symptoms, then the dosage may be increased to 1 mg twice a day, the dose used in controlled clinical trials.
- GSK will establish a prescribing program to enroll physicians who plan to prescribe alosetron HCl. Enrollment will be based on physician self-attestation of qualifications and acceptance of certain responsibilities in prescribing the medication.

GSK will enroll physicians in the prescribing program who agree to educate patients on the risks and benefits of alosetron HCl treatment and to provide patients a copy of the FDA-approved Medication Guide.

- Patients will be asked to read and sign a Patient-Physician Agreement before receiving their initial prescription for alosetron HCl. The agreement attests that they are informed about risks and benefits of alosetron HCl and agree to follow directions that are elements of the plan.

Patients will be advised to discontinue use if they have not obtained adequate control of their IBS symptoms after four weeks of treatment with 1 mg twice a day. Patients also will be advised to contact a doctor immediately if they have any symptoms of side effects.

- Pharmacists will be asked to fill only prescriptions that display a prescribing program sticker affixed by an enrolled physician, and to give patients a copy of the FDA-approved Medication Guide every time they dispense the drug.
- Physicians enrolled in the program will agree to report serious adverse events to GSK.

GSK will conduct an ongoing assessment of the Risk Management Program, including a study of the prescribing and actual use of alosetron HCl.

Group advocates even tighter restrictions

While many IBS patients lauded the FDA's decision, one consumer advocacy group condemned it. Public Citizen, based in Washington, DC, is concerned that the risk management program does not require verification of doctors' qualifications or checks to ensure that patients have been informed of the drug's risks. Tracking of adverse effects will not be mandatory, either. Finally, allowing the drug's manufacturer to administer the program is a case of "the fox guarding the henhouse," says **Larry Sasich**, PharmD, MPH, a pharmacist and research analyst with Public Citizen's Health Research Group.

Instead, the FDA should have limited alosetron HCl to research status, which requires tight controls on who receives a drug and documentation of the effectiveness and safety of a drug, he says. Under that status, the FDA should have limited the drug to women who had previously used it and had experienced no adverse effects.

Also, at a minimum, the risk management program should be restricted to registered gastroenterologists, he adds. There should be a patient registry, and the pharmacies that dispense the drug also should be registered with the FDA.

The consumer advocacy group worries that alosetron HCl's reintroduction will harm more patients. "We are quite fearful for [them]," Sasich says. ■

FDA fast-tracks pancreatic cancer drug

Immunotherapy treatment proves to be nontoxic

A nontoxic immunotherapy treatment for pancreatic cancer has been put on the fast track by the Food and Drug Administration (FDA).

Lorus Therapeutics announced in early June that its drug Virulizin has received the designation. The FDA's fast-track programs are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Virulizin currently is being studied in a double-blind, randomized Phase III clinical trial being conducted in North American medical centers, involving 350 patients with advanced (unresectable, recurrent, or metastatic) pancreatic cancer.

The benefits of the fast-track designation

include scheduled meetings to seek FDA input into development plans, the option of submitting a New Drug Application in sections rather than all components simultaneously, and the option of requesting evaluation of studies using surrogate endpoints. An applicant may use any or all of the components of fast track without the formal designation. Fast-track designation does not necessarily lead to a priority review or accelerated approval.

"The fast-track designation says that the FDA has determined that this drug has potential value for patients with serious conditions like pancreatic cancer," says **Raafat Fahim**, PhD, president and chief operating officer of Lorus Therapeutics, Toronto, Ontario. "Now they actually have to see the potential."

New treatment for a 'devastating' cancer

Virulizin had been awarded Orphan Drug Status from the FDA in 2001. This means that the FDA will help to facilitate the drug's development process by providing financial incentives and granting seven years of market exclusivity in the United States (independent of patent protection) upon approval of the drug. This status is given to drugs used in the treatment of diseases that afflict fewer than 200,000 patients annually in the United States.

Pancreatic cancer may account for a small percentage of all cancers, but it is particularly deadly. Untreated, the survival time from diagnosis is about four to four and a half months, Fahim says. "It's a devastating cancer."

The standard therapy, gemcitabine HCl (Gemzar), typically prolongs the survival of the patient by about six to eight weeks, he adds. The chemotherapy treatment also has a lot of side effects. "Almost invariably, everyone who starts with Gemzar will stop the drug at some point, either because of toxicity or because it didn't help to control the cancer."

On the other hand, Virulizin, which directly stimulates macrophages and enhances their ability to kill tumor cells, has been shown to be relatively safe. For this and other reasons, the FDA has asked Lorus to combine Virulizin with gemcitabine in clinical trials. "Combining Virulizin with another drug would not add to the side reactions profile of that drug," Fahim says.

Patients in the Phase III trial are being randomized to receive either treatment with gemcitabine or treatment with gemcitabine in combination with Virulizin. Those patients who fail or become refractory to gemcitabine then are treated with 5-fluorouracil (5-FU) or with 5-FU in combination with Virulizin in a second-line therapy. All study subjects will be monitored throughout the remainder of their lives.

"We hope the clinical trials will show that combining it with the standard therapy will add value to those patients," Fahim says. ■

Study: Two-thirds of new drugs lack novel action

Two-thirds of the prescription drugs approved by the Food and Drug Administration (FDA) between 1989 and 2000 were modified versions of existing medicines or identical to drugs already on the market. About one-third were drugs based on new molecules that often treat diseases in novel ways, a new study claims. And only 15% of drugs approved during the period both used new chemical compounds as their active ingredients and were deemed by the FDA to provide significant improvement over existing medicines.

