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Drugs approved on basis of animal studies should be 'last option'

FDA amends rule to respond to possibility of bioterrorist agents

The Food and Drug Administration (FDA) now can approve new drugs and biologics for use based on evidence of effectiveness from appropriate animal studies. The FDA took the action to respond to the need for adequate medical responses to protect or treat individuals exposed to lethal or permanently disabling toxic substances or organisms.

But one pharmacist says he hopes that any drug that falls under the new amended drug and biological product regulations would be used as a last option only. "Until we actually treat someone who is exposed to a particular toxin, we don't know whether it works or not. It's difficult to consider something like that a first-line therapy," says **Kenneth Rockwell** Jr., PharmD, MS, director of the Investigational Drug Service at the University of Pennsylvania in Philadelphia. Furthermore, if the FDA approves such a drug, even for a narrow indication such as treatment for exposure to a particular biologic agent, the possibility exists that some health professionals may try to use it in other situations.

The FDA published the amendment to its drug and biological regulations in the May 31 *Federal Register*. The rule, which took effect June 30, applies 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.

Under this rule, the FDA can rely on the evidence from animal studies to provide substantial evidence of the effectiveness of these products when:

• There is a reasonably well-understood pathophysiological mechanism for the toxicity of the chemical, biological, radiological, or nuclear substance and its amelioration or prevention by the product.

• The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model (meaning the model has been adequately evaluated for its responsiveness) for predicting the response in humans.

"Some animals will react the same way as a human, but some won't. It's hard for us to tell that off-hand," Rockwell says. "For example, we can't just test it in a rat because some drugs will act the same way in rats as in humans, but some will be the complete opposite. So we try to be as safe as we can by testing it on as many different species as possible. The FDA usually recommends at least two or three unrelated species."

• The animal study endpoint is clearly related to the desired benefit in humans, which is generally enhancement of survival or prevention of major morbidity.

• The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information in animals and humans is sufficiently well-understood to allow selection of an effective dose in humans, and it is therefore reasonable to expect the effectiveness of the product in animals to be a reliable indicator of its effectiveness in humans.

Rockwell says he hopes the FDA would perform some basic safety tests of the drugs and biologics in human beings first, at least with very small doses. The FDA says products evaluated for effectiveness under the new regulations will be evaluated for safety under pre-existing requirements for establishing the safety of new drug and biological products. "The safety of most of these products can be studied in human volunteers similar to the people who would be exposed to the product," the agency says in the rule.

The FDA also "recognizes that some safety data, such as data on possible adverse interactions between the toxic substance itself and the new product, may not be available. This is not expected to keep the agency from making an adequate safety evaluation." The FDA may take into account other data, including that involving humans, in assessing the sufficiency of animal data.

Will drug companies respond?

The amendment will help make sure essential new pharmaceutical products are available much sooner, says **Lester M. Crawford**, DVM, PhD, FDA deputy commissioner.

Rockwell, however, doesn't foresee a lot of drug companies taking advantage of the opportunity to develop these drugs. "The use is going to be extremely limited for something so toxic that it can't ethically be tested in humans. The drug company would never be able to use it until there was an actual attack or chemical exposure."

In that case, a federal agency, such as the Centers for Disease Control and Prevention in Atlanta, might purchase the medication and supply it to local governments. Rockwell says he hopes that such an action would tightly control the use of the agent. "If the FDA wanted to actually allow a product's use before testing it on humans, it should be [controlled] through a very restricted system." The drug could become part of the CDC stockpile, for example, where the need for the drug could first be assessed. ■

Patient care more of a focus in 21st century

Pharmacists play role in disease state management

Pharmacists will once again become more directly involved in patient care, reclaiming some of the ground they have lost over the years.

So says **Edward D. Rickert**, RPh, JD, partner with Smith, Rickert & Smith in Downers Grove, IL. Rickert spoke about pharmacists becoming more patient-centered in his presentation, "Practicing Pharmacy in the 21st Century: Liability and Practices Concerns," at the American Pharmaceutical Association's 2002 Annual Meeting and Exposition in Philadelphia in March.

Rickert offers this definition of pharmaceutical care: a patient-centered, outcomes-oriented pharmacy practice that requires the pharmacist to work in concert with the patient and other health care providers to promote health; prevent disease;

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and assess, monitor, initiate, and modify medication use to ensure that drug therapy regimens are safe and effective.

As part of these responsibilities, pharmacists will be playing a larger role in disease state management (DSM) activities, he says. Some signs that indicate a positive direction for pharmacists in this area include:

• **Pharmacists have documented value in DSM processes.** "There's a documented evidence of value in connection with key conditions, such as lipid management, anticoagulation, diabetes, and asthma," Rickert says.

• **The National Institute for Standards in Pharmaceutical Credentialing has developed a process to credential pharmacists to provide care in these areas.** "Let's credential pharmacists in these areas so not only can they provide the care, but they might even get paid for it, which is kind of a novel concept for pharmacists, who are used to giving away information for free," he says.

• **Twenty-four states allow some form of collaborative practice agreement for pharmacists.** Collaborative pharmacy practice and pharmaceutical care are key components of DSM, Rickert explains. Collaborative practice agreements with physicians generally allow pharmacists to initiate, modify, or more directly monitor a patient's drug therapy. If a pharmacist wants to change a patient's antibiotic because the bacteria is causing a problem, for example, the pharmacist can make the change within the confines of the collaborative practice agreement without calling the physician.

Although it is encouraging that 24 states have such an agreement, 50 states allow collaborative practice agreements between nurses and physicians and between physician assistants and physicians. "Those states that don't recognize the pharmacist as a full member of the health care team need to recognize that pharmacists can fulfill that role and allow pharmacists to enter into these types of agreements," Rickert says.

A survey of state pharmacy laws shows that several states don't say anything about collaborative practice. Instead, some state boards of pharmacy say that if a doctor wants to delegate to pharmacists the ability to make changes to a patient's drug therapy without calling the doctor, then maybe they have the freedom to do that under the Medical Practice Act. The Medical Practice Act generally holds that a physician can delegate certain duties and responsibilities to somebody else.

