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A Roadmap for the Sustainable Development of Bioresources: Bioactives for Prince Edward Island and Atlantic Canada

FINAL REPORT

February, 2002

Prepared For:
PEI Bioresources Technology Cluster Roadmap Steering Committee

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1. Executive Summary

1.1 The Prince Edward Island Context

The primary resource industries of agriculture and aquaculture, along with the related export of food products are the backbone of the economy in Prince Edward Island (PEI) and similarly in many other communities within Atlantic Canada. These primary industries support a vigorous tourism sector and a strong societal and community infrastructure. However, environmental concerns and shifting consumer preferences are having a profound effect on farming and fishing practices as well as on land use in Prince Edward Island. Remaining competitive in national and international markets while protecting the environment is an ever-increasing challenge for these primary industries in Prince Edward Island.

The PEI economy needs to continue to grow and diversify in a sustainable manner. It has already seen recent expansions into aerospace, value-added manufacturing and biotechnology. In addition, the bioresource sector is recognised as one of the six growth areas in the Government of PEI economic development strategy - *Bridging Tradition and Technology* - released in January 2000. The strategy calls for a new and integrated approach for the development of the sector through sustainability-related research and innovation. These efforts would support the creation of new bioresources-based products.

1.2 The Roadmapping Process

In the context of many potential opportunities as well as challenges in the field of bioresource utilisation, the Bioresources Technology Cluster Roadmap Steering Committee (BTCRM SC) was created. It brought together the expertise of industry executives, government experts, academic representatives, consultants and other community stakeholders to identify and chart new potential directions for technology advancement and economic development. After consideration of nearly 100 potential opportunity areas and more detailed analysis of 10 selected areas of specific interest, the BTCRM SC came to the conclusion that the island's marine as well as agriculture industries can serve as a foundation on which to build a knowledge-based bioactives cluster in Atlantic Canada and Prince Edward Island. Members of the BTCRM SC developed a common vision that can guide the endeavours of many organisations involved in the growth of the cluster.

1.3 The Vision for the Sustainable Development of Bioresources

Bioactive ingredients and their precursors, which are used in the manufacture of pharmaceuticals and nutraceuticals, can be derived from bioresources available in and around PEI. In charting any new direction, it is clear and imperative that the natural resources and environment must be protected for the benefit of future generations. Therefore, PEI's vision embraces bioactives, bioresources as well as the concept of sustainable development.

The Vision for the Sustainable Development of Bioresources is:

> ***To establish a world-recognised regional technology duster of excellence centred in Prince Edward Island and the Atlantic region, for the discovery, development and commercialisation of a spectrum of high-value bioactive compounds for human and animal health & nutrition, derived from a diversity of bioresources, based on an innovative and rigorous science & technology platform and advanced sustainable development concepts.***

1.4 The Bioactives Opportunity

Bioactive molecules and their precursors are at the very high end of the chemical products value spectrum. Bioactives, which are largely used in pharmaceutical and nutraceutical formulations, alter biological activity to provide therapeutic benefits, nutritional values and health protection to humans, animals and even plants (i.e., pesticides). The market for new effective bioactives can be considered "supply-limited" in that many diseases and ailments remain uncured or cannot be treated with currently available drugs or nutritional products. There is also a need to make bioactives more effective and lower their cost. These factors present tremendous market opportunity for the identification and commercialisation of new products.

Pharmaceuticals and nutraceuticals represent the major market applications for bioactives. However, they are also used as enzymes, pesticides,[1] in diagnostic products and in other applications. The total annual global market value for pharmaceuticals and nutraceuticals is estimated at C$ 685 billion, and growing rapidly at approximately 8% per year. The global value for bioactives is a significant portion of this total, and growing at a similar rate.

Table 1: Major Market Values for Bioactives[2]

[1] Pesticides include herbicides, insecticides, fungicides, and other crop, livestock and animal protection products, used for agricultural, industrial and household use. Pesticides are not a focus of this roadmap.

[2] Value of pharmaceutical, nutraceutical markets - not value of contained bioactive ingredients.
Pharmaceuticals valued as manufacturing shipments (not consumer retail value).
Sources: U.S. Bureau of Census, Industry Canada, trade journals for world estimates.

(C$ Billion, Year 2000)

Market area	Canada	North America	World	Annual Growth in North America
Pharmaceuticals	10	130	555	9%
Nutraceuticals	2	27	130	4%
Total	**12**	**157**	**685**	**8%**

The actual market size for bioactives themselves is difficult to quantify. One reason is that the sale of bioactives is often tied to valuable services.