The study, by the nonprofit National Institute for Health Care Management (NIHCM) Foundation in Washington, DC, also found that the bulk of the increase in spending on new prescription drugs between 1995 and 2000 was on medicines the FDA did not designate as priority for review. The FDA approved 1,035 drugs during the period 1989-2000; 361 (35%) were new molecular entities, the study says. The remaining 674 drugs (65%) contained active ingredients that were already available in previously approved drugs.

Twenty-four percent (244) of the 1,035 drugs the FDA approved between 1989 and 2000 were categorized as priority drugs with promise of significantly improved efficacy and/or safety. Seventy-six percent (791) were categorized as standard drugs.

The Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, DC, spoke out strongly against the study's conclusions, calling the NIHCM a "tool of the Blue Cross and Blue Shield companies." "From what we have been told, today's NIHCM report appears to be little more than a political and financially motivated cheap shot masquerading as science in the public interest," says **Richard Smith**, PhRMA's vice president of policy and research. This report, he says, "conveniently ignores many of the basic facts about drug research — not the least of which is that innovation rests in the lives of its beholders."

For more information about the report, visit the web site: www.nihcm.org/innovations.pdf. ▼

Few Medicare enrollees get state pharmacy benefits

State pharmacy assistance programs for Medicare beneficiaries help only a small proportion of enrollees — just 3%, or 1.2 million out of 39 million nationwide, according to a new report from The Commonwealth Fund in New York City.

The report indicates that a federal program is needed to fill this gap in coverage, and that any federal program should coordinate with the 28 state programs currently in place.

"Some states have been working for years on reducing the high cost of prescription drugs for low-income beneficiaries," says **Karen Davis**, president of The Commonwealth Fund. "Their experience shows that designing benefits that meet the needs of beneficiaries and premiums that are affordable are key to participation. Without a Medicare prescription drug benefit, state programs are unlikely to reach significant numbers of those at risk for burdensome out-of-pocket prescription expenses."

New Jersey, New York, and Pennsylvania operate three of the largest programs, accounting for three-quarters of state appropriations for pharmacy assistance. "The experience gained by the states can be of great value in the design of a national program," says **Stephen Crystal**, PhD, of Rutgers Center for State Health Policy in New Brunswick, NJ. Crystal is principal investigator of the study.

The report is based on a survey of all state pharmacy assistance programs in place throughout 2000 and interviews with state program administrators. To view the report, go to the web site: www.cmwf.org/programs/medfutur/fox_statepharmacy_530.pdf. ▼

FDA accepts animal data for some drug approvals

The Food and Drug Administration (FDA) has amended its new drug and biological product regulations so that certain human drugs and biologics may be approved for marketing based on evidence of effectiveness from appropriate animal studies.

This new rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers. The drugs or biologics must be intended to reduce or prevent serious or life-threatening conditions.

Under this new rule, certain new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances may be approved for use in humans based on evidence of effectiveness derived only from appropriate animal studies and any additional supporting data. Products evaluated for effectiveness under this rule will be evaluated for safety under pre-existing requirements for establishing the safety of new drug and biological products.

FDA proposed this new regulation Oct. 5, 1999. The final rule went on display May 30, 2002, and was published in the *Federal Register* Friday, May 31. The rule took effect June 30. ▼

FDA issues new guide on pharmacy compounding

In the June 7 *Federal Register*, the Food and Drug Administration (FDA) announced the availability of a compliance policy guide for FDA staff and industry regarding pharmacy compounding.

The FDA developed the policy guide after an April 29 U.S. Supreme Court decision invalidated the compounding provisions of the FDA

Modernization Act of 1997. The agency determined that it needed to issue guidance to the compounding industry and FDA staff on what types of compounding might be subject to enforcement action under current law.

According to the compliance policy guide, here are a few of the pharmacy compounding actions that may put pharmacists on the wrong side of the FDA:

- compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions;
- compounding drugs that were withdrawn or removed from the market for safety reasons;
- receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility;
- receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements;
- using commercial scale manufacturing or testing equipment for compounding drug products.

To read the report, go to the following web site: www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html. ▼

PhRMA adopts code on marketing relationships

The executive committee of the Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, DC, has unanimously adopted a voluntary code that addresses marketing interactions between health care professionals and sales representatives of pharmaceutical and biotechnology companies. It does not address relationships with clinical investigators relating to pre-approval studies.

The PhRMA Code on Interactions with Healthcare Professionals permits industry representatives and others speaking on behalf of a company to conduct informational presentations and discussions that provide valuable scientific and educational benefits.

The code says, "In connection with such presentations and discussions, meals [but no entertainment/recreational events] may be offered so long as they: a) are modest as judged by local standards; and b) occur in a venue and manner conducive to informational communication and provide scientific or educational value." Inclusion of a health care professional's spouse or other guests is not appropriate.

Offering "take-out" meals or meals to be eaten in the absence of a company representative, such as "dine-and-dash" programs, also is inappropriate.

In addition, the code specifies that items primarily for the benefit of patients may be offered to health care professionals if they are not of substantial value ($100 or less). The new code also provides that no grants, scholarships, subsidies, support, consulting contracts, or educational or practice-related items should be provided or offered to a health care professional in exchange for prescribing products or for a commitment to continue prescribing products.