"One view of the law is that if it's not prohibited, then maybe it's permitted," Rickert says. "The other way of viewing the law is that if it's not expressly permitted, it's prohibited. Unless the state legislators sit down and write a law that says pharmacists can do this, then they can't. I think that kind of a view of the law prevents the profession from moving forward."

Disease state management is made up of clinical activities, but it is also more proactive, Rickert says. He sees other activities falling under the description of DSM, such as:

• targeting high-risk/high-utilizing patients for education and/or intervention;

• conducting outcomes research to form the basis for educational programs;

• educating other practitioners and influencing prescribing patterns.

The issues facing DSM

Pharmacists becoming more involved in DSM activities will face several issues, one of which is the question of how these pharmacists should be credentialed. Rickert is concerned that the credentialing process may go too far, shutting out competent pharmacists who may not have access to DSM review courses or who are not good test-takers. "There is probably going to be some litigation over the disease state management credentialing process," he says.

Another issue for these pharmacists is the greater need for access to records and the sharing of health information. "You can't really provide care for a patient unless you know what's wrong with the patient and the patient's history," Rickert says.

Several questions about the sharing of health information during DSM activities need to be addressed on a state and national level, he adds. These include:

• Should other entities have access to confidential information?

• Should non-patient-identifiable information be protected?

• Is the release of information for measuring quality of care, assessing patient satisfaction, preventing fraud and abuse, and coordinating payment to providers a legitimate use of patient-identifiable information?

In regard to the privacy of health information, many states mirror the language in the National Association of Boards of Pharmacy's Model Act,

Rickert says. This language reads: "Information accessed, maintained by, or transmitted to the pharmacist in the patient's records or which is communicated to the patient as part of patient counseling, which is privileged and may be released only to the patient or, as the patient directs, to those practitioners, other authorized health care professionals, and other pharmacists where, in the pharmacist's judgment, such release is necessary to protect the patient's health and well-being."

With the Health Insurance Portability and Accountability Act of 1996, patients will be allowed to limit the amount of information that is released, he says. "They'll be able to narrow the scope of the consent, and you will have all these different consent forms. When someone calls for health information, you'll have to figure out what the patient agreed to have you disclose." ■

Peer review facilitates sharing of outcomes info

Many pharmacists lack peer review privilege

Pharmacists involved in disease state management (DSM) activities may find that they have to meet regulations specific to DSM.

Regulators are looking at DSM activities through structure, process, and outcomes, says **Edward D. Rickert**, RPh, JD, partner with Smith, Rickert & Smith in Downers Grove, IL. Rickert spoke about disease state management in his presentation, "Practicing Pharmacy in the 21st Century: Liability and Practices Concerns," at the American Pharmaceutical Association's 2002 Annual Meeting and Exposition in Philadelphia in March. "Structure is the characteristics of setting, such as personnel, computers, and equipment. Process is how available resources are used, such as counseling, drug utilization review, compliance, and the accuracy rate. Outcomes are whether the patient's health is improving or at least being maintained."

If outcomes are evaluated and health professionals try to determine what went wrong in a bad outcome, then the sharing of information is imperative. "You are going to want a free flow of information and frank discussion about what happened in connection with a patient's care," Rickert says.

Peer review can help in this situation. A peer review privilege protects information discussed during proceedings in which quality-of-care issues are analyzed and a health care professional's competence may be discussed, he explains. It also protects participants from litigation brought by a heath care professional who feels he has been injured by the peer review committee.

Peer review statutes aimed at physicians may be deemed broad enough to include participation by pharmacists, Rickert says. "But it can also be argued that the privilege is waived if a pharmacist sits on the committee."

Some people think peer review issues are really just a way of protecting the person who made the mistake or protecting the institution, the hospital, or the pharmacy from liability. "That's kind of a cynical view," Rickert says. "The reason that you have these peer review statutes is because you want to foster full disclosure, a full exchange of information, without any fear of it coming back to hurt you."

Very few states, however, recognize peer review privileges for pharmacists. Texas and California did recently pass laws that provided peer review protections for pharmacists more directly. "I think it's time that we start looking at pharmacists as members of the health care team and give them the same type of peer review protections that other members have," Rickert says. ■

Pharmacy groups oppose House drug benefit bill

Pharmacy benefit managers would control program

The U.S. House of Representatives has finally approved a Medicare prescription drug bill, but pharmacy organizations are not pleased.

"While our concerns may have been considered, they have certainly not been responded to in the House Republican bill," wrote the Pharmacy Benefits All Coalition, a pharmacy advocacy group that represents every aspect of pharmacy, in a recent press release. "We acknowledge that this legislation seeks to remedy significant concerns,

but it does so at the expense of the millions of people who benefit from the care and counseling they receive in their neighborhood pharmacy."

The House approved the Medicare Modernization and Prescription Drug Act of 2002 (HR 4954) on June 28. The legislation passed largely along party lines.

The Pharmacy Benefits All Coalition says it opposes the bill for the following reasons:

- The bill offers no coverage until after the 2004 elections.
- It would place control of the Medicare-related prescription drug program in the hands of unlicensed and unregulated pharmacy benefit managers (PBMs).
- It would encourage seniors to use mail order, where prescription costs are higher and generic use is lower.
- It would restrict the beneficiary's choice of pharmacy or require increased payment to use certain pharmacies.
- It would seriously restrict the medications available to patients.
- It provides no meaningful program for pharmacies to provide professional services to seniors at an adequate reimbursement rate.
- It pre-empts many state consumer protection and pharmacy benefit laws that are designed to protect patients.
- It includes legislative authority for the Centers for Medicare and Medicaid Services to establish a Medicare-endorsed prescription discount card. The discount card program would allow PBMs to force pharmacies to discount their prices to seniors without requiring any defined contribution from the drug manufacturer to actually lower the prescription price.

