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TAXOL, A TEST FOR TECHNOLOGY TRANSFER

by Bruce A. Chabner

Only occasionally do we have the good fortune of finding a new active agent for treating cancer. The existing array of known active agents numbers less than 50, of which only a handful are indispensable. Thus, the identification of a new, significantly active drug is cause for great excitement and interest. In the case of taxol, this is heightened by its unique mechanism of action, by the environmental issues related to securing adequate supplies, and by the legal and philosophical questions surrounding its commercial development. I will address the latter.

Following the discovery of taxol's potent antitumor activity, the National Cancer Institute (NCI) faced the necessity of finding a commercial partner to develop and market the drug, for which no patent protection exists. The Federal Technology Transfer Act of 1986 (FTTA) provides a unique mechanism, the CRADA (Collaborative Research and Development Agreement), by which the government and the private sector may cooperate as partners in product development. While in this instance a CRADA could not provide a guarantee of market exclusivity for the commercial partner, the partner would enjoy the significant advantage of exclusive access to NCI preclinical and clinical data in return for its commitment to develop the drug. In October 1989 we advertised in the *Federal Register* for a partner for taxol development, and received four responses. Of these, Bristol-Myers Squibb (BMS) was clearly the best equipped to manage taxol production and testing, as none of the other applicants had significant experience in cancer drug development. Last January, BMS and NCI signed a CRADA pledging both parties to joint testing and development of taxol. BMS accepted primary responsibility for producing the drug and bringing it to commercial status; NCI committed its support for clinical trials. The most pressing problem in taxol development was, and remains, drug supply. Expansion of clinical trials and the provision of drug for recently established indications (relapsed ovarian cancer) will require emergent access to trees and redoubling of efforts to find alternative sources of the drug. In support of the NCI-BMS CRADA, the U.S. Departments of Agriculture and the Interior signed memoranda of understanding with BMS and NCI, in which they agreed to give BMS exclusive access to yew trees on federal lands for the next five years. BMS agreed to support a detailed survey of yew trees on federal lands. Current plans call for the harvesting of approximately 35,000 trees this year, from an estimated 20 million yew trees on federal lands. At the same time, NCI began funding of 13 new grants to universities and companies to encourage identification of alternative sources of taxol (by chemical synthesis, plant culture, and other approaches).

Aspects of the plan have raised a number of questions. On July 29, the House subcommittee on regulation, business opportunity, and energy held a hearing to examine the taxol CRADA, the memoranda of understanding, and their potential effects on taxol pricing and competition in the marketplace. Among the questions raised where these:

Was the public adequately protected from price gouging in the CRADA agreement? The CRADA contains a general clause obliging BMS to charge a fair price, taking into account the government's contribution to taxol development. It stipulates that the government may revoke the CRADA at any time, if it feels that public health interests are not being served. Rep. Ron Wyden (D-OR) suggested that a formal mechanism should be in place to evaluate the "fairness" of pricing of government-licensed products. Given the complexities of determining a fair price, particularly for a product that has no patent protection, this is a formidable task—one that the National Institutes of Health (NIH), according to the head of its licensing office, Reid Adler, has neither the staff nor the expertise to handle. The FTTA does not assign a price-regulating role to agencies that enter into a CRADA with the private sector. In this instance, NIH would not seem to be the best agency to make determinations about pricing. The uncertainty of the drug's supply and the difficulty in predicting future production costs compound the problem. Interpreting and enforcing the existing "fair pricing" clauses certainly requires additional thought and possibly Congressional action. There is a possibility that in establishing a sophisticated mechanism for examining price, the government will discourage potential licensees and CRADA partners from undertaking cooperative commercial ventures with Uncle Sam's scientists.

Do the CRADA and the memoranda of understanding give BMS a "lock" on an important new drug, i.e., *are the agreements anticompetitive?* Certainly the agreements do pledge the NCI to exclusive cooperation with BMS on taxol and give BMS, at least for the short term, exclusive access to yews on federal lands. There are, however, clear benefits to the government and the public. The agreements commit BMS to supplying the drug for clinical trials, to expeditious development and marketing of an important new agent, and to a plan that will assure attention to environmental concerns and preservation of the species. Further, since no patent exists for taxol, other companies are free to develop the drug for uses other than ovarian cancer (BMS has obtained orphan-drug status for that). NCI is actively pursuing a taxol analog, taxotere, in cooperation with Rhone-Poulenc Rorer, and through its grants program supports the taxol-related research of a number of private companies and academic groups independent of BMS. NCI is thus a major force for encouraging competition.

Would the public be equally well served, or perhaps better served, by the sharing of NCI's taxol data with multiple commercial partners? While we have no clear data to answer this question, it is our experience that companies will not commit the necessary amounts of capital and staff time unless they have some guarantee of a marketing advantage. In the case of taxol, where the development costs are huge and the drug supply presents a significant, unresolved problem, we believed that no company would undertake its development without such guarantees. The few responses to the CRADA advertisement testify to these uncertainties.

The taxol case has generated widespread public interest and discussion of the environmental issues and of the partnership of government and industry in drug development. Nevertheless, it is clear that the drug represents a significant discovery and that, because of the CRADA mechanism, taxol will be available to the patients with ovarian cancer who now need it.

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