"Nothing should be offered or provided in a manner or on conditions that would interfere

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Editorial Questions

Questions or comments? Call **Paula Cousins** at (816) 960-3730.

Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcpub.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@ahcpub.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@ahcpub.com).
Production Editor: **Brent Winter**.

with the independence of a healthcare professional's prescribing practices," the code states.

For more information about the code, go to the web site: www.phrma.org/publications/2002-04-19.391.pdf. ■

New FDA Approvals

These drugs recently received final approval from the Food and Drug Administration (FDA):

• *Levothyroxine sodium (Levo-T) by Mova Pharmaceutical.* Levothyroxine sodium (Levo-T) has been approved by the FDA for the treatment of **hypothyroidism** and the **suppression of thyroid-stimulating hormone**. Levothyroxine sodium will be available in dosages ranging from 25 mcg to 300 mcg.

• *New indication for pantoprazole sodium (Protonix) delayed release tablets by Wyeth Pharmaceuticals.* Pantoprazole sodium (Protonix) has been approved for the **long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome**. It was originally approved in February 2000 for the short-term treatment (up to eight weeks) and symptomatic relief of erosive esophagitis (EE) associated with gastroesophageal reflux disease (GERD). In June 2001 it was approved for the maintenance of healing of EE and daytime and nighttime control of heartburn associated with GERD.

• *New indication for the estrogen replacement therapy system (Alora) by Watson Pharmaceuticals.* The estrogen replacement therapy system (Alora) has been approved for the **prevention of postmenopausal osteoporosis**. In 1996, the system was approved for the treatment of moderate-to-severe vasomotor menopausal symptoms, specifically hot flashes.

• *Secretin by Chesapeake Biological Laboratories.* The FDA has approved secretin (Secreflo) for injection for use as an aid in confirming **the diagnosis of pancreatic dysfunction and the presence of a pancreatic tumor (gastrinoma) that may become cancerous**. Secretin is the first of its kind to receive FDA approval.

• *New indication for rofecoxib (Vioxx) by Merck & Co.* FDA has approved a supplemental application for the use of rofecoxib (Vioxx) for **rheumatoid arthritis**. Rofecoxib previously has been approved for osteoarthritis and pain. FDA also has approved new label text and precautions that are based on the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.

• *Fulvestrant (Faslodex) Injection by AstraZeneca.* FDA has approved the breast cancer drug fulvestrant (Faslodex) Injection for treatment of **hormone receptor-positive metastatic breast cancer** in postmenopausal women with disease progression following antiestrogen therapy, such as tamoxifen. Fulvestrant is an estrogen receptor antagonist without known agonist effects. It is the only estrogen receptor antagonist to be proven effective after tamoxifen failure.

• *The angiotensin II receptor blocker (ARB) Benicar by Sankyo Pharma.* The FDA has granted marketing approval for the angiotensin II receptor blocker (ARB) olmesartan medoxomil (Benicar), a new treatment option for **hypertension**. Benicar, which can be administered alone or in combination therapy with other antihypertensive agents. ■

DRUG CRITERIA & OUTCOMES™

Lipid-based amphotericin B products formulary evaluation

By **Brad Gilchrist**, PharmD
Huntsville Hospital, Huntsville, AL

Lipid-based amphotericin B products compared

- Amphotericin B lipid complex (ABLC, Abelcet) — The Liposome Co.
- Amphotericin B colloidal dispersion (ABCD, Amphotec) — Sequus Pharmaceuticals
- Liposomal Amphotericin B (L-AmB, AmBisome) — Fujisawa

Background

Amphotericin B has a broad antifungal spectrum of activity, but poor patient tolerance and the potential for serious renal toxicity with prolonged use have limited its clinical utility. Common side effects of amphotericin B therapy are chills and fever (infusion-related), anemia, and nephrotoxic effects. Over the past 10 years, research has been done to improve the side effect profile of amphotericin B. This work has focused mainly on the delivery of amphotericin B to the site of infection. It is hoped that by developing a delivery system that limits exposure of the antifungal agent to host cells while achieving therapeutic levels of drug at the site of infection, a significant decrease in adverse effects such as renal toxicity can be achieved.

Pharmacology

Amphotericin B binds to ergosterol in the fungal cell membrane. This binding results in altered membrane permeability, leakage of essential cell contents, and cell death. The toxicity to mammalian cells is due to amphotericin B's propensity to bind cholesterol.

Lipid-based amphotericin B products are believed to be less toxic to host cells compared to the conventional product. The pharmacological change, which underlies use of the new agents, is that incorporation of amphotericin B into a nontoxic carrier vehicle can protect host cells and ensure delivery of active drug to the site of infection.

It is believed that lipid products carry the drug preferentially to specific sites in the body such as the liver, lungs, and spleen, which are rich in reticuloendothelial system tissue, rather than renal tissue. In theory, these products should reach a lower concentration in renal tissues, thus resulting in a lower incidence of renal toxicity as compared to the conventional product.

Pharmacokinetics

Pharmacokinetic data are summarized in **Table 1, below**.

