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Linking Medicinal/Nutraceutical Products Research with Commercialization

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Abstract

Thousands of bioactive phytochemicals have potential or established pharmaceutical, medicinal, or nutraceutical applications. Developing crops for bioactive compound extraction presents both research and development challenges and market-related considerations. Demonstrating that cultivation is economically viable is not sufficient. Using examples from both cultivated medicinals and our experience with *Taxus canadensis* Marsh., we discuss two types of market factors that must be considered before commercialization can proceed. Bioproduct market factors include availability of a cheaper product elsewhere from the same species; other species with the same bioactive compound; existence of a synthetic alternative to the naturally sourced phytochemical; the patent suite covering bioproduct extraction and use; commodification; and government bioresource regulation. The role and suitability of an industrial collaborator proposing to fund R&D activities also must be gauged by the R&D partner. The assessment should include the company's knowledge of the marketplace; its capacity to sustain the proposed R&D funding; whether the intent is to market raw biomass or a value-added product; and how it is proposed to handle exclusivity and proprietary information. The economics of cultivating elite *T. canadensis* cultivars are also briefly summarized. It is concluded that consideration of bioproduct marketing realities can help to focus R&D goals and timelines based on both biomass cost reduction (or improvement in quality) and meeting the industrial collaborator's specific needs.

Keywords: Bioproduct market, commercialization, medicinal crop, paclitaxel, pharmaceutical crop.

Introduction

Conventional Western medicine relies heavily on phytomedicines: 50–60% of pharmaceutical commodities contain natural products or are synthesized from them. Between 10% and 25% of prescription drugs contain one or more natural bioactive compounds (Small & Catling, 1999). New bioactive compounds are continually being found or rediscovered using information based on ethnobotanical studies and indigenous uses. One estimate of medicinal plant use suggests that more than 35,000 species are used worldwide (Farnsworth & Soejarto, 1991). Moerman (1998) lists more than 2500 plants, many with multiple uses, in the North American aboriginal pharmacopiea alone. Many medicinal products are, or originally were, derived from woodland plants, also called non-timber forest products (NTFPs). Leakey and Newton (1994) have aptly used the term "Cinderella" species to describe the undeveloped potential of such plants. However, a considerable developmental gap exists between the commercial NTFP crop produced for industrial sale, often internationally, and a traditionally used woodland-harvested (wild-crafted) plant within a local community or region.

Introduction of new plant crops for the pharmaceutical/medicinal industry is market driven. Determining which plants and compounds are realistic candidates for commercialization-oriented research from among the large number of potentially valuable bioactive compounds requires consideration of market-related factors in addition to the science and technology involved in product development. The analysis presented here, although it concentrates on woody perennial NTFP

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domestication (the process of wild cultivar selection, propagation, and cropping), is equally applicable to herbaceous medicinal species. Cropping methods for NTFPs can vary as well, from nursery or plantation-based farming to a variety of agroforestry strategies.

For the R&D specialist, attempting perhaps to expand a rural industry or to assist a local bioproduct enterprise to diversify, the wide spectrum of choices for development of new crops for the pharmaceutical and medicinal industries leads immediately to two questions. First, which plants and compounds from among the large number of potentially valuable bioactive compounds are *realistic* candidates for research directed at commercialization. Second, having selected a phytochemical or species, what additional market-related factors should be considered?

The first question is quite easily answered: NTFP domestication and commercialization is more likely to yield a saleable product when a market preexists for which there already is, or is likely to be, a product shortage. Indeed, Leakey and Izac (1996) suggest that agroforestry or field cultivation can be viewed as the fourth or fifth evolutionary stage of an exploitation process that begins with extractivism for personal use and culminates with high-technology applications (e.g., biosynthesis, cell culture, genetic engineering) when the bioproduct becomes sufficiently valuable or scarce. Bioproduct activity itself—even if the compound is uniquely valuable for a potentially large market such as cancer chemotherapy—is unlikely to be sufficient rationale prior to its commercial emergence to justify jumping ahead of anticipated demand by cropping to stockpile a supply. The reason is simple: new compounds require a long and expensive development period even after their efficacy is demonstrated. For instance, in the pharmaceutical industry, arguably the most difficult sector in which to introduce a new medicinal product, it is estimated that less than one pharmacologically active compound in 5000 will reach the marketplace (Iwu, 2002b), requiring 15 years of development (Iwu, 2002a) at a cost up to US$800 million (DiMasi et al., 2003). Realistically, then, for most bioproducts, only species already for sale in established, widespread markets are likely to be good candidates for domestication and commercial cropping unless the industrial partner in the R&D collaboration has the resources to sustain a prolonged period of no returns from cultivation prior to product marketing and sales.