Bioactives are complex and span a large range of molecular weights from small organic molecules (e.g. taxanes, calcitonin) to large proteins and polysaccharides. Only minute quantities (e.g., milligrams or micrograms) in small doses are usually needed for them to have an effect on target cells, tissues and organs. These minute quantities of final bioactives, or even precursors from which they are derived, can have values that are in the millions of dollars per kilogram. These prices are required to support the large investments in research and other value-adding components.

1.4.1 Market Drivers

Pharmaceuticals and nutraceuticals have some common key market drivers. Some of the major drivers in these bioactives market areas include:

- desire to find new products;
- desire to find new lower cost sources of existing products;
- improved standards and enforcement of existing standards for products;
- desire for suppliers to differentiate products through formulation and altered chemical structures;
- desire to reduce the price and costs of products; and
- trend toward incorporating nutraceuticals in foods, drinks and cosmetics.

The completion of the mapping of the human genome, interest in protein interactions (proteomics) as well as other bioactives, has emerged as a discipline to not only increase the fundamental understanding of living processes, but also to provide the potential to improve human health to an unprecedented extent. Previously, for example,

the understanding of interactions with the potential to lead to disease conditions was limited to approximately 400 to 600 target systems. It is expected that proteomics will reveal up to 6,000 to 10,000 (varying estimates from different experts and literature sources) targets where intervention may be beneficial to address disease and/or improve nutritional conditions.

The huge growth in target biological systems, coupled with advances in the related sciences bodes well for the growth in bioactives demand, especially proteins and peptides (short proteins - say up to 50 - amino acids). With more biological sites to target, greater demand for bioactives for use in pharmaceuticals and nutraceuticals is expected.

1.5 The Bioresources

There is a great diversity of marine and plant species available in Atlantic Canada. Marine bioresources present a special and unique source of opportunity for the region. A recent analysis of bioresources available in PEI along with the ingredients they contain found many bioactives, many with established commercial values.[3]

Organisations in Atlantic Canada are only beginning to realise the potential of the bioresources available in the region for production of bioactives. A notable example is Ocean Nutrition Canada of Bedford, Nova Scotia, which has been successful in making nutraceutical products from bioresources available in the region (as well as other sources). Ocean Nutrition Canada makes high purity essential fatty acids (EFAs) such as omega-3 and 6 oils from fish. It also makes glucosamines for the nutraceutical market. Glucosamines are made from the chitin contained in crustacean shells (e.g., lobster) that would alternatively be sent to waste. Some of the bioresources available in the Atlantic Canada region are known to contain bioactives that are already in commercial pharmaceutical use. For example, ground hemlock (Taxus *canadensis)* is a known source of taxanes. Taxanes have been approved by regulatory authorities for use in the treatment for certain forms of cancer.

3 Food Technology Centre, *PEI Bioresources Inventory*, December 2001.

1.6 Technology Challenges and Priorities

The technologies in the bioresources and bioactives areas can be grouped in four categories related to value-adding stages. These are:

- Identification of the bioactives;
- Production in bioresources;
- Processing bioresources; and
- Utilisation of bioactives.

A fifth group of technologies of importance in the PEI context are those involved with operationalising or developing the sustainable development framework.

The bioactives field, oriented to providing final products that are derived from natural sources, encompasses a great many individual technologies and many areas that are under research and development. Due to the present relatively low use of renewable feedstocks and taking into account the value chain of manufacture of bioactives, it is useful to segment the significant factors that need to be addressed to advance the development of bioactives into key groupings.

Table 2: Components of Stages Advancing Development of Bioresource-Based Bioactives

Identification	Production	Processing	Utilisation
• Bioprospecting • Bioactivity • Bio-informatics • Molecular modelling	→ • Yield • Costs • Consistency • Genomics • Sustainability • Bioresource Management	→ • Extraction • Separations • Conversion • Purification • Refining • Control	→ • Efficacy • Marketing • Regulation • Ethics • Standards
Education, Training, Infrastructure, Sustainability and Rural Development			

1.6.1 Bioactives Identification

Expertise in the discovery arena is vital for organisations aiming to find or produce bioactives or their precursors that can be used in pharmaceutical or nutraceuticals. While a certain level of in-house expertise is generally deemed essential, discovery service companies have also emerged and are able to provide solutions to bioactive suppliers in often expensive and highly specialised services such as high throughput assays. In addition, service providers are also targeting the newly emerging bio-chip and bio-informatics approaches. Synthesising appropriate compounds for pharmaceutical companies is a critical component for drug discovery service organisations. These companies can offer customised expertise to provide the most consistent delivery of appropriate compounds to help build their customers' development pipelines.

Three key research activity areas include:

- protein characterisation;
- development of bio-informatics and molecular modelling approaches; and
- improved functionality of screening systems.