Table 1. Pharmacokinetic parameters

Variable	ABCD				ABLC	L-AmB			CAB
Dosage mg/kg/d	3	4	5	6	5	1	2.5	5	0.6
V (L/kg)	3.88	4.10	4.30	4.50	131	0.14	0.16	0.10	5.0
Total Cl (L/h/kg)	0.105	0.112	0.117	0.121	0.436	0.017	0.022	0.011	38
$T_{1/2}$ (h)	27.5	28.2	28.6	28.8	173.4	7	6.3	6.8	91.1
C_{max} (ug/mL)	2.6	2.9	3.1	3.4	1.7	12.2	31.4	83	1.1
AUC (ug/mL/h)	29	36	43	50	14	60	197	555	17.1

Key: CAB = Conventional amphotericin B; V = Volume of distribution at steady state; AUC = area under the curve.

Indications and dosage

• **Amphotericin B Lipid Complex (ABLC)** — Indicated for all invasive fungal infections in patients for whom conventional amphotericin B (CAB) is unacceptable due to renal impairment or other toxicity, or in whom CAB has failed.

The recommended dosage of ABLC is 5 mg/kg/d IV in both adults and children.

• **Amphotericin B Colloidal Dispersion (ABCD)** — Indicated for invasive aspergillosis infections in patients for whom CAB is unacceptable due to renal impairment or other toxicity, or in whom CAB has failed.

The recommended initial dosage of ABCD is 3-4 mg/kg/d IV in adults and children. If there is no improvement or the disease progresses, the dose may be increased to 6 mg/kg/d. Dosages up to 8 mg/kg/d have been used.

• **Liposomal amphotericin B (L-AmB)** — Indicated for use in patients whose renal impairment or toxicity precludes the use of CAB. Indicated as initial intervention in empiric therapy in cases of presumed fungal infections in febrile neutropenic patients and in the treatment of visceral leishmaniasis.

Recommended dosage:

— For empiric treatment of fungal infections: 3 mg/kg/d.

— For visceral leishmaniasis in immunocompetent patients: 3 mg/kg/d on days 1-5 and on days 14 and 21.

— For visceral leishmaniasis in immunocompromised patients: 4 mg/kg/d on days 1-5 and on days 10, 17, 24, 31, and 38.

— For invasive fungal infections: 3-5 mg/kg/d depending on response and toxicity.

• **Conventional amphotericin B (CAB)** — Amphotericin B is effective for the treatment of serious infections due to *Cryptococcus neoformans*, *Candida albicans*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Aspergillus fumigatus*.

Usual doses range from 0.25 to 1.0 mg/kg/d for patients with normal renal function. The total daily dose should not exceed 1.5 mg/kg/d.

Common adverse effects

The most common adverse effects for the lipid-based amphotericin B products are the same as those seen with CAB, except to a lesser degree.

Table 2. Adverse effects of lipid products

	ABLC (%)*	ABCD (%)**	L-AmB (%)*
Chills/rigors	18	77	40.0-48.1
SCr increased	11	20	18.5-22.4
Nausea	9	8	25.9-39.7
Vomiting	8	9	22.4-31.8
Hypotension	8	12	7.4-14.3
Sepsis	7	NA	7.4-14.0
Diarrhea	6	NA	15.3-30.3
Headache	6	< 5	9.4-19.8
Hypokalemia	5	17	37.6-42.9
Hypertension	5	12	7.9-19.8
Abdominal pain	4	≥ 5	7.0-19.8
Bilirubinemia	4	16	11.1-18.1
Rash	4	≥ 5	22.2-24.8
Anemia	4	< 5	26.7-47.9
Chest pain	3	NA	8.2-12.0

*Information for L-AmB and ABLC were taken from their respective package inserts.

**The safety information for ABCD was compiled from several different trials and resources.

These adverse effects include: infusion-related reactions such as chills/rigors, nausea, vomiting, hypertension, tachycardia, dyspnea, and hypoxia. Other effects including nephrotoxicity, sepsis, diarrhea, headache, thrombocytopenia, hypotension, abdominal pain, anemia, hyperbilirubinemia, hypokalemia, rash, chest pain, infection, gastrointestinal hemorrhage, increase in liver function tests, and leukopenia. Adverse effect rates for ABLC, ABCD, and L-AmB can be found in **Table 2, above**.

Clinical studies

• **ABLC:** Linden et al examined the relationship between dosage and therapeutic response of amphotericin B lipid complex by analyzing underlying diseases, types of infections, and therapeutic outcomes with different dosages as second-line antifungal therapy.[1]

This was a retrospective study that analyzed low-dose ABLC from three open-label, clinical, second-line treatment trials. Of the 555 patients enrolled (five enrolled twice) with invasive fungal infections, 289 failed and 267 were intolerant to conventional antifungal therapy.

Efficacy and safety data are presented in **Tables 3 and 4, p. 3**.

This trial did not originally intend to differentiate between two doses of ABLC. The original protocol was for all patients to receive 5 mg/kg/d, but the physicians had flexible guidelines with regard to dosing and some patients received < 3

Table 3. Efficacy

Low-dose ABLC (≤ 3 mg/kg) (n = 62)	
Complete response	20 (32%)
Partial response	20 (32%)
High-dose ABLC (> 3 mg/kg) (n = 396)	
Complete response	87 (22%)
Partial response	134 (34%)

Table 4. Serum creatinine trends from baseline to end of therapy

Trend	≤ 3 mg/kg group	> 3 mg/kg group
Deteriorated	15 (20.5%)	117 (24.2%)
Normal-high	5 (6.8%)	58 (12.0%)
High-higher, > 20%	10 (13.7%)	59 (12.2%)
Stable	34 (46.6%)	247 (51.1%)
Normal-normal	17 (23.3%)	134 (27.7%)
High-high	17 (23.3%)	113 (23.4%)
Improved	23 (31.5%)	92 (19.0%)
High-normal	9 (12.3%)	45 (9.3%)
High-reduced > 20%, still high	14 (19.2%)	47 (9.7%)
Not enough information	1 (1.4%)	27 (5.6%)

mg/kg/d. This study did show that ABLC does have efficacy in regard to the treatment of invasive fungal infections, but the 5 mg/kg/d dosage is still the recommended dose.