Resolution of the second question—the consideration of market factors—is more complex, even when technical or biological problems associated with cultivation can be overcome. With global sales for medicinal plants estimated at US$60 billion by the World Health Organization and given the many plant species in the marketplace, it is tempting to regard the prospect of commercial crop production as a straightforward process of cropping followed by sales to eagerly waiting clients provided the price is right. The reality is that 70–90% of medicinal plant species are wild-harvested for local or regional use (Iwu, 2002b) by populations with limited or no access to Western-style medicines. Even in contemporary Western medicinal markets where, in addition to pharmaceuticals, the consumer-driven range of medicinals and nutraceuticals is expanding, the actual number of different mainstream plant species accounting for the bulk of over-the-counter (OTC) sales is small. In the USA in 1998, US$1.7 billion in OTC medicinal sales were dominated by just five botanical products (Gingko, St. John's wort, ginseng, Echinacea, and garlic) which accounted for more than three-times the sales of the next five (Iwu et al., 2002). The small number of commercially cultivated medicinal plants, thought to be about 50–100 species (Iwu, 2002b), suggests that issues in addition to those such as volume of demand (tonnage), market niche, and/or sustainability should be considered. This presentation focuses on some aspects surrounding strategic market factors using examples from both commercially bioactive crops produced worldwide and our experience at the Canadian Forest Service–Atlantic Forestry Centre (CFS–AFC) with *Taxus canadensis* (Taxaceae) Marsh., commonly known as ground hemlock or Canada yew.

The Case for a Commercial *Taxus* Crop

A cursory analysis of the commercial potential of yew, and particularly *T. canadensis*, suggests that entry into the pharmaceutical marketplace should be straightforward. Paclitaxel, also called Taxol, is a well-established cancer drug that has been sold by Bristol Meyers Squibb (BMS) for clinical use since 1992 and has been called the largest selling anticancer drug in the world (Goodman & Walsh, 2001). Taxol and the closely related taxane Taxotere (docetaxel, produced by Aventis) had sales in 2001 of US$2.3 billion (Anonymous, 2002). Recently, BMS's exclusivity has ended, resulting in generic paclitaxel available for sale by other large pharmaceutical companies (e.g., Ivax, Mayne, and Mylan). Market demand is expected to grow by 10% each year for at least the next decade and new, second- and third-generation paclitaxel formulations and analogues may serve to lengthen the compound's life span (Anonymous, 2002).

Although the paclitaxel molecule has been synthesized, it is an expensive process. Fermentation and cell culture methods are still under development. Plant biomass continues to be the most economical source of the drug (Anonymous, 2002), but woodland sources are increasingly in short supply globally (Schippmann, 2001). Commercial nurseries in the United States produce millions of plants for sale in the horticultural market, but our discussions with industrial sources indicate that the amount of nursery biomass remaining for sale to the taxane industry is inadequate to meet the total demand.

The *Taxus* domestication project began at CFS–AFC in 1997 at the behest of an industrial client with the goal of rearing *T. canadensis* as a hedged- or row-crop for paclitaxel production. The term ''domestication'' in the current context may be defined as the interrelated phases in the process whereby a wild species is genetically selected to produce elite cultivars, propagated, then reared as an industrial crop. The industrial client was ultimately unable to find a successful path to commercialization and thereby raise the funds necessary to provide adequate support for the project. Subsequently, a number of other prospective collaborators—companies both large and small—followed the same pattern, initially enthusiastic about commercialization, only to be frustrated in their attempts to craft a successful strategy that would permit product sales. A careful analysis by Lyceum Ltd. of 10 failed commercial initiatives in Atlantic Canada over the past 8 years revealed fairly predictable causes such as undercapitalization, underestimation of chemical engineering development and validation costs, failure to meet the expectations of understandably skeptical clients, lack of industrially acceptable standard operating procedures (SOPs), and inadequate knowledge of taxane biology and chemistry (K. Kierstead, 2003, personal communication). *Taxus* R&D infrastructure is similarly limited. Pockets of scientific expertise exist in eastern Canada but they are small, fragmented, and almost always proprietary, with widely differing premises, resources, and assumptions.

