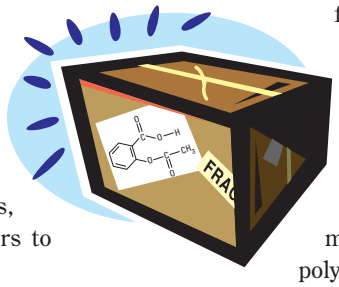
# Specialized delivery

*Safety and efficacy can depend on the delivery method of therapeutic compounds—PEGylation may hold a key.*

Medicinal chemistry is a funny thing, and whereas diethylene glycol is a kidney-destroying toxin (see The Time Line, January, p 25), polyethylene glycol (PEG) turns out to be a profound aid to the timed-release delivery of lifesaving drugs.

Several clinical trials are under way to determine the best use of this expanding method of drug polymerization with PEG and other compounds to provide maximal therapeutic results for many deadly diseases, from immune disorders to cancer (*1*).



## The promise of PEG

For all the hype about expanding oral bioavailability, many of the most important therapeutics still rely on intramuscular or intravenous injection as their chief delivery method. When injected, polypeptide drugs tend to have depressingly short half-lives. Conjugation with polymers such as PEG, however, improves their longevity, and hence their effectiveness, tremendously. In fact, two PEG conjugates—Enzon Pharmaceuticals' (*www.enzon.com*) PEG–adenosine deaminase and PEG–asparaginase—were the first such compounds to receive market approval in the 1990s (*2*).

PEG has long been considered a safe vehicle by the FDA and has routinely been used for food, cosmetic, and drug applications. "PEG alone is nontoxic, nonimmunogenic, and is cleared by the body intact through the urine and feces" (*3*).

## Trials . . .

Original efforts to use PEGylated peptides were problematic for several reasons. The first polymers used were linear and had molecular weights of less than 12,000 Da. These proved relatively ineffective at protecting polypeptides from enzyme degradation or kidney excretion. In addition, the PEG was not uniform, with contaminating variants leading to the production of inactive species. Batch-to-batch variability was high, and in early clinical trials, most of the conjugated drugs failed to perform better than the unconjugated forms (*3*). Luckily, that was not the end of testing.

Today, companies rely on formulations such as those produced by Nektar Therapeutics (*www.nektar.com*), whose advanced PEGylation method uses branched-chain polymers with molecular weights of 40,000 Da or higher and is used with greater success. For example, PEGylated interleukin-6 has 100 times the half-life and 500 times the thrombopoietic activity of the nonPEGylated form, and clinical trials of PEG-conjugated tumor necrosis factor (TNF) showed 4–100 times the antitumor activity (*3*).

Clinical trials are under way to investigate PEGylated versions of a variety of polypeptide drugs, with key players in their development including Amgen, Pfizer, Roche, and Schering-Plough. These polymerized drug candidates include a human growth hormone receptor antagonist (for acromegaly), an anti-TNF-α antibody fragment (for rheumatoid arthritis), an anti-vascular endothelial growth factor (for advanced ocular disease), and filgrastim (a granulocyte colony stimulating factor used to boost white blood cells after chemotherapy) (see box, "Clinical Trials Web").

## . . . and tribulations

PEGylated compounds in use today are by no means an unalloyed miracle. Costs are comparatively high for several of these drugs and are bitterly protested by many patient rights activists. Side effects are also not trivial; for hepatitis C treatment, they range from flulike symptoms and depression to diabetes and kidney damage (*4*). Even without the high costs and side effects, the continuing need for injections (however much decreased) results in a tremendous problem of patient eligibility and compliance, such that "70% of potential patients are found ineligible for treatment because medical or psychological factors make them unlikely to endure its rigors" (*4*). But clinical trials continue to recruit patients, and it is to be hoped that with expanded testing and an increased therapeutic umbrella, the problems of the technology will be even more outweighed by its promise.

### References


(1) Duncan, R. *Nat. Rev. Drug Discov.* **2003,** *2,* 347–360.
(2) Harris, J. M.; Chess, R. B. *Nat. Rev. Drug Discov*. **2003,** *2,* 214–221.
(3) www.worldpharmaweb.com/ddcr/spr03/article2.pdf.
(4) www.amfar.org/cgi-bin/iowa/td/feature/print.html?record=78.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## clinicaltrialsweb

PEGylated doxorubicin liposomes and ovarian cancer (Phase III):

**www.clinicaltrials.gov/ct/show/NCT00043082?order=3.**

PEGylated filgrastim after intensive chemotherapy (Phase I):

**www.clinicaltrials.gov/ct/show/NCT00004853?order=37.**

PEGylated anti-VEGF for advanced ocular disease (Phase I):

**www.clinicaltrials.gov/ct/show/NCT00056199?order=7.**

PEGylated interferon for chronic hepatitis D (Phase II):

**www.clinicaltrials.gov/ct/show/NCT00023322?order=11.**

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