An article published in *Clinical Infectious Disease* in 1996 examined the safety and efficacy of ABLC as compared to CAB in the treatment of cryptococcal meningitis in patients with AIDS.[2]

This randomized trial included 55 patients who were assigned to receive six weeks of therapy with ABLC or CAB. Patients in the ABLC group (n = 38) were divided into three cohorts based on the dose. Twenty-one patients received the recommended dosage of 5 mg/kg/d.

Efficacy data can be found in **Table 5, below**.

There was no significant difference between infusion-related adverse events in the two groups. Statistically significant differences in the mean changes of serum creatinine and hemoglobin values from baseline favored patients who received ABLC 5 mg/ kg/d as compared to those receiving CAB. Hypokalemia and hypomagnesemia occurred in similar percentages in the ABLC 5 mg/kg/d group and the CAB group.

This trial had many limitations. The treatment groups produced by randomization were dissimilar in several aspects. Significantly more ABLC recipients than CAB recipients had three of four baseline characteristics that have been shown in prior studies to predict treatment failure. Also, the study design included treatment groups of insufficient size to give significant differences in efficacy.

The authors concluded that ABLC is an effective and less toxic alternative to CAB in the treatment of cryptococcal meningitis in patients with AIDS. The authors did point out that further study is needed.

• **ABCD:** White et al retrospectively compared 82 patients with proven or probable aspergillosis with 261 patients who received amphotericin B.[3]

Enrollment criteria included:

— failure of fungal infection to respond to amphotericin B treatment, defined as receipt of at least 15 mg/kg of amphotericin B without clinical improvement and extension of existing lesions or development of a new focus of infection, or use of amphotericin B for at least seven days without clinical improvement, and/or microbiological studies remaining positive for fungi;

— nephrotoxicity, defined as a doubling of serum creatinine or an increase of > 1.5 mg/dL from the pretreatment level;

— pre-existing renal impairment, defined as a serum creatinine of > 2.0 mg/dL;

— development of an invasive fungal infection after bone marrow transplantation and willingness to participate in a dose-escalating trial with ABCD.

A complete response was defined as resolution of all radiographic evidence of infection and the disappearance of all clinical signs of aspergillosis. A partial response was defined as clinical improvement with partial clearing of infection or stabilization of findings on relevant

Table 5. Efficacy

	ABLC (5 mg/kg/d) (n = 21)	CAB (n = 17)
Clinical response (success)	18 (86%)	11 (65%)
Mycological response (success)	8 (42%)	7 (50%)
Overall response (success)	8 (42%)	7 (50%)

Note: In regard to clinical response, 21 and 17 patients were assessed for each group. For mycological and overall response, only those patients who received more than 12 doses were used, which were 19 and 14 patients, respectively.

radiographic tests.

The development of renal toxicity during treatment was defined as a doubling of the serum creatinine level from baseline, an increase in the serum creatinine level of at least 1 mg/dL, or a 50% decrease in the calculated CrCl.

Table 6. Dosing guidelines

Entry criteria	Daily dose of ABCD (mg/kg)
Unable to tolerate or failure to respond to ≥ 7 days of amphotericin B	2.0-4.0
Receipt of bone marrow transplant	0.5-8.0
Renal insufficiency with amphotericin B	4.0-6.0
Failure to respond to ≥ 15 mg/kg of amphotericin B	4.0 or 6.0 (randomized)

The dose of ABCD given ranged from 2.0 to 6.0 mg/kg. More dosing information is available in **Table 6, above**.

Of patients who received ABCD therapy, 23% received it because of failure to respond to amphotericin B, 32% because of nephrotoxic effects during amphotericin B therapy, 13% because of pre-existing renal impairment, and 32% because of enrollment in a dose-escalating trial.

Only limited information was presented about efficacy of treatment (**see Table 7, below**); there was no breakdown of how the different doses correlated with outcome.

Renal toxicity developed during treatment in 43.1% of amphotericin B patients compared with 8.2% of ABCD patients. No breakdown was given concerning dose and adverse experiences.

This study concluded that ABCD does appear to be a safe and efficacious alternative to CAB in the treatment of aspergillosis. This study had several limitations, including the fact that it was a retrospective, unblinded study comparing two different populations of patients. In the ABCD group, 85.4% of patients had received recent treatment with CAB. This could have had some effect on safety as well as efficacy. A true randomized, controlled trial is needed to support the role of ABCD as primary therapy for aspergillosis.

A study by Oppenheim et al enrolled 168 patients that exhibited one of the following characteristics:[4]

— responded incompletely to at least seven days of treatment with CAB;

— had experienced CAB-induced nephrotoxic effects;

— had pre-existing renal impairment;

— had experienced other CAB-related, treatment-limiting toxic effects.