1.6.2 Bioactives Production

Commercial bioactives need to be produced in sufficient quantities to serve market demands. Technologies are required to enhance sustainable development and economic growth as well as the harvest of animals or plants. Many of these technologies are already subject of research and advancement in PEI, other Atlantic Canada provinces, as well as in many other regions where agriculture and aquaculture enhancement is required. The bulk of the technology advancement is oriented to sustaining and enhancing traditional food crops and fish, not necessarily focused on bioactives that may be contained in them.

1.6.3 Bioactives Processing

Separation and purification technologies for isolating often dilute components from natural feedstocks represents a critical technology barrier for developing a bioresource-based bioactives industry. The major and ongoing technology challenge is to extract, isolate and concentrate the bioactive ingredients economically. The innovation process in these technology fields is therefore often focused on reducing capital and operating costs, minimising raw materials requirements, increasing purity and minimising wastes. The scale-up of laboratory techniques to economical continuous processes remains a critical challenge.

A significant and well recognised barrier to the development of processing natural based products is the current lack of trained practitioners. The present focus of chemical engineers and technologists on traditional chemical manufacturing principles and lack of biochemical process subject matter in most curricula must be altered to provide the necessary trained workforce. Illustrative of this need is the serious lack of scientists, engineers and technologists trained in c-GMP knowledge.

1.6.4 Bioactives Utilisation

Bioactives must meet general market and customer requirements when in use. Driven usually by the need for regulatory approval, new materials need to be tested for their functionality and safety in human or animal trials. Metrology is an important component of this sector, providing consistent determination and reporting of active ingredients. Technologies for dosage provide control of the timing and location of release of active ingredients. Packaging technologies provide protection of the packaged materials from decomposition induced by light, oxygen, humidity, and other environmental factors, while providing appealing design, at low cost.

1.6.5 Sustainability

Sustainability is a key factor affecting economic development of the Atlantic Region and particularly PEI. Economic growth in PEI is constrained by limited land availability, limited water supply and the often negative interactions between the commercial strengths of its economy: tourism, agriculture and aquaculture. Continued economic development must occur within the physical constraints of the Island. The bioresource industry will need to grow within the environmental and social context of these constraints.

The development of a bioactives cluster could relieve some of the sustainability pressures currently confronting the region since it entails a greater economic return from a reduced amount of bioresource. However, verification of this implication would benefit from a more comprehensive study of sustainability as described later.

An examination of the potential sustainability and eco-efficiency issues for bioactives reveals several areas where technology development may be required to mitigate future impacts. Key among these is the development of by-products from the biomass waste generated and the production of the bioactives through farming or synthesis to relieve the load on natural ecosystems.

Given the complexity of sustainability, PEI offers a very practical opportunity for advancing our understanding of sustainable development and establishing a Sustainable and Environmental

Modelling Framework (SEMF) on a scale that is tractable and relevant for the continued economic development of bioresources.

PEI and Atlantic Canada have a good infrastructure for leading the development of a SEMF and can co-ordinate the necessary range of experimental research activities. These include: field studies and data gathering conducted by departments such as Agriculture and Agri-Food Canada (AAFC), Environment Canada and Department of Fisheries and Oceans (DFO); data management, storage and Geographic Information System (GIS) capability of the Province of PEI; and the science strength of University of Prince Edward Island (UPEI) and the Atlantic Veterinary College (AVC) complemented by the work of the Centre for Island Studies. From this core capability, critical complementary collaborations with other leading centres in Atlantic Canada and elsewhere both nationally and internationally can be established.

1.6.6 Key Research and Development Actions

The key research and development actions required to overcome barriers were identified in a similar roadmap process undertaken by the U.S. Department of Energy (DOE) in their Technology Roadmap for Plant/Crop-Based Renewable Resources 2020. Building on some of the findings in that roadmap, the present study identified key activities given in Table 3. These have been ranked from top to bottom in order of priority for impact on the development of bioresource-based bioactives.

Table 3: Key Research and Development Activities and Priorities

Identification	Production	Processing	Utilisation
Develop analytical tools for compounds of interest, and functionality screening systems.	Agronomic/aquaculture optimisation technologies for materials of interest.	Develop new separation methods.	Develop better understanding of structure-function relationships.
Development of bio-informatics and molecular modelling approaches	Yield improvement via plant productivity and harvestable parts	Develop improved conversion methods.	Study sustainability of infrastructure to optimise impact on rural economies.
Develop improved functionality of screening systems.	Sustainability and environmental monitoring and modelling	Develop/optimise enzymes.	Develop standards and methods to support product quality.
	Develop technologies that assist in quantifying availability, growth and depletion in large regions	Develop hybrid bio and chemical systems	Materials development for controlled bioactives delivery.
	Harvesting machinery for biomass collection	Develop new reactor methodology	Develop packaging and labelling formats.
		Explore reactive enzymes	

		within plants.	