The search to find support for the *Taxus* domestication project, now funded, has been the source of valuable experience on the R&D/phytopharmaceutical industry interface and other important factors to consider prior to collaboration. We quickly realized that, in order for the *Taxus* domestication project to succeed, we needed to know more about both the bioproduct marketplace and any potential partner's suitability to better position scarce R&D resources—despite the obvious demand for paclitaxel, its high value, and the apparent commercial feasibility of cropping.

Important Bioproduct Market Factors

The R&D partner needs to acquire some elementary knowledge about the commercial aspects of the niche into which the candidate bioproduct must fit, preferably even before approaching potential collaborators. For example, an estimate of the longevity of the bioactive compound as a saleable marketplace commodity is important. If product sales are likely to continue for an indefinite period, as may be the case with many of the well-known nutraceuticals, such as glucosamine or Echinacea, then long-term consumer demand may be assumed. In contrast, the life span of compounds such as pharmaceuticals may be shorter, as new, more effective drugs and therapies emerge to replace them. The significance of a bioactive compound's product life is that timing is an important component in planning realistic research objectives. Additional basic questions about the economic consequences of the biology also need to be asked.

Can the same species be harvested and the crude product extracted more cheaply elsewhere in the world?

Many species have a wide distribution, some worldwide, and biomass containing the same bioactive compounds may be collected in different regions. Alternatively, and particularly if wild-harvested biomass is in short supply and/or prices are sufficiently high, it may be possible to cultivate plants from seed as agricultural or agroforestry crops, thereby making cropped biomass widely available. An added advantage is that cultivated plants can be fertilized, tended, selected, and bred to produce uniform crops of elite cultivars with a higher bioactive content. Species such as American ginseng (*Panax quinquefolius* Araliaceae L.), evening primrose (*Oenothera biennis* Onagraceae L.), and cranberry (*Vaccinium macrocarpon* Ericaceae Ait.) are only three of numerous examples where cultivation has replaced wildcrafting.

The production of paclitaxel presents an interesting hybrid of commercial and biological constraints. Because the North American pharmaceutical industry is the main market for paclitaxel sales, U.S. Food and Drug Administration (FDA) regulations apply. Introducing natural products into the U.S. pharmacopoeia is a highly regulated and complex process (McChesney, 2000). High standards of manufacturing (cGMP) are required, and a company's complete manufacturing process must be documented in a drug manufacturing file (DMF II), specifying the species and plant part, geographical location, and processing of the raw material (Shaw, 1987). Consequently, even though paclitaxel can be extracted from more than one *Taxus* species, once a pharmaceutical company has specified a particular species, it is not a trivial matter to amend the DMF II to change the source material. Wild-crafted material is also subject to an FDA sustainability requirement through the U.S. Code of Federal Regulations (21 CFR, part 25 ''Environmental Impact Considerations''). Biomass collection must be demonstrated to be sustainable and thereby subject to ''categorical exclusion'' from an EI assessment (i.e., wild harvesting must be shown to have no effect on abundance or biodiversity), which complicates the addition or substitution of a species.

Does another plant species (or genus) with the same suite of phytochemicals, perhaps in higher abundance, exist elsewhere?