Patients, depending on severity of infection and the investigator's judgment, were given dosages initially of 0.5, 1.0, 2.0, 3.0, or 4.0 mg/kg/d but were increased as required up to 6 mg/kg/d.

Ninety-seven of the 168 enrolled patients were available for clinical evaluation. Of these patients, 48 (49%) exhibited a favorable response to treatment. Reasons for exclusion from evaluation were as follows: insufficient documentation of fungal infection, administration of less than four doses of ABCD, concomitant administration of itraconazole, and investigator judgment.

Fourteen (8%) of the 168 patients withdrew from the study. Eleven of these patients withdrew due to chills, fever, and hypotension that may have been related to ABCD infusion. The other three patients exhibited elevated bilirubin or serum creatinine levels, which led to withdrawal. Sixty-four patients (38%) experienced infusion-related chills. Fever occurred in 44 patients (26%).

Seventeen of 126 patients (14%) who entered the trial with SCr £ 2.5 mg/dL had final SCr ³ 2.5 mg/dL. Thirty-nine of 124 patients (32%) had elevated transaminase levels at the end of treatment. Of the 39, 24 patients had elevated aspartate aminotransferase at enrollment.

This study provided evidence that ABCD is a viable alternative for patients intolerant or unresponsive to amphotericin B in the treatment of invasive mycoses. ABCD had favorable effects on renal function as compared to the data available on CAB. This study proved that ABCD should be considered for second-line treatment for invasive fungal infections.

Table 7. Response rates

	ABCD (n = 82)	CAB (n = 261)
Response rate (overall)	40 (48.8%)	61 (23.4%)
Bone marrow transplant	14/39 (35.9%)	22/113 (19.5%)
Hematologic malignancies	18/24 (75%)	16/86 (18.6%)
Pulmonary aspergillosis	32/66 (48.5%)	48/198 (24.2%)

• **L-AmB.** A randomized, double-blind, multicenter trial by Walsh et al

included 687 patients who were febrile despite receiving at least 96 hours of broad-spectrum antibacterial therapy.[5]

— 343 patients were randomized to receive liposomal amphotericin B at a dose of 3.0 mg/kg/d. Investigators were permitted to increase the dose to a maximum of 6 mg/kg/d if deemed necessary.

— 344 patients were randomized to receive CAB at a dose of 0.6 mg/kg/ d. Investigators were permitted to increase this dose to a maximum of 1.2 mg/kg/d if deemed necessary.

All baseline categories were similar. Success was determined by five criteria: 1) survival for seven days after initiation of the study drug; 2) resolution of fever during the period of neutropenia; 3) successful treatment of any baseline fungal infection, if present; 4) absence of breakthrough fungal infections during administration of the study drug or within seven days after the completion of treatment; and 5) absence of premature discontinuation of the study drug because of toxicity or lack of efficacy.

The mean daily doses throughout the study were 3.0 ± 0.9 mg/kg/d for liposomal amphotericin B and 0.6 ± 0.2 mg/kg/d for CAB. The average duration of therapy was 10.8 days for liposomal amphotericin B and 10.3 for CAB.

This study proved the efficacy and safety of liposomal amphotericin B as compared to the conventional product. This study compared these two products for empiric therapy in neutropenic patients. The two products had similar efficacy, but the liposomal product had a better adverse effect profile. This study appears to have established liposomal amphotericin B as an appropriate alternative in patients who are intolerant of CAB therapy. Study results are summarized in **Table 8, below**.

Comparison of lipid-based products

• **ABLC vs. L-AmB.** Cannon et al performed a prospective and retrospective observational study set in an urban 350-bed teaching hospital.[6] The patient population included 67 nonhemodialysis patients who were prescribed ABLC or L-AmB for more than three days.

The reason for the initiation of lipid-based formulations was assessed for all patients and found to be similar between the two treatment groups. These reasons included the following patient characteristics: 1) refractory to a prior course of antifungal therapy; 2) intolerant to prior antifungal therapy; 3) underlying renal dysfunction; 4) receipt of lipid-based therapy before hospitalization; and 5) lipid-based therapy chosen as first-line treatment.

The rationale for antifungal therapy was significantly different between ABLC and L-AmB ($P < 0.044$). ABLC was prescribed most frequently for documented fungal infections (50%), followed by neutropenic fever (33%). L-AmB was used more for neutropenic fever (62%), followed by the treatment of documented fungal infections (29%).

Forty-six patients (69%) received ABLC, while 21 patients (31%) received L-AmB. Patient demographics, dosage, and duration of ABLC and L-AmB, and underlying conditions were similar in both groups. Baseline serum creatinine was

Table 8. Study results

	L-AmB	CAB
% still receiving initial dose during the final three days of therapy	51%	56%
% receiving reduced dose	15%	27%
% receiving increased dose	33%	18%
Success rate	50.1%	49.4%
Incidence of invasive breakthrough fungal infections	3.2%	7.8%
No. of patients who died	25	36
Infusion-related reactions (3,622 infusions for L-AmB and 3,403 infusions for CAB)		
Day 1 — Fever	267 (7.4%)	544 (16.0%)
Other infusion-related reactions except fever	746 (20.6%)	1,776 (52.2%)
Nephrotoxicity (doubling of SCr or SCr > 3.0)	12%	26%
Mean change from baseline	0.48 mg/dL	0.77 mg/dL

significantly higher in patients receiving ABLC as compared to those receiving L-AmB (1.77 vs. 1.0, P = 0.003).