1.7 The Bioactives Cluster Strengths and Gaps

The full North American bioactives/bioresource sector embraces quite a number and variety of organisations that support as well as compete with one another. Customers in the cluster define market needs that are addressed by their suppliers. Suppliers include those organisations that provide raw materials, R&D services, equipment, consulting services, and a source of suitably educated and trained personnel. This drives technology innovations to meet evolving market needs. Governments and regulatory authorities that represent general public interests can also play supporting as well as regulatory roles.

A cluster functions best when there is close collaboration as well as competition occurring among participants. Atlantic Canada, similar to any geographic region has certain strengths as well as gaps with respect to all components of the cluster. Regions therefore need to leverage their strengths and address their gaps to the degree possible. Often new participants in a specific region must adopt focus-type strategies to provide high quality, specialised niche products or services to participate effectively in the cluster. Atlantic Canada's key strengths and gaps in the context of the bioactives market segments can be summarised as follows:

Key Strengths

- marine bioresources locally available;
- plant bioresources available for selected bioactives (e.g., blueberries, ground hemlock);
- universities and government research organisations with strengths in marine bioresources, agriculture, and some aspects of bioactives;
- growth of companies in processing of bioresources for high value products;
- provincial priority on sustainable development of bioresources;
- proximity to a large number of major cluster participants in northeast portion of North America;

Gaps

- bioactives discovery organisations with knowledge based on local marine and plant species;
- research organisations specifically focused on deriving bioactives from local bioresources.
- pharmaceutical companies and supporting products and service suppliers in the field of bioactives;

A number of conclusions can be derived from the analysis conducted in the roadmap exercise. The sustainable development of the bioresources industry in Atlantic Canada, and particularly in PEI, implicates focusing on high value-added components of the bioresources supply chain, moving from "once-through" to recycling of resources, and moving away from commodity products. Consistent with these considerations is the selection of bioactives as a high value bioresource opportunity and its development in a sustainable manner, requiring a better understanding of the environmental, social and economic systems of the region.

The ready availability of marine sources of bioresource-based bioactives provides Atlantic Canada with an advantage not available to other regions, while links to other centres of bioactive development could complement local strengths. The Atlantic region's resource base is complemented with research strengths in marine biosciences, sustainable agriculture, food science, and nutraceuticals, along with emerging growth of companies in high value added bioresource products.

A cursory analysis of the sustainability issues surrounding bioactives indicates the need to manage populations of natural feedstock, large amounts of waste biomass, and energy requirements for processing. PEI offers a unique opportunity to conduct comprehensive experimental studies and modeling of the bioactives (and other) systems to provide an integrated approach to developing bioresources sustainably, which could be transferred to other sectors and regions. Building capacity in modeling would complement existing strengths in experimental data from agriculture and marine bioresource sectors and of environmental quality.

2. Introduction

2.1 The PEI Context

Although the PEI economy continues to diversify with expansions into aerospace, value-added manufacturing and biotechnology, the primary resource industries (agriculture and aquaculture), along with the export of food products continue to be the backbone of the Island economy. These primary industries support a vigorous tourism sector and a strong societal and community infrastructure. However, environmental concerns and shifting consumer preferences are having a profound effect on farming and fishing practices as well as on land use in Prince Edward Island.

Farmers and fishers are faced with an increasing range of consumer attitudes and opinions toward production and harvesting practices. Remaining competitive in national and international markets while protecting the environment is an ever-increasing challenge for primary industry producers.

PEI is also reaching the physical limits of the landmass that supports the three pillars of its economy: agriculture, aquaculture and tourism, and future economic growth is limited by sustainability. Over the last decade, the rapid expansion of the potato industry, increased soil erosion, accelerated land clearing, clear-cutting of forests, increased pesticide use and conflicts between producers and their non-farming neighbours have raised concerns about land use practices in PEI. The size of the province and the interplay of marine, freshwater and terrestrial ecosystems put sustainability pressures on the Island. The tourism industry is the second largest contributor to the Province's economy. Following the opening of the Confederation Bridge in 1997, the industry experienced a 50% activity increase. Each of these areas has grown to the point that they interact with each other and are reaching the physical limits of the Island.

In an effort to guide the industry through a changing market, the province introduced the concept of a PEI Food Strategy in 1998. The strategy calls for greater emphasis placed on the production and marketing of high-quality food products from sustainable systems. Strategic elements include:

- establishing an industry-led PEI Food Alliance that will guide the development of the strategy;
- developing a PEI Brand based on the image that this Province is a world-class producer of premium-quality food from sustainably managed resources;
- increasing on-farm sustainability and food quality initiatives;
- increasing sustainability and food quality initiatives for fishers and aquaculturists;

- measuring and reporting the impact of the strategy on the economy and the environment;
- integrating the role of agriculture, fisheries and aquaculture in the tourism industry.