A study conducted by **Kenneth E. Thorpe**, PhD, chairman of Health Policy and Management in the Rollins School of Public Health at Emory University in Atlanta, found that even with the plan, Medicare beneficiaries would still have to pay 70% of the costs of their prescription drugs. Thorpe is a health policy analyst who served as deputy assistant secretary for health policy in the U.S. Department of Health and Human Services from 1993 to 1995. His study also found that 6.8 million of the Americans who receive Medicare benefits would have to pay the full catastrophic limit of $3,700 a year for prescription drugs.

Furthermore, 11.7 million Medicare recipients would have to pay an average of $2,200 per year under the House-approved plan, Thorpe says. He used Congressional Budget Office projections for the year 2005, when the plan would go into effect.

"Many Medicare beneficiaries who incur high drug expenses may expect that the House-passed bill will reduce substantially their out-of-pocket spending," he says. "Yet, as the analysis reveals, this is not likely to be the case."

The Pharmacy Benefits All Coalition now turns its attention to the Senate, which was expected to take up prescription drug legislation by mid-July. The bill that the Senate passes will have to be reconciled with the House version in conference committee. ■

Pharmacists want flexible workplaces, survey says

Pharmacy directors are offering flexible scheduling and providing incentives to work non-preferred shifts to combat the continuing shortage of pharmacists in hospitals and health systems, according to a recent survey conducted by the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD.

Hospitals that provide benefits such as offering flexible scheduling, job-adequate references and electronic information sources, and collaborative relationships with other health professionals reported a statistically lower pharmacist vacancy rate. "The results provide pharmacy directors with a blueprint for designing a workplace environment that can help attract and retain pharmacists," says **Douglas J. Scheckelhoff**, MS, FASHP, director of ASHP practice management and leadership division.

Pharmacy directors at 548 hospitals and health systems throughout the United States answered questions about vacancy levels, available positions, and the supply of qualified pharmacists. The survey also gauged whether hospital and health-system settings had an impact on ability to recruit pharmacists. Forty-four percent of the respondents reported that vacancies exist at their institutions, down from 50% in 2000. The overall vacancy rate was 6.9%.

For more information about the survey, go to www.ashp.org. ▼

President Bush signs reauthorization of PDUFA

President Bush authorized the third five-year extension of the Prescription Drug User Fee Act (PDUFA) of 1992 on June 11. The reauthorization of PDUFA was included in bioterrorism legislation.

The law maintains the performance goals of PDUFA II, which included reduced drug review times and increased and accelerated consultations between the Food and Drug Administration (FDA) and product sponsors. In addition, PDUFA III meets two FDA goals by remedying resource shortages that have affected the program in recent years.

The law authorizes the agency to collect $1.2 billion in user fees over the next five years. This will enable the FDA to increase the staffing of the drug program by 450 full-time employees. The law also includes authorization to spend $70 million of the user fees to increase the agency's surveillance of the safety of drugs during the first two (or, for potentially dangerous medications, three) years on the market. It is during this initial period, when new medicines enter wide use, that the agency is best able to identify and counter adverse side effects that did not appear during the clinical trials. ▼

Alliance to develop health technology standards

Groups representing health care providers, information technology vendors, and national health and technology associations announced in June the creation of the National Alliance for Health Information Technology, a coalition to develop voluntary standards for health information technology (IT). Founding members of the alliance include the American Society of Health-System Pharmacists in Bethesda, MD, and the American Hospital Association in Chicago.

The alliance's first project is applying bar coding to medication and biological product packaging. The alliance plans to work with the Food and Drug Administration to be a part of its bar coding regulatory process. Other areas of focus could include automated medication administration, electronic medical records, and improving communication and transaction networks among physician offices, hospitals, payers, and throughout the supply chain.

The alliance says it believes that creating voluntary IT standards will enhance patient safety and increase hospital and health care operating efficiencies by allowing computer systems to communicate both within a health organization

and across organizations and locations and making patient-centered data accessible, efficiently linking clinical, administrative, and financial data.

For more information about the alliance, visit the web site at www.nahit.org. ▼

FDA strengthens selected drug warnings

The Food and Drug Administration has revised the warnings on the labels of the following drugs:

• **Tamoxifen citrate (Nolvadex).** Labeling changes for tamoxifen citrate have been prompted by serious, life-threatening, or fatal events associated with the drug in a risk-reduction setting (for women at high risk for cancer and women with ductal carcinoma in situ). These events include endometrial cancer, uterine sarcoma, stroke, and pulmonary embolism. Health care providers should discuss the potential benefits vs. the potential risks of these serious events with women considering tamoxifen citrate to reduce their risk of developing breast cancer. To see the label changes, go to www.fda.gov/medwatch/SAFETY/2002/safety02.htm#nolvad.

• **Irinotecan hydrochloride (Camptosar).** The label of irinotecan hydrochloride has been revised to identify patients at higher risk of severe toxicity, clarify dose modification guidelines, and augment information about management of treatment-related toxicities, including severe and occasionally life-threatening diarrhea. To see the label changes, go to www.fda.gov/medwatch/SAFETY/2002/safety02.htm#campto. ▼

Study: Seniors' drug prices rose faster than inflation

The prices of the 50 most prescribed drugs for senior citizens rose, on average, by nearly three times the rate of inflation last year, according to a new report released today by Families USA, a consumer advocate group in Washington, DC.

The study, titled "Bitter Pill," analyzed price increases for the 50 most commonly prescribed drugs for seniors over the last year (January 2001 to January 2002), the past five years, and the past 10 years. The report found that nearly three-quarters (36 out of 50) of these drugs rose at least 1.5 times the rate of inflation last year, while more than one-third (18 of 50) rose three or more times the rate of inflation.

Families USA also compared price increases of generic vs. brand-name drugs in its report. The report showed that brand-name drug prices rose 4.5 times faster than the rate of price increases for generic drugs — 8.1% vs. 1.8%. Other highlights include:

• Ten of the 50 most prescribed drugs for seniors are generics. The average annual price for those drugs was $375. Nine of those 10 drugs did not increase in price at all.