Nephrotoxicity was defined as the increase of serum creatinine levels of 100% or more over pretreatment levels. In the ABLC group, two patients developed nephrotoxicity, while four patients in the L-AmB group developed nephrotoxicity.

Efficacy was based on the clinical response of patients with documented fungal isolates at the end of therapy. Clinical response was graded as complete response, partial response, or deterioration. Of patients with documented fungal infection, 20 of 23 patients (87%) treated with ABLC and four of five patients (80%) treated with L-AmB had a complete or partial response to therapy (no significant difference).

The authors concluded that there was no significant difference in nephrotoxicity or efficacy between the two products. They also concluded that until future studies show a clinically significant difference in nephrotoxicity between the products, economics should continue to be the major determinant for product selection.

Wingard et al conducted a randomized, double-blind comparative trial involving 244 neutropenic patients with unresolved fever after 72 hours of broad-spectrum antibiotic therapy.[7]

Patients were randomized to receive ABLC 5 mg/kg/d, L-AmB 3 mg/kg/d, or L-AmB 5 mg/kg/d. The main focus of this trial was comparing frequency of chills/rigors and other infusion-related reactions, frequency of nephrotoxicity, and other safety parameters of the two lipid products.

Patients were deemed ineligible if their serum creatinine was ³ 3.0, or if they had uncontrolled bacteremia, had received more than two doses of CAB, had liver disease, or had an anticipated survival of two weeks or less. Administration of premeds prior to the first administration of medication was prohibited. After day 1, premedication was allowed. Saline loading was not standardized between patients.

According to the protocol, therapy was continued until the patient recovered from neutropenia or for up to three days after neutrophil recovery, up to a maximum of 42 days.

On day 1, infusion-related reactions occurred significantly less frequently in patients who received L-AmB compared to ABLC. After day 1, premedication was allowed before each infusion. The frequency of infusion-related reactions was reduced in the ABLC group, but remained the same in the two L-AmB groups. The difference was significant between the ABLC group and the 5 mg/kg L-AmB group. Also, the proportion of patients needing medication for infusion-related reactions following day 1 was not significant between any of the groups.

Nephrotoxicity, defined as an increase in serum creatinine value of more than 100% (if older than age 16, SCr must be > 1.2 at post-baseline serum creatinine), was significantly increased in the ABLC group as compared to the 5 mg/kg L-AmB group (P < 0.01). Nephrotoxicity was not significantly different between ABLC and the other L-AmB group. Overall, the average increase in serum creatinine between the three groups was 0.2-0.7 mg/dL.

There were no significant differences between the groups in terms of hepatotoxicity, hypokalemia, and anemia. Other than infusion-related effects and nephrotoxicity, the only significant difference was the increase in hypoxia in the ABLC group as compared to the 5 mg/kg L-AmB group.

There was no statistically significant difference in response between the three groups.

The authors concluded that L-AmB was associated with significantly less nephrotoxicity and significantly fewer infusion-related reactions than ABLC. There were several limitations to this study that need to be addressed. In terms of the data on infusion-related reactions, there were no premeds given on the first day of therapy, which is common practice for either agent. After the first day of therapy, premeds were allowed, and the incidence of infusion-related reactions trended downward in the ABLC group. The analysis of nephrotoxicity examined peak serum creatinine values rather than comparing baseline and end-of-therapy values like most other studies.

Pharmacoeconomics

Pharmacoeconomic data are presented in **Table 9, on p. 7. Table 10 on p. 7** provides a cost analysis example of a 72 kg patient with an invasive fungal infection.

Recommendations

The lipid-based amphotericin B products have been proven in clinical trials to be safer than and as efficacious as the CAB product. The three products available at this time — ABLC (Abelcet), ABCD (Amphotec), and L-AmB (AmBisome) — must distinguish themselves from one another based on adverse effect profile and cost.

The safety and efficacy of ABLC and L-AmB have been studied in two trials. ABCD has yet to be compared to the other two products in a

Table 9. Cost of therapy

Abelcet (ABLC)	
100 mg vial	$116.82
Amphotec (ABCD)	
100 mg vial	$78.27
AmBisome (L-AmB)	
50 mg vial	$137.21
CAB	
50 mg vial	$4.43

Table 10. Cost analysis

ABLC	
360 mg at 5 mg/kg/d	$420.55
ABCD	
216 mg at 3 mg/kg/d	$169.13
288 mg at 4 mg/kg/d	$225.50
432 mg at 6 mg/kg/d	$338.26
L-AmB	
216 mg at 3 mg/kg/d	$591.84
360 mg at 5 mg/kg/d	$986.40
Conventional amphotericin B	
43 mg at 0.6 mg/kg/d	$3.81

formalized trial. In clinical trials, all three products have been shown to be safer than and as efficacious as conventional amphotericin B.

In choosing a formulary agent, the available literature comparing the products must be examined. With no comparative literature on ABCD, it is not a suitable choice as the formulary agent.

After evaluation of the trials comparing ABLC and L-AmB, there appears to be little difference between these agents in terms of safety and efficacy. Recent data show that there could be a decreased incidence of infusion-related reactions with L-AmB as compared to ABLC. This incidence can be minimized by using premeds prior to infusion. In terms of nephrotoxicity, it appears that the rate of nephrotoxicity is similar. In one of the comparative trials it did appear that L-AmB was associated with less nephrotoxicity. Due to limitations of this study, a judgment based on nephrotoxicity would be suitable when more information regarding these agents is available.

