

Taxol—Update 1992

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One year ago in December 1991 at the I.P.P.S. Eastern Region in Long Island, I presented a paper with the same title as this one with the exception of the word 1992. I do not intend to repeat last year's words, but I will present a brief review for the sake of continuity.

The key word in the title of this paper is TAXOL, which is one of many taxane compounds. According to a December 18, 1991 Wall Street Journal article, taxol having shown effectiveness against ovarian tumors, "Now appears to be a promising treatment for advanced breast cancer." This statement is predicated on studies conducted by doctors at the University of Texas' Anderson Cancer Center in Houston.

One year ago, I mentioned an organization named "The Alliance for the Production of Taxol", and although loosely structured, it is still viable. This Alliance consists of nursery producers of *Taxus*, Ohio State University (OARDC), and the University of Mississippi. One of many purposes of the Alliance is to convince governmental agencies, and the pharmaceutical industry, that the drug can be economically produced from various plant parts of the ornamental cultivars of *Taxus* rather than destroying our native *Taxus brevifolia* by stripping bark. At an August, 1992 Pacific Yew Conference in Oregon, Dean Bibles, Division of Land Management, stated that 400,000 pounds of *T. brevifolia* is the commitment for 1992. That, good people, represents a tremendous number of irreplaceable trees from our Northwest forests. Best estimates tell us that in three years three million pounds of bark will be harvested! On August 5, 1992, I was in Virgin Flats, Oregon, in an old growth forest and saw 200-year-old, plus, *T. brevifolia* denuded of bark—dead!

Returning to history, starting on January 8, 1992 and terminating on May 15, 1992 the Alliance shipped 40,449 pounds of dry needles/twiglets of *T. × media* 'Hicksii' to the National Cancer Institute (NCI). The order was shipped to two NCI contract extractors, Polyscience, New Jersey and Hauser Chemical, Colorado. This was the first movement in the commercial processing of ornamental *Taxus* plant parts. Incidentally, that dry total of 40,449 pounds came from 102,000 pounds of green biomass, and at 0.02% taxol is enough drug to treat 1,250 women.

Obviously, there are a myriad of questions relative to this topic. In reflection, I shall address a few of the most asked questions I have answered in the past four years.

First, and probably foremost, what is the status of a taxol market other than bark, in December, 1992? I have answered this question countless times with this answer: There is, unquestionably, a world wide market for the drug but there is only one United States buyer (Bristol-Meyer Squibb), who is limited by NCI to using bark from *Taxus brevifolia*. In this light, Bristol-Meyer Squibb announced at the August conference in Oregon that they will be "out-of-the-woods" in 1995 and that 30% of the biomass will be from "plantations" (nursery community). I desperately want to believe that statement, however I am skeptical! We all must

be aware that federal approval (NCI) has not been given for drug manufacturing derived from needles rather than bark. Our dreams and aspirations are to have federal approval for the genus *Taxus* rather than specific species, varieties, or cultivars. This is not going to be easy to achieve since there are still a few native *T. brevifolia* trees to rape of their bark. According to Paine-Webber Securities, taxol is a potential billion dollar drug.

A second most asked question is what cultivars of *Taxus* are best for taxol production? Although *T. x media* 'Hicksii' is well documented for taxol content, researchers are vigorously exploring the possibility of taxane content in *T. cuspidata*, *T. cuspidata* 'Capitata', *T. x hunnewelliana*, *T. x media* 'L.C. Bobbink',

PRE-DRYING STORAGE RECORD

TAXUS VARIETY _____

CARRIER: _____ REEFER TEMP _____ °F

NURSERY: _____

RECEIVING TIME _____ : _____ AM/PM DATE: ____/____/____

FACILITY

NAME/LOCATION _____

BUILDING TYPE _____

INTO STORAGE

TIME _____ : _____ AM/PM DATE ____/____/____

CONDITION OF BIOMASS _____

SIGNATURE _____

STORAGE CONDITIONS

TEMPERATURE: MINIMUM _____ °F MAXIMUM _____ °F

HUMIDITY: MINIMUM _____ % MAXIMUM _____ %

DATA RECORDED BY: _____

OUT OF STORAGE

TIME _____ : _____ AM/PM DATE ____/____/____

SIGNATURE _____

STORAGE PROBLEMS

PLEASE NOTE PROBLEMS: (MOLD, REFRIGERATION, ETC.)