Some industries have already taken measures to diminish the environmental impact of their activities by reducing fertiliser use, adopting more environmentally friendly farming practices, etc. More needs to be done to reinforce these initiatives.

> ***Our vision is… that Island food products, produced in a sustainable manner, be world renowned for their quality and be marketed around the globe with the most advanced information technology tools.…***
>
> **Bridging Tradition and Technology**
> **Province of Prince Edward Island**
> **January 2000**

Recent studies on the PEI bioresources base have reached the following conclusions[4]:

The *agricultural* sector is reaching a plateau of production, where no further physical expansion is possible, save at the expense of the forest bioresource base, or in competition with rapidly expanding rural housing developments. Therefore, value-adding and new technologies to increase yield and quality are the major avenues for growth.

Aquaculture is fast reaching a limit of growth in the estuaries, based on biological carrying capacity, and dependence primarily on a single species (mussels) puts the industry at risk from trade barrier and market fluctuations in the USA and abroad. New markets must be sought for increasingly value-added products, and programs must be expanded for development of appropriate alternate speci3es.

The *fishery* continues to seek sustainable development and new market share for its wild catch products. With lobster catches at a plateau, and other fish species generally of low value and depleting stock availability, the only major room for growth is in value-adding the raw material to a maximum.

Forestry, of all bioresources, has been misunderstood in the past, with only very recent efforts to rise above the most basic of market products, driven mainly by stud-wood and pulpwood. The excellent efforts of the Department of Forestry have had limited uptake from this relatively undeveloped industry, and there is great room for value adding and implementation of modern silviculture, management and harvest practices.

[44] Abiogen Agri-Food Services, The Bioresource Industry on PEI, December 2001.

Major initiatives are needed in studying environmentally-based impacts on *health*, including water quality, agrichemical residues, and dietary choices from PEI food supply.

Food products continue to be the most innovation and sustainable value-adding occurring in PEI bioresource base.

The bioresource sector is recognised as one of the six growth areas in the Government of PEI economic development strategy - *Bridging Tradition and Technology* - released in January 2000. The strategy calls for a new and integrated approach for the development of the sector through sustainability-related research and innovation. These efforts would support the creation of new bioresources-based products. The approach would contribute to establish a "PEI brand" of environmentally friendly products opening new opportunities on international markets.

> ***To strengthen the Province's trading reputation and assist exporters, a food strategy will create a "PEI brand" based on the quality of the environment, sustainable production methods and the excellence of our products and services.***
>
> **Bridging Tradition and Technology**
> **Province of Prince Edward Island**
> **January 2000**

2.2 The PEI and Atlantic Canada Bioresource Cluster

Two dominant bioresource-based clusters have emerged in Atlantic Canada, a food processing cluster and an aquaculture cluster.

2.2.1 Food Processing Cluster

The Prince Edward Island and New Brunswick food processing cluster offers a complete supply chain from agricultural inputs such as produce and bulk milk all the way to world-renowned multi-line brand name packaged products widely available in supermarkets throughout North America. Major players in this market include McCain Foods, Baxter Foods, Cavendish Farms and Brunswick.

In a recent study (The PEI and NB Food Processing Cluster) the potential growth opportunities and challenges were identified for the cluster, which are:

- to diversify the agricultural inputs, machinery and equipment and specialised services that originate inside the cluster; and
- to squeeze still higher levels of value-added from the existing supply chain (more niche products).

Atlantic Canada benefits from food products manufacturers who carry multi-line name brands. McCain Foods, an international exporter of processed foods had sales of over $4 billion in 1996. McCain Foods is responsible for processing the largest part of the potato harvest from this region.

Cavendish Farms raises, harvests and processes potatoes for the export of value-added products. Although significantly smaller than McCain Foods it is a major player in this region.

Baxter Foods with over $170 million in annual sales is the second largest food processor (of those who provide sales figures) in Atlantic Canada. Baxter Foods' primary products are related to the dairy and plant products industry.

2.2.2 Aquaculture Cluster

Aquaculture (the farming of marine organisms) is expanding rapidly and currently represents approximately 25 percent of the total amount of seafood landings world-wide. Canada ranks 27th and accounts for 0.3 percent of world aquaculture production. The total economic value of the output from this industry in Atlantic Canada is estimated to be $200 million annually. These figures are somewhat out of date and can be considered to be very conservative as the output from New Brunswick alone was estimated to rise to $200 million by 2000.