ABLC currently is the lipid-based product used in Huntsville Hospital. It is used even more than CAB. Currently available data prove that all of the lipid-based products have similar safety and efficacy. With only two trials comparing ABLC and L-AmB, there are limited data on which to make a formulary decision. The cost of ABLC is considerably less than that of L-AmB; until further comparative trials prove otherwise, formulary decisions should be based on economics.

Cost is a very important consideration when choosing whether to use a lipid-based amphotericin B product. The cost of a lipid-based product is hundreds of dollars a day. The drug cost of a day of treatment with the conventional product would cost just a few dollars. Thus, strict criteria need to be developed regarding the use of the lipid-based products.

Indications for the use of a lipid-based amphotericin B product are as follows:

— Treatment of susceptible fungal infections in patients with poor renal function (SCr ³ 2.5 mg / dL in adults or ³ 1.5 mg / dL in children, or an estimated CrCl of £ 25 mL / min) who are either refractory to or inappropriate candidates for itraconazole or fluconazole therapy.

— Patients who are either refractory to or inappropriate candidates for itraconazole or fluconazole therapy and have developed nephrotoxicity prior to or while receiving conventional amphotericin B (SCr increase to ³ 2.5 mg / dL in adults or ³ 1.5 mg / dL in children, doubling of SCr, or estimated CrCl of £ 25 mL / min).

— Infusion-related toxicities that persist seven days after initiation of conventional amphotericin B, despite use of pretreatments before infusion, or significant hypotension (drop in systolic blood pressure of 40 mmHg and / or a drop in diastolic blood pressure of 20 mmHg).

— Patients with end-stage renal disease requiring hemodialysis should not receive amphotericin B lipid products unless one of the above indications apply. Patients undergoing peritoneal dialysis should be regarded as candidates for lipid-based therapy because they do have some kidney function remaining.

— Patients with invasive mold infection (i.e., aspergillus, mucor, fusarium).

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therapy in patients with persistent fever and neutropenia. *N Engl J Med* 1999; 340:764-771.

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Additional Resources

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• Micromedex Healthcare Series. Englewood, CO: MICROMEDEX Inc.; 2000.

• Product Information: Abelcet, amphotericin B lipid complex. Princeton, NJ: The Liposome Company, Inc.; 1996.

• Product Information: AmBisome, amphotericin B liposome. Deerfield, IL: Fujisawa USA, Inc.; 1997.

• Antigenics has announced that investigators have enrolled the first patient in a Phase III trial of its personalized cancer vaccine HSPPC-96 (Oncophage) for the treatment of **metastatic melanoma**.

• Boston Scientific Corporation has announced that the Food and Drug Administration (FDA) has authorized full enrollment of its TAXUS IV clinical trial. The prospective, randomized, double-blind trial is designed to assess the safety and efficacy of a slow-release dose formulation, paclitaxel-eluting TAXUS stent system for the treatment of **coronary restenosis**.

• Inspire Pharmaceuticals has announced the launch of two Phase IIa studies for INS37217 intranasal solution in a nasal spray formulation. Both studies are double-blind, placebo-controlled, dose-ranging studies. One is being conducted in 60 patients with **chronic rhinitis**. The other is being conducted in 90 patients with **upper respiratory infections**.

• Protein Design Labs has initiated a Phase II clinical trial to evaluate its humanized SMART Anti-Gamma Interferon Antibody in **Crohn's disease**.

• Paris-Immuno-Designed Molecules, S.A. (IDM), and its U.S. subsidiary, IDM, have announced approval from the FDA to begin a Phase III clinical trial in the treatment of **ovarian cancer** using IDM's Cell Drug Osidem (also known as IDM-1).

• Cell Therapeutics has announced that it is continuing a Phase II clinical trial of polyglutamate paclitaxel (Xyotax) in **non-small cell lung cancer**.

• Human Genome Sciences has announced that the FDA has cleared the company's Investigational New Drug application to begin clinical trials of LymphoRad(131) (LymphoRad). The initial Phase I clinical trial will evaluate LymphoRad in patients with **multiple myeloma**.

• Oncolytics Biotech has received approval from Health Canada to initiate a Phase I/II clinical trial to investigate the use of the human reovirus (Reolysin) as a treatment for patients with **recurrent malignant glioma**.

• Avanir Pharmaceuticals has completed enrollment in a Phase II/III clinical trial of Neurodex in the treatment of **emotional lability**. Neurodex is a patented, orally administered combination of dextromethorphan (DM) and an enzyme inhibitor that sustains elevated levels of DM in the human body and allows for a 12-hour dosing schedule.

• Amylin Pharmaceuticals has initiated a dose titration study of pramlintide acetate (Symlin) in patients with **Type 1 diabetes** who are actively trying to improve their glucose control.

• Telikhas initiated a Phase I-IIa clinical trial of the TLK199 small molecule product candidate in patients with **myelodysplastic syndrome**.

• DynPort Vaccine Co., a joint venture between DynCorp of Reston, Va., and Porton International, announced that it would enter into a Phase I clinical trial for a new **smallpox vaccine**.

* Pharmacyclics is planning to conduct an additional Phase III clinical trial of its lead product motexafin gadolinium (Xcytrin) Injection. Last year, the company reported results of a randomized controlled Phase III trial of motexafin gadolinium in patients with **brain metastases.** ■