FRESH WEIGHT

_____ POUNDS _____ OUNCES OR _____ KILO _____ GRAM

NUMBER OF PLANTS _____

TIME _____ : _____ AM/PM Date ____/____/____

DATA RECORDED BY _____

DATE ____/____/____ LOT # _____

PRE-DRYING ACTIVITIES

Root Removal _____

Signature _____ Date ____/____/____

DRYING CONDITIONS RECORD

INTO DRYER

Time _____ : _____ AM/PM DATE ____/____/____

OUT OF DRYER

Time _____ : _____ AM/PM DATE ____/____/____

PLANT PARTS DRYED

CIRCLE ALL THAT APPLY

NEEDLES _____ STEMS _____ ROOTS _____ WHOLE PLANT _____

DRY WEIGHT

_____ POUNDS _____ OUNCES OR _____ KILO _____ GRAM

NUMBER OF PLANTS _____

TIME _____ : _____ AM/PM DATE ____/____/____

DRYER NOTES

DRYER TURNED OFF: TIME _____ : _____ AM/PM

PLANT POSITION IN DRYER: _____

OTHER: _____

DRYER CONDITIONS

TEMPERATURE: MINIMUM _____ °F MAXIMUM _____ °F

OUTSIDE TEMP: MINIMUM _____ °F MAXIMUM _____ °F

DATA RECORDED BY: _____

DATE ____/____/____ LOT # _____

CHEMICAL SAMPLES

WHOLE PLANT - 1 PLANT PER 1,000 PLANTS
CUT TOPS AND FREEZE

CUTTINGS/CLIPPINGS

FRESH AND FREEZE _____

DRY AND FREEZE _____

DRY TO COMMON STORE _____

DRY TO COMMON STORE _____

SIGNATURE _____

DATE ____/____/____ LOT # _____

Figure 1. Nursery Field record and storage record for taxus plant parts.

T. × media 'Dark Green Spreader', *T. × media* 'Densiformis', *T. × media* 'Henryii', *T. × media* 'Runyan' (Media #8), and *T. × media* 'Wardii'. European research is also being conducted using *T. baccata*. Dr. Ed Croom (Mississippi), Dr. Dave Ellis (Wisconsin), Dr. Bob Schutzki (Michigan), and Dr. Nick Wheeler (Washington) are a few of many researchers conducting extensive cultivar evaluations.

A third often asked question would be "Who are the major players relative to this topic?" It is obvious that Bristol-Meyer Squibb (B-MS) is at the top of the list due to their CRADA obligation to NCI. The B-MS facility in Puerto Rico to produce the drug is indeed impressive. Governmental "players" are headed by the National Cancer Institute, and include U.S.D.A., Forest Service, and the Bureau of Land Management. There is also Canadian Government involvement particularly in the Province of British Columbia. Many colleges and universities are exploring various avenues of research largely dependent on grants to supply research dollars. Dr. Dave Ellis and Dr. Brent McCown (Wisconsin) are doing intercellular research to determine where taxane compounds are found in cells. Dr. Ed Croom (Mississippi) is conducting a seasonal hedging study of various *Taxus* cultivars in production nurseries. Dr. Pete Kaufman (University of Michigan) is doing clinostat studies to simulate microgravity. He hopes to have potted *Taxus* liners in an upcoming NASA space shuttle! Dr. Bob Schutzki (Michigan State University) is including field fertility studies with various rates of nitrogen. Virtually every university in our country has some degree of research in this area. During the recent I.P.P.S. Western Region tour, we saw a poster relative to Dr. Don Durzan's taxol research at the University of California, Davis, California.

Other important "players" include Hauser Chemical Research (Colorado), Indena (Italy), and Weyerhaeuser (Washington). Hauser has stated that in 1993 they will have a production capacity to extract 200 kilos of taxol. Indena is presently a producer for Bristol, and are processing roots of *T. × media* 'Hicksii' for an unannounced substance. Weyerhaeuser have had extensive R & D studies for the past five years relative to taxol production via cultivation. They recently published in the "Journal of Natural Products" the taxol content in various *Taxus* species and cultivars. They commented at the August 4, 1992 Oregon conference that field cultivation (plantations) was 700,000 units in 1991, 4,000,000 units in 1992 and perhaps 10,000,000 units in 1993 in Washington.

In my view, *Taxus* growers in the nursery community have a second market for this genus. The early pioneers, Croom specifically, have emphasized biomass from a sustainable source of supply and at long last, certain people are listening to his words. I am attaching to this paper copies of forms used in the Alliance shipment to NCI on the chance that someone in the room might make *Taxus* plant part shipments. These records are very, very important, and Croom and Shugert wish to share this with you.

I wish to close this paper by quoting, in part, from a letter received from Mrs. Claude Petek, Brecksville, OH. "I am a survivor of ovarian cancer because of the drug taxol. In my opinion along with my doctors at the Cleveland Clinic feel I received a second chance on life. I feel that it is a miracle drug that needs to be made available to more women".

There isn't much more to add to those poignant words. Repeating my words of one year ago, "As plant propagators, we once again have the opportunity to utilize the plant parts of *Taxus* to save lives, in addition to beautifying the world." By seeking and sharing we can accomplish this humanitarian goal.