Products of the aquaculture industry include salmon, trout, cod, blue mussels scallops arctic char crabs, lobsters, novel shellfish species and seaweed.

In support of the aquaculture industry there is a secondary industry, which has been established to ensure fish health. Of particular interest is Atlantic Fish Health Inc., which is part of Atlantic Veterinary College - AVC - in Charlottetown, PEI. Atlantic Fish Health develops diagnostics, treatment and disease preventing technologies for fish species.

2.3 The Bioactives/Bioresources Roadmap

The technology roadmap report identifies market drivers and barriers, future business opportunities, as well as technologies required (advanced ad conventional) for the sustainable growth of the Prince Edward Island (PEI) bioresources-based technology cluster over the next ten years.

The Bioresources Technology Cluster Roadmap Steering Committee (BTCRM SC) composed of industry leaders, government representatives, academic experts and other stakeholders, was established to oversee the development of the roadmap. Key steps in the roadmapping process included:

- Identification and recruitment of nearly 280 participants in the roadmap process;
- Input received from these participants to identify nearly 100 opportunity areas (OPAs) that could be further pursued;
- Selection of 10 OPAs by participants and SC that offered the best potential for further development;
- Research, analysis and preparation of a profile for each of the 10 OPAs by the consulting team;
- Selection of "bioactives" as the cross-cutting "product" field of interest (encompassing nutraceuticals, pharmaceuticals as main market opportunity areas), and sustainability and environmental modelling as framework for the growth of the bioresources sector;
- Development and adoption of a vision by the BTCRM SC;
- Development of a draft roadmap report by the consulting team; and
- Review of the draft roadmap report by the BTCRM SC and participants at a workshop in PEI.

The roadmap report presents:

- the Vision arising out of the roadmapping process;
- a general description of a potential sustainability and environmental modelling framework for PEI and Atlantic Canada as well as the supporting technologies;
- an overview of the bioactives opportunity as identified through the roadmapping process for the future growth of the bioresources sector in PEI and Atlantic Canada including market trends, drivers and challenges as well as priorities for technology development; and
- an analysis of the bioactives cluster strengths and gaps.

2.4 The Vision for the Sustainable Development of Bioresources

Executives from the PEI industry, as well as academic and government leaders came to the conclusion that the island's marine as well as agriculture industries can serve as a foundation to build a knowledge-based bioactives cluster in PEI and the Atlantic region. Bioactive ingredients and their precursors, which are used in the manufacture of pharmaceuticals and nutraceuticals, can be derived from bioresources available in and around PEI. PEI's vision embraces the concept of sustainable development. In charting any new direction, it is clear and imperative that the natural resources and environment must be protected for the benefit of future generations.

The Vision for the Sustainable Development of Bioresources is:

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>
> ***BTCRM SC***

3. The Bioactives Opportunity

3.1 The Bioactives Market

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Table 4: Major Market Values for Bioactives

(C$ Billion, Year 2000)

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The actual market size for bioactives themselves is difficult to quantify. One reason is that the sale of bioactives is often tied to services. There is also substantial captive bioactives

[5] Pesticides include herbicides, insecticides, fungicides, and other crop, livestock and animal protection products, used for agricultural, industrial and household use. Pesticides are not a focus of this roadmap.

manufacturing. That is, many companies manufacturing pharmaceuticals, nutraceuticals and pesticides conduct research as well as make their own bioactive ingredients synthetically from basic chemicals or from natural bioresources. Another complexity with respect to sizing the value of the "market" for bioactives is that there is a substantial amount of valuable research activity related to bioactives that is conducted at universities and government funded organisations. Many institutions are involved with enhancing the understanding of causes and finding treatments for numerous diseases and ailments. Some of this research can be directly linked to the discovery of bioactives, and therefore could be considered as part of the total value of the bioactives market or business. However, information on the total monetary value of this body of research that is linked to bioactives is not readily available.

3.1.1 Bioactives Have High Values

Bioactives are complex and span a large range of molecular weights from small organic molecules (e.g. taxanes, calcitonin) to large proteins and polysaccharides. Only minute quantities (e.g., milligrams or micrograms) in small doses are usually needed for them to have an effect on target cells, tissues and organs. These minute quantities of final bioactives, or even precursors from which they are derived, can have values that are in the millions of dollars per kilogram. Key factors contributing to these high values are:

- bioactives require a significant amount of time as well as human knowledge, financial capital and other resources to identify, make and commercialise;
- investments in research to understand the cause of diseases requires returns through sale of products;
- investments in research into many potential bioactives does not result in commercially viable products;
- it is costly to synthetically make bioactives or extract and purify them from natural bioresources;
- bioactives need to be suitably extensively tested and approved by regulatory authorities to ensure their safety and efficacy; and
- unique technology innovations regarding how they are identified, made or applied can often be patented to ensure investments are properly rewarded.