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Editorial Questions

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

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

• The 40 brand-name drugs on this list had an average annual price of $1,106 — three times that of generics. All but three of the brand-name drugs rose in price last year.

A spokeswoman for the Pharmaceutical Research and Manufacturers of America in Washington, DC, disputed the report, saying Families USA was issuing "more misleading statements to confuse the facts."

"On the issue of drug prices, Families USA ignores the fact the retail prices of the same medicine can vary by more than 100% within a few city blocks," says **Jackie Cottrell**. ▼

Hormone replacement trial stopped due to risk

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) has stopped a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer.

The large multicenter trial, a component of the Women's Health Initiative (WHI), also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit. The study, which was scheduled to run until 2005, was stopped after an average follow-up of 5.2 years. The study did not address the short-term risks and benefits of hormones for the treatment of menopausal symptoms.

"The bottom-line answer from WHI is that this combined form of hormone therapy is unlikely to benefit the heart," says NHLBI director **Claude Lenfant**, MD. "The cardiovascular and cancer risks of estrogen plus progestin outweigh any benefits — and a 26% increase in breast cancer risk is too high a price to pay, even if there were a heart benefit. Similarly, the risks outweigh the benefits of fewer hip fractures."

The report from the WHI investigators on the findings of the estrogen plus progestin study were published in the July 17 issue of the *Journal of the American Medical Association*. ■

• EntreMed has begun a Phase II clinical trial with its angiogenesis inhibitor Endostatin for the treatment of **Stage IV metastatic melanoma**. In February, EntreMed's angiogenesis inhibitor received orphan drug status from the FDA.

• Millennium Pharmaceuticals has announced the initiation of a Phase I clinical trial of MLN518 in patients with **acute myeloid leukemia**. MLN518 is the first receptor tyrosine kinase (RTK) inhibitor of Millennium's RTK program to enter human clinical trials.

• Cell Genesys has initiated a Phase II clinical trial of GVAX pancreatic cancer vaccine in patients with **inoperable or metastatic pancreatic cancer**.

• Medinox has started a Phase I clinical trial of NOX-700, an orally active nitric oxide blocking agent in development for **diabetes mellitus**. ■

DRUG CRITERIA & OUTCOMES™

Pegfilgrastim formulary evaluation

By **Jeremy Vandiver**, PharmD Candidate
Auburn University, Auburn, AL

Colony-stimulating factors

- Sargramostim (Leukine)
- Filgrastim (Neupogen)
- Pegfilgrastim (Neulasta)

Mechanism of action

Similar to filgrastim and sargramostim, pegfilgrastim stimulates neutrophil proliferation, differentiation, maturation, and activation by acting on specific receptors on progenitor cells. It also stimulates their migration and cytotoxicity. Currently, it is indicated only to lower the risk of infection in patients undergoing chemotherapy regimens known to cause febrile neutropenia. This condition is clinically important because duration of neutropenia has been directly correlated with risk of infection.

While filgrastim and pegfilgrastim act primarily on neutrophils, sargramostim also acts on eosinophils and monocytes to increase their proliferation and activity.

Pegfilgrastim and filgrastim are both produced by inserting a human G-CSF gene into *Escherichia coli* via a plasmid. In the case of pegfilgrastim, a polyethylene glycol molecule then is added to the filgrastim molecule at the N-terminal methionyl residue.

Sargramostim is produced using recombinant DNA technology in yeast.

Dosing

Pegfilgrastim is given once per chemotherapy cycle as a subcutaneous (SC) 6 mg injection one day after the cytotoxic chemotherapy regimen.

Pegfilgrastim currently is not approved for use in infants or children. It also is not approved for adolescents weighing less than 45 kg. For patients meeting these criteria, 6 mg once per chemotherapy cycle should be administered subcutaneously.

Filgrastim is dosed as a 5 mcg / kg / d SC or intravenous (IV) infusion beginning 24-72 hours after the chemotherapy regimen and continuing for 7-14 days or until absolute neutrophil counts (ANC) reach 10,000 / uL.

Sargramostim is dosed 250 mcg / m^2 / d SC or IV infusion 24-72 hours after chemotherapy regimen completion continuing until ANC reaches 10,000 / uL.

Pharmacokinetics

The kinetics of pegfilgrastim are interesting: Clearance decreases as the dose is escalated. This is because elimination of the drug is directly dependent on neutrophil numbers. As neutrophil numbers increase, so does the elimination of the drug. For more information on pharmacokinetics, **see Table 1, below**.

Monitoring parameters

- **Pegfilgrastim:** Complete blood count (CBC) and platelet count should be taken before beginning chemotherapy. After initiation, platelets and hematocrit should be monitored regularly.

Table 1. Pharmacokinetic parameters

Kinetic parameter	Pegfilgrastim	Filgrastim	Sargramostim
Dose	6 mg/chemo cycle	5 mcg/kg/d	250 mcg/m^2/d
Onset	—	~ 24 h	7-14 d
Time to peak	24-72 h	2-6 h	1-2 h
$T_{½}$	15-80 h	1.8-3.5 h	2 h

• **Filgrastim:** CBC and platelets should be obtained prior to chemotherapy, then twice per week during therapy. White blood counts (WBC) should be monitored regularly, especially during the expected rise following chemotherapy-induced nadir.

• **Sargramostim:** CBC is recommended twice per week during therapy. Renal and hepatic function should be evaluated every two weeks during therapy in patients with a prior history of dysfunction. Body weight and hydration status also should be monitored.

Indications

Pegfilgrastim currently is indicated only for chemotherapy-induced neutropenia.

Filgrastim currently is indicated for the following:

• Treatment of severe chronic congenital neutropenia, chronic cyclic neutropenia, and idiopathic neutropenia.

• Treatment of patients with neutropenia due to HIV or its treatment, or to prevent infectious complications.

• Treatment of myelodysplastic syndrome.

• Primary or secondary prophylaxis for patients on chemotherapeutic regimens with a 40% or higher incidence of febrile neutropenia.

• Primary prophylaxis for febrile neutropenia or to speed neutrophil recovery time for patients with acute lymphoid leukemia.