Many phytochemicals occur widely in different plant families. The commercial outcome is that wild-craft

harvesting or cultivation in a competitive market may be more economically feasible elsewhere with a species other than the one available locally. Mayapple (*Podophyllum peltatum* (Berberidaceae) L.), although distributed widely in North America, is not the main source of podophyllotoxin, which also can be found in the Himalayan species *Podophyllum hexandrum* (Berberidaceae) Royle (Moraes et al., 2000), now placed on the Convention on International Trade in Endangered Species (CITES) list due to overharvesting (Schippmann, 2001). A number of other species are reported to contain minor amounts as well (Schmidt, 2002). Similarly, camptothecin, an anticancer alkaloid, is found in different trees from China (*Camptotheca acuminata* Nyssaceae Decne.) and India [*Mappia foetida* Miers. or *Nothapodytes foetida* Icacinaceae (Wight) Sleumer] (Govindachari & Viswanathan, 1972). Diverse plant distribution potentially can also be of positive benefit, permitting a greater latitude in the choice of which plants to cultivate, as is the case, for instance, in the production of the nutraceutical antioxidant ellagic acid, which occurs in commercial strawberry, raspberry, and blackberry cultivars (Anonymous, 1999).

Paclitaxel occurs in varying amounts in all *Taxus* species (Croom, 1995), as well as some endophytic fungi (Walker & Croteau, 2001). The taxanes are a family of well over 350 diterpenoid compounds (Baloglu & Kingston, 1999), many of which are unique to a single species. Like many other phytomedicinal species, the *Taxus* species in several of the major wild-craft harvesting regions (India, Nepal, China) have already been placed on the CITES list of at-risk or endangered species (Schippmann, 2001).

The potential of *T. canadensis* to substitute for other *Taxus* species is considerable. First, the commercially available horticultural *Taxus* varieties are cultivars (clones) derived from plant breeding crosses chosen for their form, color, and so forth, and not for taxane content and, therefore, have only a limited potential for improved yields through genetic selection. *T. canadensis* has an extensive natural range and, therefore, a wide genetic base from which individuals with exceptional growth and taxane levels may be selected. Second, other taxanes are present, including 10-deacetyl baccatin III (10-DAB III), the semisynthetic precursor for docetaxel production, as well as one taxane found in high abundance uniquely in ground hemlock, 13-acetyl-9-dihydrobaccatin III (9-DHB III), which can also be used for semisynthesis (Nikolakakis et al., 2000).

Is there an identical, easily synthesized compound that can be commercially produced more economically than the naturally sourced phytochemical?

As noted in the ''Introduction,'' as more than half of all medicines come from natural sources (or have in the past), it is reasonable to expect the substitution of cheaply synthesized chemically identical compounds or even analogues of the natural material modified to improve their medicinal properties. One of the best examples of commercial chemical evolution is aspirin, or acetylsalicylic acid which is the modern substitute for the salicylates traditionally used for pain relief and found in various members of the willow (*Salix* spp.) genus (Marles et al., 2000).

Implicit to the notion of an easily synthesized alternative is that the bioactivity derives from a single compound. Often synergistic effects are found to occur when phytomedicinal extracts are used. The therapeutic effect(s) in medicinal products such as cat's-claw [*Uncaria tomentosa* Rubiaceae (Willd.) D.C.] is caused by a combination of different compounds in the plant (Williams, 2001). It is unlikely that synthetic alternatives can easily be found for such species, which makes a stronger case for their continued commercial wild-crafting and/or cultivation.

Although it is possible to produce taxanes, both through direct synthetic chemical methods and bioreactor culture (Walker & Croteau, 2001), neither route appears to be used extensively at present (Anonymous, 2002). Biomass remains the predominant resource for taxane supplies. As noted previously, the two advantages of genetic diversity and the presence of a unique taxane potentially give *T. canadensis* a competitive edge as an intensively cultivated Canadian crop over other species in regions where labor costs are low and/or biomass is in short supply. Several industrial sources have indicated to CFS–AFC that the comparatively high cost of woodland-harvested ground hemlock biomass is the chief disadvantage of sourcing Canadian purchases, illustrating that, though biomass is allegedly scarce elsewhere, *T. canadensis* must still be competitively priced.

Will commercialization of the compound(s) or bioactive derivatives be limited significantly by existing patents and/or their licensing costs?

A search of the existing patent literature should be regarded as a mandatory part of any new commercially oriented R&D project. Small searches may be performed without charge on both the U.S. and Canadian Internet patent sites, and patent information is useful in identifying the names of companies in the marketplace, the segment of the market they serve, and which ones might be interested in commercial exploitation of a particular bioproduct. The Internet also can quickly provide a snapshot of financial and technical information on specific companies.

