poses; barbiturates; smoking cessation; prescription vitamins and minerals (except prenatal vitamins and fluoride preparations); benzodiazepines; drugs sold with associated tests or monitoring services which are available exclusively from the manufacturer; over-the-counter medications; and cough and cold products. The Secretary of Health and Human Services is authorized to add to this list if data obtained from state drug utilization reviews suggest that such addition is warranted.

The budget legislation also mandates a number of studies, among them a prospective and retrospective drug utilization review program that includes an educational outreach component targeted at improving drug prescribing and dispensing practices. The legislation also requires the Secretary to study the impact of prior approval programs on beneficiary and provider access to drugs, the impact of states developing prior approval restrictions based on costs, and to make recommendations on reforms of prior approval programs, if needed.

- *Research and experimentation tax credit.* The budget bill extends the 20 percent research and experimentation tax credit for qualified research expenditures until December 31, 1991.
- *Orphan drug tax credit.* H.R. 5835 also extends the 50 percent tax credit for clinical testing of drugs for rare diseases until December 31, 1991. Because the final version of H.R. 5835 is not yet publicly available, it is not known whether the tax credit had simply been reauthorized without changes or whether it had been expanded to cover preclinical testing expenses.
- *Capital gains tax differential.* The bill also contains a small capital gains differential for upper bracket taxpayers.

The legislation creates three tax brackets: 15 percent, 28 percent, and 31 percent. For taxpayers in the 15 percent and 28 percent brackets, capital gains will be taxed at the same marginal rate as earned income. For taxpayers in the 31 percent bracket, however, capital gains will only be taxed at a marginal rate of 28 percent. (The 31 percent bracket begins at incomes of approximately $115,000 for single taxpayers and $168,000 for couples filing jointly.)

—Lisa J. Raines

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DRUG DELIVERY

CORTECS WHETS SOME APPETITES

LONDON—With the reliability of a comet but the brightness of a supernova, the phenomenon of oral insulin delivery reappears periodically to tantalize pharmaceutical executives with the prospect of totally eclipsing competitors' market shares. Every five to ten years since 1926, wary watchers say, the story returns. The latest sighting—the Macromol technology from the small U.K. company, Cortecs (Isleworth), an 85 percent owned subsidiary of Australian pharmaceutical investors, Western Capital (Perth)—is attracting more serious attention than most.

At least part of the reason is that this time there are more polypeptides than insulin to deliver. Also, confidence in the prospect of oral delivery is growing: "There is no doubt that the premise of oral delivery is fine and there are a number of promising systems," said one U.S. drug delivery expert. The question is, "Is the Cortecs system one of them?"

In essence, the Cortecs polypeptide delivery system supplies the active polypeptide with aprotinin (as a protease inhibitor) disguised as fat—in the aqueous interior of artificial chylomicra. Chylomicra are the protein-lipid complexes which form naturally at the intestinal mucosa during the absorption of triglycerides. Once formed, the chylomicra enter the lymphatic drainage system of the gut which leads to the lymphatic system, entering the circulation via the thoracic duct. What is contentious about the Macromol technology is the mechanism needed to cross the gastrointestinal (GI) tract. According to the head of one eminent group working on oral delivery, the Cortecs proposals "bear no relation to any known mechanism in physiology. They ignore the whole process of fat digestion; I don't find it plausible." Conventional thinking would dictate that artificial chylomicra in the gut could not in effect be absorbed intact through the intestinal epithelium.

Michael Flynn, Cortecs' chief executive, is frank about this apparent leap of faith: "Macromol technology is based upon the assumption that we don't know what is happening to the fats....We cannot comment from the high ground of knowledge—the only thing to do is try it. Whether that is the mechanism, we don't know—but it works."

And clearly it does work well enough to interest a number of major companies. In 1989, Cortecs came to licensing agreements with Rorer (Fort Washington, PA) for the use of the Macromol system for calcitonin and antidiuretic hormone and with American Cyanamid for porcine calcitonin. In August this year, development collaborations involving Hoffmann-La Roche (Basel, Switzerland) on α-interferon and Ortho (Rahway, NJ) on erythropoietin (EPO) were announced. Small-scale human volunteer trials of oral EPO and human growth hormone have been conducted and, according to a Roche spokesman, feasibility studies with oral α-interferon will begin soon. The Rhone-Poulenc (Paris)/Rorer merger and a disappointing volunteer trial in London, however, have set the calcitonin project back 12 months.

Doubts still linger in both industrial and academic quarters, especially concerning the data that the Cortecs sales group has made available on a very selective basis. Claims made for 50 percent bioavailability of oral EPO need to be contrasted, said one consultant, with bioavailabilities of only 20 percent for oral ampicillin or one percent with nasal insulin. Another felt that the clinical trials had "thrown up odd data which look incorrect."

The other major cause for concern was the absence of knowledge of the mechanism of transfer across in the GI tract. "If you don't understand the science, you may find you're causing some damage," explained a British drug delivery expert. "They are throwing everything except the kitchen sink into the system. There are huge amounts of oleic acid [a known surfactant] in the formulation, so the question is whether it is really a chylomicron or there is some other mechanism." The U.S. Food and Drug Administration (Bethesda, MD), for one, is not happy with such unknowns even when, as is the case for all the Cortecs formulations, the active principle and excipients are all approved entities. Its attitude is "If you're defeating a natural barrier, we want to know how."

It doesn't look as if Macromol will have an easy ride to the multi-billion dollar market for oral polypeptides. Travers summarizes the difficulties: "We could probably struggle through without further cash calls. On the other hand, we may need further financing...As long as the science performs, it's possible to finance it through. But we won't be believed until we produce decent data." That, for Macromol, Cortecs, and Western Capital, must be the next step.

—John Hodgson