• Peripheral blood stem cell mobilization prior to and during leukapheresis for patients undergoing bone marrow ablation.

• Decreasing febrile and non-febrile neutropenia for bone marrow transplant patients.

• Decreasing length of neutropenia following reinfusion of peripheral blood stem cells.

• Treatment of aplastic anemia.

Sargramostim currently is indicated for the following:

• Treatment of patients with neutropenia due to HIV or its treatment, or to prevent infectious complications.

• Treatment of myelodysplastic syndrome.

• For myeloid recovery following bone marrow transplantation.

• Decreasing length of neutropenia following reinfusion of peripheral blood stem cells.

• Peripheral blood stem cell mobilization prior to and during leukapheresis for patients undergoing bone marrow ablation.

• Prevention of chemotherapy-induced neutropenia and decreasing the incidence of febrile neutropenia in patients receiving myelosuppressive therapy.

• Treatment of acute myelogenous leukemia for patients age 55 and older.

• Treatment of aplastic anemia.

• Adjuvant treatment of malignant melanoma following surgery for Stage III or IV melanoma in patients who are at high risk for recurrence.

• Treatment of HIV infection.

Contraindications/warnings

• Pegfilgrastim should not be used in patients who are allergic to pegfilgrastim, filgrastim, *E. coli*-derived proteins, or any component of the formulation.

• Pegfilgrastim should not be used concomitantly with chemotherapy, radiation, or myelosuppressive therapy.

• Pegfilgrastim should not be used 14 days before or within 24 hours following cytotoxic chemotherapy.

• Pegfilgrastim can act as a growth factor for any tumor type.

• Pegfilgrastim should be used cautiously in patients with myeloid malignancies.

• Allergic-type reactions have occurred in patients receiving pegfilgrastim's parent compound.

• Splenic rupture and adult respiratory distress syndrome have been reported in rare cases.

• Sickle cell crisis has been reported following pegfilgrastim administration.

• Pegfilgrastim is not approved for use in pediatric patients.

• Pegfilgrastim is not approved for use in adolescents weighing less than 45 kg.

Adverse drug reactions

Other adverse effects included nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. However, it is difficult to determine whether these were attributable to the drug, chemotherapy, or underlying disease.

Serious reactions that should also be considered included splenic rupture, adult respiratory distress syndrome, sickle cell disease crisis, and allergic reactions. Warnings of these reactions are primarily due to the experience with pegfilgrastim's parent compound.

Table 2. Adverse drug reactions (ADRs)

Adverse reaction	Sargramostim	Filgrastim	Pegfilgrastim
First dose effect (fever, hypotension, rigors, tachycardia, nausea, flushing, etc.)	< 10%	N	N
Diarrhea	< 7%	< 9%	+
Bone pain	10%	24%	26%
Fluid retention	< 4%	N	+
Headache	< 2%	< 2%	+
Lethargy	< 4%	< 4%	+
Weight gain	< 4%	N	
Renal failure	< 4%	< 4%	
Hepatotoxicity	< 4%	< 4%	+
Gastrointestinal effects (nausea, vomiting, pain)	< 6%	< 7%	+
Leukocytosis	< 5%	< 5%	< 1%
Eosinophilia	< 1%	N	
Increased uric acid level	N	< 7%	9%
Fever	< 2%	< 2%	+
Cardiac events (myocardial infarction, arrhythmia)	< 4%	< 3%	
Local reactions	5%, 24%*	< 5%	+

+ indicates that occurrence is noted in literature but incidence is not reported.
N indicates that reaction is not known to occur.
* indicates incidence with preventive measures vs. without preventive measures.

As with any newly released drug, there is limited clinical experience, and unknown adverse drug reactions may surface as it is used in complex clinical situations not evaluated in clinical trials.

Pegfilgrastim and filgrastim should be avoided by those with a hypersensitivity to *E. coli*-derived preparations.

Those with a hypersensitivity to yeast should avoid sargramostim.

Adverse drug reaction information is summarized in **Table 2, above**.

Drug interactions

Formal drug interaction studies are not yet available for pegfilgrastim. However, it is expected that, as with the other colony-stimulating factors, drugs that potentiate neutrophil release may have some interaction (i.e., lithium and corticosteroids).

Pegfilgrastim also should not be given 14 days before a cytotoxic chemotherapy agent or within 24 hours of administering a cytotoxic chemotherapy agent. This is due to pegfilgrastim's stimulatory effect that causes rapid proliferation of cells, and the cytotoxic agent actively targeting rapidly proliferating cell lines.

Clinical studies

Study No. 1: Holmes FA, et al. Blinded, randomized, multicenter study to evaluate single-administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk Stage II or Stage III/IV breast cancer. *J Clin Oncol* 2002;20:727-731.

Objective: To evaluate whether pegfilgrastim (100 mcg/chemotherapy cycle) is as safe and effective as daily filgrastim (5 mcg/kg/d) in reducing chemotherapy-induced neutropenia.

Study design/patient population: Blinded, randomized, multicenter trial involving 310 patients. Patients were stratified with regard to sex, age, race, prior chemotherapy and prior radiotherapy, disease stage, and baseline ANC.

Inclusion criteria:

• Men or women age 18 and older diagnosed with high-risk Stage II or III/IV breast cancer.

• Patients had to be chemotherapy-naïve or have completed no more than one regimen of chemotherapy; previous regimen must have been completed more than four weeks before randomization.

• ANC greater than 1.5 X 10^9 cells/L; platelet count greater than 100 X 10^9 cells/L.

• Adequate hepatic and renal function.

Exclusion criteria:

• Patients currently enrolled in investigational studies or who had been enrolled in studies in the past 30 days.

• Prior exposure to pegfilgrastim; prior bone marrow or stem-cell transplantation.

• Pregnant or breast-feeding.

• Had received antibiotics within 72 hours of chemotherapy.

• Had radiation therapy in the past four weeks.

• Lifetime total cumulative dose greater than 240 mg/m^2 of doxorubicin or more than 600 mg/m^2 of epirubicin.