Based on the distinction ''... between products of nature and ... human inventions'' (Manual of Patent Examining Procedure, 2001) neither wild plants nor naturally occurring compounds may be patented. However, both the therapeutic applications and modified

derivatives of the originally discovered phytochemical may be patented. The anticancer compounds betulinic acid (DasGupta & Pezzuto, 1997) and camptothecin (Wall et al., 1990), both secondary compounds from trees, are examples where patent protection has been implemented long in advance of clinical testing, marketing, and widespread use. Often, other companies or individuals rapidly follow with complementary patents covering additional applications, extraction processes, derivatives, and methods of administration.

A search performed at CFS–AFC in spring 2001 on the terms "Taxol," "paclitaxel," "taxane," and "Taxus" produced a list of more than 1800 U.S. and Canadian patents on items ranging from biomass drying ovens, through extraction, semisynthesis, and purification methods, to pharmaceutical formulations and new taxane analogues. Because *T. canadensis* biomass contains both paclitaxel and 9-DHB, the patent literature was of particular interest to us. The practical significance of an awareness of the patents held by a particular pharmaceutical company is that the information helps determine which taxanes they are likely to find of interest. A company owning only the patents for efficient paclitaxel extraction is less likely to be interested in 9-DHB, a taxane uniquely abundant in *Taxus canadensis* foliage, and therefore may not regard ground hemlock as particularly valuable in comparison with other *Taxus* species. A second company whose patents would allow efficient paclitaxel semisynthesis from 9-DHB III may value ground hemlock highly as they may need to purchase only half or less the amount of foliage or crude extract to meet their paclitaxel production target.

Is the bioactive compound already a pharmaceutical/medicinal commodity or about to become one?

Commodification is the converse of patent protection and may occur when the patent period protecting a company's rights to market a compound, process, or treatment expires, although many medicinal NTFP plants become commodities once the information about their efficacy becomes widely known, without ever having been patented. The consequence of commodification is an immediate increase in demand for the product and, in the case of pharmaceuticals, a decrease in the drug price. The case of *Prunus africana* Rosaceae (Hook. f. Kalkman), an African tree species whose bark is used for treatment of benign prostate disease, provides a well-known case of where, even despite the best intentions of the exporting company and local government, the massive increased commercial demand that began in the 1970s has resulted in chronic shortages (Cunningham & Mbenkum, 1993) and a current CITES Appendix II listing.

During 2001, the pharmaceutical company Ivax successfully litigated against Bristol Meyers Squibb, who had originally patented formulated paclitaxel under the tradename Taxol, allowing the sale of generic paclitaxel into the North American and European markets (Garber, 2002). Subsequently, several pharmaceutical companies interested in paclitaxel sales have entered the marketplace, with the result that the prices of both pure paclitaxel and the formulated drug have significantly decreased, as well as a rapid increase in the global demand for both *Taxus* biomass and the crude extract, which is sold at various purities for further refinement. The closely related synthetic analogue marketed by Aventis, docetaxel or Taxotere Trademark sign, remains under patent protection until 2007 in Europe and 2010 in North America. However, it can be anticipated that, when patent protection lapses, commodification may stimulate a similar increase in demand for 10-DAB III, which occurs in both *T. canadensis* and other *Taxus* species.

What role(s) does local government have in regulating access to the bioresource?

Governments are mandated both to protect the wild resource and to promote its sustainable development. Jurisdictional positions and policies define how conservation is implemented to limit commercial alternatives (e.g., the ability to harvest and export nonprocessed biomass). The vacuum created by the absence of effective legislation and/or enforcement can lead to abuses such as overharvesting.

Conversely, government economic development incentives (grants, loans) may be employed to entice prospective industrial clients to invest in infrastructure locally, for instance, by installing a processing facility close to the biomass source to produce a value-added product such as a high-quality extract. Such a strategy is beneficial to all parties: saving the company bulk transport costs and providing skilled employment opportunities to the local labor force. Government also may be the repository for accurate knowledge of existing wildcraft inventory through biomapping by natural resources departments.