3.2 Bioactives in Pharmaceuticals

Pharmaceuticals are chemicals that have specific bioactivity useful in treating, curing or relieving the symptoms of ailments in humans and animals.[6] Pharmaceuticals include prescription drugs as well as over-the-counter products. Commercial pharmaceutical products are formulated compounds containing a variety of materials including: the bioactive ingredient(s); solubilisers; stabilisers; fillers; colourants; flavouring ingredients; solvents (e.g., liquids); and a variety of other materials. Some pharmaceuticals are extracted and purified from natural sources. The pharmaceutical producers are major customers for bioactive molecules, as well related services (e.g., bioactives or precursor synthesis) and technologies. The pharmaceuticals market can be used to analyse the use and trends for bioactives that are contained.

The total North American domestic consumption of pharmaceutical products is estimated at C$ 133 billion for the year 2000, at the wholesale level. This represents the sales of the pharmaceutical suppliers. The retail value of sales to consumers would be a much larger figure. Manufacturers' sales of drugs world-wide for human use increased by 10.4% to approximately C$ 555 billion in 2000 from 1999 levels. In Canada, total manufacturers' sales of all drugs for human and animal increased to an estimated total of $10.2 billion at the wholesale level, an increase of approximately 12.4% from the previous year. The Canadian market for drugs represents 2% of the world total. Pharmaceutical companies view the market as global in that once a drug is it patented and approved for use, it has applicability to treat common target disease around the world. Global patent protection is therefore a key business success.[7]

Table 5: Size of North American Pharmaceutical Market

(Wholesale Level - C$ billion, Year 2000)

	Canada	United States
Domestic Consumption	10	123
Value of Manufacturing Shipments	6	121
Imports	6	9
Export	2	7

Source: Industry Canada for Canada, U.S. Bureau of Commerce for U.S.

6 This is a working definition - not a legal statutory definition.
7 Annual Report 2000, Patent Medicine Prices Review Board, Ottawa, ON (http://www.pmprb-cepmb.gc.ca/PDF/ar00e6.pdf) based on *Scrip Magazine*, February 2001, p.31.

The value of domestic consumption of pharmaceuticals products in Canada has grown at an average annual rate nearly 10% per year since 1990 (current dollar basis). Similarly, the U.S. market has been growing rapidly. The global pharmaceutical market has been forecast to grow at approximately 6 to 7 percent per year over the near term on a value basis.[8] On a regional basis, the fastest growing areas are expected to be Southeast Asia, including China at 11%, the Middle East by 10% and North America by 9%. Japan and Western Europe pharmaceutical markets are expected to grow at rates slower than the global average.

There are thousands of pharmaceutical product formulations available on the market.[9] Generally, products sold in Canada are available in the United States, and many other countries. When a patent and the related monopoly to make or sell a pharmaceutical expires, generic pharmaceutical producers often become involved in the manufacture and sale of the product. Original patent holders, faced with expiration of valuable patents, often seek to patent innovations for their product design, its use, and/or manufacturing process to retain exclusive rights to the pharmaceutical. When patents expire there is added incentive to find ways to manufacture the bioactives in innovative ways at lower cost. This drives technology innovation related to synthesis and processing technologies. Sales of patent medicines make up approximately two-thirds of the sales in Canada.

Table 6: Major Types of Drugs Sold in Canada

Anaesthetics	Contraceptives	Psychotherapeutic agents
Anti-infectives	Cardiac drugs	Sedatives
Antibacterials	Dermatological preparations	Sulphonamides
Antibiotics	Diuretics	Vaccines
Anticholinergics	Haematological agents	Vasoconstrictors
Anticonvulsants	Hormones and synthetic substitutes	Vasodilators
Antinauseants	Internal analgesics and antipyretics	Vitamins
Antitoxins	Laxatives	
Central nervous system stimulants	Muscle relaxants	

Source: Industry Canada[10]

8 Source: IMS HEALTH Global Pharma Forecast

9 A long list of patented products available in Canada can be found at the website of the Patent Medicine Prices Review Board. http://www.pmprb-cepmb.gc.ca/. A list of drugs sold in the U.S. is available at the Food and Drug Administration.: www.fda/

10 Industry Canada, Strategis, http://strategis.ic.gc.ca/SSG/io37412e.html

It is difficult to characterise the pharmaceuticals industry on a quantitative basis. Most of the mass of the final formulations is filler (e.g., in tablets), carrier (e.g., solvents in liquids), and dose packaging materials (e.g., coatings). The mass of active ingredients is usually a small portion of the total mass of the product. However, the active ingredients are usually the most valuable chemicals in the formulation. The value of the U.S. market demand for pharmaceuticals is shown below.