Endpoints: The primary efficacy endpoint was duration of grade 4 neutropenia in cycle 1 (**see Table 3, below,** for information on duration of grade 4 neutropenia). Other efficacy endpoints included duration of grade 4 neutropenia in cycles 2-4, depth of ANC nadir in each cycle, rate of febrile neutropenia, and time to ANC recovery in each cycle. Safety endpoints included incidence of adverse events, changes in lab values, and presence of antibodies.

Treatment regimens: Patients received either pegfilgrastim 100 mcg/kg SC or filgrastim 5 mcg/ kg/d SC 24 hours after each chemotherapy cycle. Patients in the pegfilgrastim group received placebo injections to remain blinded. Both groups received doxorubicin (60 mg/m^2) followed one hour later by docetaxel (75 mg/m^2). Chemotherapy was repeated every three weeks for up to four cycles.

Results:

• Depth of ANC nadir: Pegfilgrastim achieved a 1.132:1 ratio of higher nadir over filgrastim.

• Rate of febrile neutropenia: Febrile neutropenia occurred in 9% of the pegfilgrastim group vs. 18% of the filgrastim group (P = 0.029).

• Time to ANC recovery: Pegfilgrastim was favored by 0.4 days (9.3 vs. 9.7).

• Adverse drug reaction occurrences were very similar in the two groups.

• Both groups had mild, transient increases in LDH, AST, and ALT.

• No neutralizing antibodies were detected in either group.

Conclusion: The authors concluded that pegfilgrastim is as safe and effective as filgrastim in decreasing chemotherapy-induced neutropenia.

Limitations:

• Small sample size.

• Statistical methods were not described.

• P values were not reported in some instances.

• Trial was supported by Amgen, the manufacturer of pegfilgrastim.

Strengths:

• Study objective is clearly stated.

• Study endpoints were clearly defined.

• Intent-to-treat analysis was performed.

• Patients were closely matched with regard to sex, age, race, prior chemotherapy or radiotherapy, disease stage, and baseline ANC.

Study No. 2: Johnston E, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. *J Clin Oncol* 2000;18:2522-2528.

Objective: To evaluate the safety, clinical response, and pharmacokinetics of pegfilgrastim compared with filgrastim in patients with non-small cell lung cancer (NSCLC).

Study design/patient population: Randomized, open-label, single-center, dose-escalation trial involving 13 patients.

Inclusion criteria:

• Men and women age 18 and older who had a diagnosis of NSCLC.

• ANCs greater than 1.5 X 10^9 cells/L, platelet counts greater than 100 X 10^9 cells/L, and hemoglobin of at least 9 g/dL.

• Patients had to have adequate renal and hepatic function.

Exclusion criteria:

• Previous systemic chemotherapy or extensive radiotherapy.

• Current uncontrolled infection.

• Cancer other than NSCLC that was not in remission.

Table 3. Duration of grade 4 neutropenia

Cycle	Filgrastim	Pegfilgrastim	P
1	1.8 days	1.7 days	> 0.500
2	1.1 days	0.7 days	0.001
3	1.2 days	0.6 days	< 0.001
4	1.3 days	0.9 days	< 0.025

• Known HIV infection.
• Sensitivity to *E. coli*-derived products.
• Women could not be breast-feeding and had to take adequate measures to avoid becoming pregnant.

Treatment regimens: Patients were randomized in a 3:1 ratio to receive 30, 100, or 300 mcg/kg/d of pegfilgrastim or 5 mcg/kg/d of filgrastim. The study was divided into two cycles, a 14-day prechemotherapy cycle and a 21-day postchemotherapy cycle. Pegfilgrastim patients received one dose in each cycle. Filgrastim patients received daily doses for five days in cycle 0 and then daily injections 24 hours following chemotherapy in cycle 1. Carboplatin (given to area under the curve of six) and paclitaxel 225 mg/m^2 were given on day 1 and 2, respectively, to both groups in cycle 1.

Monitoring techniques: In cycle 0, daily CBCs were performed, and chemistry panels were drawn on days 1, 8, and 15. CD 34+ cells were assayed daily. In cycle 1, chemistry panels were performed on days 1, 8, and 15. Antibody testing was done on days 1 and 22, and CD 34+ cell counts were performed daily. In each cycle, samples for pharmacokinetic analysis were obtained several times during the first 48 hours and then daily. Patients were interviewed daily by telephone and examined once weekly. Adverse events were reported with investigators determining severity and causality.

Results:
• Both groups had a rapid ANC increase upon initiation; however, the duration of this response was more sustained in the pegfilgrastim regimens.
• Duration of ANC response and peak ANC response were dose-dependent in the pegfilgrastim groups.
• CD 34+ count of pegfilgrastim at 30 mcg/kg/d was similar to filgrastim.
• Clearance of pegfilgrastim was observed to decrease with increasing dose, but increased as ANC returned to normal levels.
• Lab values showed all groups experiencing an almost identical decrease in platelets. All groups also experienced mild, transient increases in LDH, ALP, and uric acid.
• The only adverse event directly correlated with pegfilgrastim was mild-to-moderate bone pain.
• Seroreactivity occurred in four of 19 samples taken in the pegfilgrastim group; however, no neutralizing antibodies were discovered.

Conclusion: The authors concluded that a single dose of pegfilgrastim allows adequate drug concentration without developing toxicity. They also concluded that pegfilgrastim was therapeutically equivalent to filgrastim.

Limitations:
• Very small sample size.
• Open-label design increases the risk of bias.
• Patient stratification data were not shown.
• Endpoints were not defined.
• Statistical tests were not described.
• Study was supported by Amgen.

Study No. 3: Green M, et al. A randomized, double-blinded Phase III study evaluating fixed-dose, once-per-cycle pegylated filgrastim (SD/01) vs. daily filgrastim to support chemotherapy for breast cancer. *Proc Amer Soc Clin Oncol*; 2001. Abstract available at: www.asco.org/prof/me/html/01abstracts/0009/90.htm. Accessed June 10, 2002.