CFS–AFC is coordinating the definition of scientifically validated guidelines for long-term sustainable *Taxus* harvest practices. However, in the absence of provincial government support, there is very little that can be done to ensure compliance and, thus, the long-term sustainability of the species. Therefore, endorsement by various jurisdictions (federal, provincial) has been sought to ensure universal commercial acceptance. Collateral benefits include increased confidence by multinational pharmaceutical companies in the stability and availability of the biomass resource and the resulting ability of local harvest contractors to secure long-term agreements with them.

One valuable method of compiling and integrating the above information is to engage initially in a

precommercial market study, either independently or preferably in collaboration with a prospective industrial collaborator. The value to the R&D partner of detailed market knowledge, in our opinion, cannot be overstated. Despite the value of the product, taxane manufacturing is a small, niche industry consisting of 30–40 companies, many of modest size, with only a few large, well-known corporations controlling most of the market. Other medicinal plant businesses are more highly fragmented and widely distributed.

Assessing the Industrial Collaborator's Suitability

It is helpful to focus on the concept that "the customer is always right." An R&D partner and their industrial collaborator are, in a very real sense, each other's customer. Getting the right fit to the market and to each other maximizes the chances for both successful R&D and subsequent commercialization, which are the goals for both partners. This means that the R&D partner should ask some basic questions about the qualifications of a prospective business partner in the same way that the potential industrial collaborator does their own "due diligence" to appraise the proposed research.

Does the company intending to finance the R&D work have adequate knowledge of the market in which they intend to sell the end product?

To submit a realistic business plan to a board of directors and/or an external funding agency that is likely to include funding for the R&D project, the industrial collaborator must be able to show profitability within a reasonable period or some measure of a competitive edge that makes the investment in research worthwhile compared to the alternatives. The better their acquaintance with the market, the sooner and more likely it is that a collaborative agreement can be successfully completed.

In discussions at CFS–AFC with a number of potential partners, we found that their level of market knowledge varied widely, from the extremes of having heard or read positive (and sometimes unrealistic) information through the public media to a detailed and proprietary appreciation of the paclitaxel market. The reasons for their interest were just as diverse, ranging from businesses with a general desire to expand into new product lines to those already in the taxane industry with very specific requirements.

Does the industrial collaborator have the size and infrastructure to sustain the proposed R&D funding?

A collaborator does not have to be a large corporation. However, if the company is small and new, their cash flow may be limited. Typically, they may be attempting to put together a combination of loans, grants, and sales agreements with other industrial partners. The R&D partner should see (and understand) the industrial partner's business plan before signing a collaborative agreement. Doing so can help highlight potential problems, such as the undue dependence of cash flow on, for instance, yet-unsigned contracts for processing biomass or a need for government assistance not yet granted.

The capacity of a small company to immediately start operation and generate profit is important. Their infrastructure, or lack thereof (for example, proposed cropland acquisition or purchase of specialized processing equipment as part of the business plan) can delay them getting started.

The potential concerns are different in collaboration with a large company (for instance, a corporation supplying pharmaceutical-grade paclitaxel to a major drug company or even the pharmaceutical company itself). Such a company, having already invested in the taxane market at another location, may wish to cultivate a crop or do the processing elsewhere. Particularly in dealing with a company already in the taxane marketplace, signing a nondisclosure agreement can be a valuable asset. It allows the R&D partner access to market information not available in the public domain.

Does the industrial collaborator intend to market the raw biomass or process it into a value-added product?

Biomass harvesting is a valuable source of income for rural, seasonally employed people. High-end employment (chemists, process engineers) accrues during the value-added, postharvest stage of biomass processing.

Generating high-quality skilled employment in eastern Canada is of great interest to both regional and federal governments for infrastructure development. The infrastructure exists to completely process *Taxus* biomass after drying, semisynthesize, and purify paclitaxel and other taxanes to pharmaceutical grade, reportedly at competitive prices. Nonetheless, the expressed intention of one potential industrial collaborator was to send *Taxus* biomass overseas for all further processing. Although it may make business sense to process offshore, it becomes more difficult to find a good fit with such a company. They also risk complicating their long-term biomass supply strategy, as several provincial governments are in the midst of legislating restrictions on transporting unprocessed biomass harvested on Crown land outside the province where it was harvested. One solution is to reach a compromise with the collaborator where the early steps of extraction and refinement to intermediate purity levels are done locally, and the extract is then exported for further processing.

