# More Uses for Taxol and Neem

*The drug Taxol has recently been approved by the Food and Drug Administration for treatment of breast cancer in addition to ovarian cancer. Pending FDA approval, new methods of production will put the issue of harvesting Pacific yew trees to rest. Neem-based biopesticides are being introduced for use on food crops.*

In mid-April 1994, Taxol, previously approved for the treatment of ovarian cancer, was also approved by the U.S. Food and Drug Administration (FDA) to treat breast cancer. Treating other forms of cancer with Taxol is still being explored.

With the approval for use on breast cancer, the demand for Taxol is expected to increase. The number of patients being treated with Taxol is already on the rise, as the drug is now commercially available for both breast and ovarian cancer. Patients may receive Taxol treatment from their own doctors as well as through the National Cancer Institute (NCI). NCI is now completing smaller scale studies and moving on to larger (Phase III) studies, in which even more patients will be treated. Currently, NCI receives all of its Taxol from Bristol-Myers Squibb (BMS).

**Will Needles Be a Source of Taxol in the Future?**

To date, deriving paclitaxel (the bulk drug containing Taxol) from the bark of the Pacific yew tree is the only FDA-approved process. The leading supplier is Hauser Chemical Company, currently the sole supplier of paclitaxel to BMS. However, BMS has announced that it will not renew its contract with Hauser for paclitaxel from Pacific yew bark when the current arrangement expires in August 1994. Pacific yew bark is not currently being harvested; the 1993 harvest is still supplying paclitaxel. Also, BMS does not anticipate additional harvesting in 1994. This is due in large part to recent advances in semi-synthetic production methods, particularly needle- and twig-derived paclitaxel. Such a process is currently awaiting FDA approval and, if granted, will supply BMS with a precursor used to produce Taxol.

BMS, working with an Italian natural products company, has successfully commercialized a semi-synthetic method using needles and twigs from European and Asian yews to produce 10-deacetylbaccatin III, a precursor of paclitaxel. Unlike the bark-removal method, the trees are not destroyed and may be reharvested in the future. Use of this process is pending completion of a small clinical test to insure safety of the product. Results will be submitted to FDA for evaluation.

**Other Production Methods Also Gain Ground**

Currently, BMS still has a firm hold on the U.S. Taxol market, and the competitiveness of other companies and methods depends on FDA approval and economic feasibility. However, competitiveness does seem to be increasing as individuals and organizations are applying for patents and FDA approval on specific processes and paclitaxel-like analogs and compounds.

Pharmaceutical and other biomedical research companies are involved in taxane (paclitaxel and related compounds) research and development, and combined efforts are often key to "new" taxane products. Phyton Catalytic, Inc., and BMS have agreed to continue studying paclitaxel production using Phyton's plant-cell culture technology, which is based on a patent by USDA's Agricultural Research Service (ARS). Phyton Catalytic has established a wholly owned subsidiary in Germany to begin scale-up production. Though no pharmaceuticals in the United States are commercially produced using this technology, several companies see potential for low-cost production in the future.

PHYTOpharmaceuticals, Inc., a subsidiary of ESCAgenetics, is also working on tissue culture production. This process is now entering a preclinical scale-up and commercialization agreement with Sun Hill Glucose Company, Ltd., a Korean firm that manufactures food and pharmaceutical products. This technology is still under development. The scale of production will have to rise and costs will have to come down to compete with bark and needle methods.

In addition, PHYTOpharmaceuticals and Enzon, Inc., have been working to develop new forms of paclitaxel using PHYTOpharmaceuticals' tissue culture technology and Enzon's PEGnology (attachment of polyethylene-glycol molecules to therapeutic molecules). This technology will hopefully reduce allergic reactions to treatment and increase solubility, thus shortening treatment administration time. ESCAgenetics has received a Phase I Small Business Innovation Research grant from NCI to produce novel taxoids, and has patents on its tissue culture process to produce taxoids.

Total synthesis of paclitaxel has been achieved by two separate groups using two different methods. One group, at Florida State University, used a linear approach in which the molecule is built piece by piece. The other group, at Scripps Research Institute (University of California, San Diego, CA), used a convergent strategy in which two halves of the molecule are built separately and then joined. Though both procedures are scientific break-

throughs, the complex, multi-step processes are not currently economically competitive.

**International Taxane Research Expanding**

Worldwide taxane research and development is growing. Foreign-based pharmaceutical manufacturers are competing for market share. Celex Laboratories, Inc., a subsidiary of Multiplex Technologies, Inc., (Vancouver, B.C.), has produced paclitaxel using hairy root cultures of Pacific yew trees. The cultures grow quickly, and contain harvestable quantities of target materials within 3 weeks. Celex has applied for U.S. and international patents, and is waiting for FDA approval. Pending approval, the company hopes to begin production by the end of 1994.

Another Canadian pharmaceutical company, Towers Phytochemical, has also entered into an agreement with Vestar, Inc., to develop, produce, and market a generic form of paclitaxel in Canada. Towers is supplying the paclitaxel, while Vestar is researching a liposomal encapsulated product.

As stated in the June 1993 issue of this report, European pharmaceutical company Rhone-Poulenc Rorer is continuing research on its paclitaxel-like compound Taxotere. Phase II clinical trial results indicate that Taxotere may be useful in treating patients with various types of cancer.

**Neem-Based Biopesticides To Be Used on Food Crops**

According to a Business Communications Company, Inc., (BCC) report, use of biopesticides is expected to increase as new regulatory restrictions remove some synthetic pesticides from use. As reported in the *Chemical Marketing Reporter*, BCC anticipates "soft pesticide" (pyrethoids) sales to surpass $1 billion by 2002. Other biopesticide sectors expected to grow over the next decade are bacterial, viral, and fungal pesticides.

As mentioned in the December 1993 issue of this report, seeds of the neem tree, which is native to India and Burma, have shown much promise as a natural pesticide. Azadirachtin, the seed's primary active ingredient, has been found to be effective against more than 200 types of insects while being "environmentally friendly." Azadirachtin seems to have little toxicity to mammals and many beneficial insects, and degrades quickly in the environment.

Since the U.S. Environmental Protection Agency (EPA) approved neem-based biopesticides for use on food crops in July 1993, specialty chemical manufacturer W.R. Grace and Company has registered its Neemix brand biopesticide in 39 states. Widespread commercial use may be possible in the future, as Grace announced in March 1994 that it was marketing Neemix through Helena Chemical Company in Florida for use on vegetable crops.

AgriDyne Technologies, Inc., also has entered the neem-based pesticide market. The company has patented a neem-seed refining process, as well as its own insecticide formulations. AgriDyne has registered two azadirachtin-based insecticides with EPA. These are in addition to Azatin EC, which is currently used on greenhouse and nursery crops.

In addition to pesticide uses, neem-based extracts are being tested for other applications that range from medicinal cures to agricultural uses. Folk medicine has been known to use neem to treat anything from fevers and ulcers to various kinds of tumors. Recent studies by ARS scientists have shown potential for neem oil to protect stored apples from fungal rot and slow the natural softening process. [Charles Plummer (202) 219-0886]