Study objective: To compare fixed-dose, once-per-cycle pegylated filgrastim to daily filgrastim to provide support to patients receiving chemotherapy.

Study design: Randomized, double-blinded Phase III study.

Patients and procedures: One hundred fifty-seven patients being treated with doxorubicin and docetaxel at 35 centers were randomized to receive either SD/01 6 mg SC or filgrastim 5 mcg/kg/d one day after chemotherapy, then placebo or 5 mcg/kg/d filgrastim until ANC was greater than 10 X 10^9 cells/L or for 14 days, whichever came first.

Results:
• Sixty-eight SD/01 and 62 filgrastim patients with similar incidences of severe neutropenia (82% vs. 84%) were evaluated.
• The mean duration of severe neutropenia differed by less than 0.2 days; SD/01 was slightly favored.
• Severe neutropenia incidence was 13% vs. 20%, also slightly favoring SD/01.
• Adverse events were comparable, including an assessment of bone pain.

Conclusion: A single fixed dose of SD/01 at 6 mg was comparable to multiple daily injections of filgrastim at 5 mcg/kg/d in providing ANC support. The authors believed this could lead to simplified management in chemotherapy patients.

Limitations:
• Only abstract is available.
• All patients not accounted for and evaluated.

• Actual numbers were not provided, only percentages.

• Confidence intervals and P values were not included.

• Only reported information evaluated in chemotherapy cycle 1.

• Specific adverse events and incidences were not reported.

• Relatively small number of patients.

Study No. 4: Holmes FA, et al. A single dose of pegfilgrastim is as effective as daily filgrastim to reduce the duration of severe, chemotherapy-induced neutropenia. *Proc Amer Soc Clin Oncol*; 2000. Abstract available at: www.asco.org/prof/me/html/00abstracts/bmt/m_191.htm. Accessed June 10, 2002.

Study objective: To determine if a single dose of pegfilgrastim is as effective as daily filgrastim to reduce the duration of severe, chemotherapy-induced neutropenia.

Study design: Randomized, double-blinded with additional cohorts.

Patients and procedures: One hundred fifty-two Stage II-IV breast cancer patients were treated with doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) followed with either pegfilgrastim (100 mcg/kg) or filgrastim (5 mcg/kg/d), repeated every 21 days for four cycles. Additional patients were randomized to receive open-label 30, 60, or 100 mcg/kg doses of pegfilgrastim.

Endpoints: The primary endpoint was duration of severe neutropenia in cycle 1 (ANC < 500 cells/L). Additional endpoints included:

• The duration of severe neutropenia in cycles 2-4.

• ANC profile, including time to ANC recovery.

• Pharmacokinetics in cycle 1.

• Safety profile in cycles 1-4.

Results:

• Patients treated with 30 or 60 mcg/kg of pegfilgrastim were at an increased risk of inadequate neutrophil recovery.

• Pegfilgrastim displayed non-linear kinetics with a mean half-life of approximately 80 hours compared to five hours for filgrastim.

• The safety profile of pegfilgrastim was similar to filgrastim.

• No antibody formation to either agent was observed.

• Pegfilgrastim dosed 100 mcg/kg once per cycle required fewer injections, yet resulted in the same duration as filgrastim daily.

Conclusion: Pegfilgrastim administered once per chemotherapy cycle is as effective as filgrastim administered daily.

Limitations:

• Only abstract available.

• No actual numbers, percentages, confidence intervals, or P values were reported.

• Study included blinded and unblinded patients.

• Inclusion and exclusion criteria were not stated.

• Conclusion of authors was reported without reporting information analyzed to reach these conclusions.

• Open-label study is prone to bias.

Study No. 5: Vose MD, et al. Single-dose pegfilgrastim (SD/01) is as effective as daily filgrastim following ESHAP chemotherapy for subjects with non-Hodgkin's lymphoma or Hodgkin's disease: Results of a randomized, open-label study. *Blood* 2001;98:799a.

Study objective: To compare the safety and efficacy of a single dose of pegfilgrastim (100 mcg/kg) with daily doses of filgrastim (5 mcg/kg/d) in 60 subjects with relapsed or refractory non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD) receiving ESHAP (etoposide, methylprednisolone, cisplatin, and cytarabine) chemotherapy.

Study design: Randomized, open-label trial.

Patients and procedures: Pegfilgrastim patients received a single SC injection per chemotherapy cycle. Filgrastim patients received daily SC injections for 12 days or until ANC was greater than 10 X 10^9 cells/L, whichever occurred first. The primary endpoint was the duration of grade 4 neutropenia (ANC less than 500 cells/L).

Results:

• The incidence of grade 4 neutropenia was 68% for filgrastim and 69% for pegfilgrastim.

• Mean duration of severe neutropenia was 2.4 days for filgrastim and 2.8 days for pegfilgrastim.

• Incidence of febrile neutropenia in cycles 1 and 2 was 19% for filgrastim and 21% for pegfilgrastim (ANC less than 500 cells/L with fever higher than 38.2° C).

• The median time for ANC recovery in cycle 1 was 15 days for filgrastim and 16 days for pegfilgrastim (ANC greater than 2,000 cells/L).

• No differences were noted in incidence, duration, severity of bone pain, or other adverse events between groups.

Conclusion: A single SC injection of pegfilgrastim provided neutrophil support with safety and

efficacy profiles that were similar to those provided by daily SC injections of filgrastim in subjects with NHL or HD receiving ESHAP chemotherapy. The once-per-cycle dosing regimen of pegfilgrastim simplifies the management of neutropenia and may improve patient quality of life.

Limitations:

- Only abstract available.
- Small study population.
- Open-label design increases risk of bias.
- No actual numbers, confidence intervals, or P values were reported.
- Inclusion and exclusion criteria were not described.

Study No. 6: Crawford J, et al. A Phase II multicycle trial of pegfilgrastim compared to filgrastim after myelosuppressive chemotherapy. International Association for the Study of Lung Cancer. World Conference on Lung Cancer. Tokyo; September 2000.