What impact will the industrial collaborator's entry into the marketplace have on the resource?

To generate cash flow, the industrial collaborator likely will want to enter the bioproduct market as soon as possible—probably long before a commercially reared crop is ready for harvest—which means the company may have to depend on wild harvesting to source the required biomass. If significant amounts of biomass are needed (possibly by several competing companies), the impact on wild stocks can be immediate and severe. It is in the industrial collaborator's interest to ensure that not only their portion of the woodland harvest is sustainable, but that other competitors comply as well. Otherwise, their competition may commercially benefit from cheaper, unsustainably harvested biomass. They thereby ensure that they comply with FDA or other government environmental impact regulations, as well as maintaining a continuing supply of biomass for future harvest until the cropped biomass becomes available.

As a government department, part of the CFS–AFC mandate is to promote sustainable use of forest resources. An important part of the *Taxus canadensis* project has been the development of sustainable harvest guidelines, to which our industrial collaborator has agreed to comply. As noted above, the intent of the guidelines is to prevent overharvesting of existing woodland *Taxus* biomass, especially during the crop development R&D period prior to harvesting significant amounts of elite nursery biomass. It would be in direct conflict of CFS policy to partner with any industrial collaborator unwilling to adhere to sustainable harvest practices. The implications of practices and costs associated with ethical harvesting (preferably certified if that option is available) are issues that should be clarified early in discussions between the R&D and industrial partners.

How does the industrial collaborator propose handling exclusivity and proprietary information?

In return for supplying research funds, the collaborator may reasonably expect some degree of exclusive access to the findings from that work. In turn, the collaborator may also contribute expertise in developing the IP (Intellectual property) and integrating unique new developments into their production methods and/or patent holdings. The value of patenting capability should not be underestimated. It is, at best, a formidable, expensive process of preparation, research, and defense (patent examination) that is characteristically underestimated by both the scientists and the industrial partner involved. The collaborator may also know which existing patents are currently unencumbered by commercial licenses and therefore potentially useful.

The potential conflict between commercialization and the public good presents an interesting dichotomy. The process of reconciling commercial goals with government R&D policy is an issue too large to discuss here. However, some of the reasons for the CFS initial choice from among several prospective industrial partners and the practical accommodations subsequently negotiated with our industrial collaborator are worth noting.

Different companies offered to fund the *Taxus* project on several occasions before an agreement was finally signed. Exclusivity was one important consideration in the final choice of a partner. The alternatives were (1) to sign on with a single pharmaceutical supplier to give them sole exclusive rights to the domestication technology, or (2) to link with a local entrepreneur who could, in turn, market taxanes to several of those same suppliers based on separate biomass and (or) processing contracts with them. We chose the second alternative on the basis of the government perspective that choosing a company supplying more than one customer would be more beneficial overall to the taxane industry in eastern Canada. This follows the industrial model the pharmaceutical companies themselves use, which is always to have a second source for raw materials if possible to ensure no interruption in their supply.

IP within the *Taxus* domestication project is held jointly between Natural Resources Canada (CFS–AFC) and the industrial collaborator, who has access to patenting resources. However, all IP at CFS–AFC obtained before the agreement was signed remains CFS–AFC property. For the *Taxus* domestication project, this means that the 1300 individual cultivars or plants continue to belong to the government. The industrial collaborator has the exclusive right to commercialize the elite cultivars, plus all propagation and growing techniques, subject to some limitations—notably that neither the plant material nor technology may be taken out of Canada without prior permission of CFS–AFC because the Canadian taxpayer is a co-owner. The intent is to prevent export to other countries where, for example, the cost of land or labor may be cheaper, with the concomitant loss of jobs in Atlantic Canada. This fulfills the mandate of the CFS to promote development of the local economy.

Conclusions

As with any commodity, marketplace economics determine the options for NTFP production. To make a commercial case for cultivation of *T. canadensis* or any other NTFP, the two final issues that need to be resolved are the capacity of the woodland resource to meet the demand and the price and quality of cultivated biomass in comparison with the wild-harvested biomass.

The world market demand is currently about 300–400 kg per year, with, as previously noted, a predicted rise over the next decade to perhaps 1000 kg per year (5–10% annual increase in demand). This growth estimate does *not* include

Table 1. Price (in Canadian dollars) and volume estimates for *Taxus canadensis* biomass produced by wild harvest or cultivation (Cameron and Smith, unpublished data).

	Target: 100 kg of paclitaxel per year from		
	Harvested woodland biomass	Nonelite cultivated crop	Elite cultivar crop: 2 × paclitaxel content
Biomass needed (kg dry wt)	1.0 million	1.0 million	0.5 million
Harvest or cultivation and drying costs	$8.8 million	$22.1 million[a]	$5.7 million
Cost per kg of biomass	$8.80	$22.10	$14.30
Cost per kg paclitaxel	$25,100	$63,100	$20,400

[a]Including federal assistance for new crop development.

either the increase in demand as the North American/European population ages or increased consumerism in the large, newly emerging middle classes of China and India. No good region-wide estimates of the amount of sustainably harvestable *Taxus* exist, but commercial harvester estimates suggest that the annual limit for sustainable harvest of biomass in eastern North America (mostly in eastern Canada) is approximately 1.5–3 million kg dry weight per year, sufficient to produce 150–300 kg paclitaxel annually. However, several different large pharmaceutical supply companies each are interested in acquiring *T. canadensis* biomass or crude extract equivalent to more than 100–200 kg of paclitaxel. The implication is obvious: if more than one or two pharmaceutical clients choose to purchase biomass sourced within eastern Canada, the woodland resource will not be able meet the demand on a sustainable basis.

The current cost of woodland-collected *T. canadensis* biomass is approximately $10.00 CAD/kg dry weight (as of August 2004, $1.00 CAD = $0.80 USD). According to industrial buyers, similar quality biomass is reportedly available from Asia for approximately $7.00–8.00 CAD/kg dry weight. However, it is also noteworthy that Asian companies are purchasing eastern Canadian biomass and extracts, suggesting an insufficiency of supply overseas. Typical of other crops, biomass is the least profitable stage of taxane supply. A kilogram of paclitaxel, although selling at perhaps $200,000 CAD or more at 99% purity, is only worth $32,000 CAD/kg calculated based on the paclitaxel content of dried, unextracted biomass (unpublished data).

Nursery cropping is expensive. Therefore, even without assuming future scarcity of biomass from overseas sources, a compelling case must be made for cultivation (i.e., using a cultivated product with equal or better quality sold for the same or less cost). Table 1 shows estimated biomass volumes and prices based on a comparative analysis done at CFS–AFC.

Neither wild-crafted biomass nor a nursery crop produced from cuttings taken from wild stock plants would be competitive with the price of overseas biomass (provided it is available and not in short supply). However, cultivated crops using cultivars selected for fast growth and elevated taxane levels are price competitive, even if only very modest assumptions are made about the magnitude of crop improvement. Using a conservative assumption of only 2 × taxane content, our analysis of biomass costs from the three sources suggests that the biomass component of paclitaxel costs can be decreased by at least 20%. Because biomass accounts for 30–50% of total production costs, the savings are potentially significant. Note that the valuation includes no premium for either the long-term security of a cultivated biomass supply or its increased taxane content (which would lower postharvest processing costs), either of which would also be attractive to pharmaceutical clients.

The *Taxus* domestication project has demonstrated to us at CFS–AFC that an R&D partner needs to be aware of market realities in order to focus research objectives, make pragmatic decisions to eliminate nonessential though interesting parts of a study, and choose among alternative routes to meet commercial objectives with realistic timelines. Equally important is a critical examination of the market opportunity and competition, and the strengths and weaknesses of prospective industrial collaborators. Finally, a good economic case for domestication is required. This presentation has focused on the phytopharmaceutical market, NTFPs, and nursery cropping. However, the barriers to successful collaboration and the commercial or market intelligence needed to address them should generally apply to the entry of any other plant bioactive product into the industrial marketplace and alternative cultivation methods as well.

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