Study objective: To evaluate the pharmacodynamic and safety profile of a single dose of SD/01 in multicycle chemotherapy.

Study design: Phase II, randomized trial.

Patients and procedures: Eighty patients were randomized to receive 30, 60, or 100 mcg/kg of pegfilgrastim as a single injection or filgrastim 5 mcg/kg/d until adequate ANC was achieved (ANC greater than 10 X 10^9 cells/L).

Results:

- Mean duration of ANC less than 500 cells/L was one day (range 0-4).
- No differences were seen with thrombocytopenia or anemia in each cycle.
- Safety profile was very similar between the groups.
- SD/01 developed no dose-limiting toxicity.
- No antibodies developed; however, some seroreactivity was noted.
- SD/01 100 mcg/kg demonstrated greater improvement in neutropenia during later cycles and moved on to a Phase III trial.

Conclusion: SD/01 as a single dose 24 hours following chemotherapy appears comparable to daily filgrastim multiple doses.

Limitations:

- Only abstract available.
- Small sample size.
- No confidence intervals or P values are reported.
- Numbers are not given to evaluate some of the authors' conclusions.
- Very limited information reported.

Study No. 7: George TK, et al. Pharmacokinetic profiles of fixed-dose single pegfilgrastim administration in patients with non-Hodgkin's lymphoma. *Blood* 2001;98:27b.

Study objective: To characterize the pharmacokinetics of pegfilgrastim and ANC responses after administration of fixed-dose pegfilgrastim in newly diagnosed non-Hodgkin's lymphoma patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy.

Study design: Open-label, multicenter trial.

Patients and procedures: Patients were treated with a single 6 mg injection of pegfilgrastim approximately 24 hours following chemotherapy. Pharmacokinetics, duration of grade IV neutropenia, time to ANC recovery, safety profile, and incidence of febrile neutropenia were measured.

Results:

- Maximal concentration of pegfilgrastim occurred 24 hours after dosing.
- ANC had recovered by day 11, and serum concentration of pegfilgrastim was 0.93 ng/mL.
- Serum levels of pegfilgrastim declined as ANC returned to normal, demonstrating a neutrophil-mediated, self-regulating clearance.
- Median terminal half-life was 42 hours.
- Grade IV neutropenia occurred in 43% (95% confidence interval [CI]) of patients with a mean duration of 1 ± 1.4 days.
- Median time to ANC recovery was 10 days (ANC greater than 1,000 cells/L).
- Febrile neutropenia occurred in 11% (95% CI) of patients (ANC less than 500 cells/L with temperature of 38.2° C).
- Body weight had no effect on duration of grade 4 neutropenia.
- Duration of severe neutropenia was longer in patients older than age 65 and in patients with bone marrow involvement; febrile neutropenia also occurred at an increased rate. Study stated that neither was statistically significant.
- Mild-to-moderate bone pain occurred in some patients.
- Baseline and therapy lab values were similar.

Conclusion: The authors concluded that in non-Hodgkin's lymphoma patients treated with CHOP, a single 6 mg injection of pegfilgrastim provided adequate drug exposure for neutrophil support regardless of body weight.

Limitations:

- Only abstract available.
- Small sample size.
- No P values were given to assess statistical significance.

• Not all numbers reported for each endpoint.

Evaluation of literature

Few full-text articles are currently available to evaluate the use of pegfilgrastim. The first study in this evaluation provides enough information to adequately evaluate it and possibly apply its results. However, the other available full-text study lacks a sufficient sample size for its results to be applicable to a population. The remaining evaluations are abstracts of clinical trials. Although these do trend toward the results found in the full-text articles, abstracts do not provide enough complete data to make a decision regarding therapy.

Cost

The cost figures below assume 10 days of therapy for filgrastim and sargramostim because the literature estimates ranged from six to 11 days of required therapy for ANC levels to rise to the required range. It also assumes pegfilgrastim would act equivalently to 10 days of daily injections of filgrastim and sargramostim. Weight figures assume ideal body weight of six-foot male. Values were calculated to give an estimate of the average cost per chemotherapy cycle of each drug.

Huntsville (AL) Hospital spent approximately $340,000 on colony-stimulating factors during the last year. If the assumptions used in calculating the average cost per chemotherapy cycle were carried over and pegfilgrastim were to be utilized in 30% of the annual usage, cost would increase by approximately $56,000.

Storage

Pegfilgrastim should be stored in a refrigerator (2-8° C). It should not be frozen. It may be kept at room temperature for 48 hours. It should be protected from light.

Pegfilgrastim should be allowed to reach room temperature prior to injection. If accidentally frozen, allow to thaw in refrigerator. If frozen more than once, discard.

Ways to decrease potential medication errors with colony-stimulating factors

Because each of these colony-stimulating factors has a unique dosing regimen, there is an increased possibility of medication errors. Some of these errors may be avoided by the following measures:

• conducting multidisciplinary education programs;

• educating about differences between dosing of colony-stimulating factors;

• stressing that pegfilgrastim is a once-per-chemotherapy-cycle dose instead of daily;

• stressing that pegfilgrastim should only be administered SC; whereas the others can be administered SC or by IV infusion;

• stressing that pegfilgrastim is formulated in milligrams, whereas the others are in micrograms;

• stressing the fact that pegfilgrastim should not be diluted, as the other two colony-stimulating factors are.

Conclusion and recommendation

Based on the currently available literature, pegfilgrastim appears to be very similar to filgrastim and sargramostim in safety and efficacy. With safety and efficacy being similar, cost becomes a consideration with formulary evaluation. While use in the outpatient setting could decrease hospital use and overall cost, this is an unpredictable situation that cannot be accurately described. As illustrated in the previous cost section, addition to the formulary would cause a considerable increase in the cost of treating individual patients within the hospital with colony-stimulating factor therapy. Also, inventory cost would have to be considered, as well as the possibility of increased medication errors due to the different dosing regimens of each of the colony-stimulating factors. Based on these aspects, it is currently recommended that pegfilgrastim be assessed non-formulary status and not be routinely stocked.

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