Table 7: U.S. Market Demand for Pharmaceuticals

(C$ Billion)

Products, or Target Organs, Diseases	**Average Annual Growth 1996 to 2000**	**Demand 2000**
		(C$ billion)
Central nervous system and sense organs	20%	28.2
For parasitic and ineffective diseases	14%	16.8
Respiratory system	23%	15.7
Digestive or genito-urinary system	8%	15.5
Neoplasms, endocrine system, metabolic diseases	21%	13.8
Cardiovascular system	10%	13.8
Vitamin, nutrient, and hematinic preparations	9%	10.3
Skin	11%	4.5
Veterinary use	5%	2.9
Total	**14%**	**121.4**

Source: U.S. Bureau of Census, August 2001.[11]

3.2.1 Growth in Demand for Pharmaceuticals

The global pharmaceutical market has been forecast to grow at approximately 6 to 7 percent per year over the near term on a value basis. The market for bioactives used in pharmaceuticals is expected to grow at the same rate. On a regional basis, the fastest growing areas are expected to be Southeast Asia, including China at 11%, the Middle East by 10% and North America by 9%. Japan and Western Europe pharmaceutical markets are expected to grow at rates slower than the global average.[12]

11 A more detailed breakdown of products is available from the Bureau of Census: www.census.gov/
12 Source: IMS HEALTH Global Pharma Forecast

Table 8: Pharmaceutical Market Growth by Region 1999-2003

Regions	Forecast of Average Annual Growth
North America	8.6%
Europe	5.3%
Japan	-0.2%
Latin America	7.2%
S. E. Asia & China	11.1%
Eastern Europe	9.4%
Middle East	10.4%
Africa	3.2%
Indian Sub-Continent	7.9%
Australasia	9.2%
Commonwealth of Independent States (CIS)	6.1%
Total World Market	6.6%

Source: IMS HEALTH Global Pharma Forecast

3.2.2 Bioactives Customers and Distribution Channels

The pharmaceutical companies represent the major market for bioactives. Pharmaceutical suppliers are always seeking new bioactives as well as molecules that are precursors to bioactives. These companies have strong interests in bringing new products to market, as soon as possible. However, at the same time pharmaceutical companies are themselves active in seeking new bioactives that can be made synthetically, from biotechnology methods or derived from natural bioresources. Most bioactives are made through organic chemical synthesis. Some pharmaceutical companies are shifting their emphasis from seeking new bioactives in natural plant and animal sources to designing synthetic bioactives, such as peptides.[13] This may present opportunity to conduct bioresource-based research in bioactives.

The global pharmaceutical industry is comprised of large multinational enterprises. Most multinationals have Canadian subsidiaries, which along with some domestic pharmaceutical firms, account for majority of the manufacture, sale and distribution of drugs in Canada.[14]

13 Personal conversation Abbott Laboratories, Theratechnologies.
14 Annual Report 2000, Patent Medicine Prices Review Board, Ottawa, ON (http://www.pmprb-cepmb.gc.ca/PDF/ar00e6.pdf)

3.2.2.1 Pharmaceutical Intermediates Suppliers

An important component of the pharmaceutical bioactives business system is the pharmaceutical intermediates suppliers. A trend in the pharmaceutical industry has been for drug companies to outsource their requirements for a portion or all of their bioactives synthesis needs as well as other manufacturing related services. In this way they alleviate capacity constraints and allocate resources on key business priorities, namely discovery, approvals, marketing and distribution. Pharmaceutical intermediate chemical suppliers therefore represent an important link in the distribution channel. There are less than a dozen companies in Canada and between of 100 to 200 in the United States engaged in providing products and services to the pharmaceuticals companies. BioVectra dcl of Charlottetown, PEI is an important Atlantic Canada participant. Other Canadian firms include: Delmar Chemicals of LaSalle, QC; Torcan Chemical Ltd. (division of Avecia) of Aurora, ON; Raylo Chemicals Ltd. (a division of Degussa AG) of Edmonton, AB and Dalton Chemical of Toronto, ON.

Most of these firms do not usually undertake proactive research into bioactives discovery and development endeavours. They are focused on responding to their pharmaceutical company customer requirements to make specific bioactives (already discovered or of interest to pharmaceutical companies). Generally, they do not compete with their pharmaceutical customers. However, for bioactives derived from bioresources they are potential important links in the value-adding chain, in that some bioactives may require synthetic modification, which these companies are well equipped to undertake.

3.2.2.2 Fine Chemical Suppliers

Fine chemical suppliers sell some bioactives. Industrial, medical, analytical, government, academic, environmental laboratories and pharmacies collectively require a host of fine chemicals including bioactives, as well as purified chemicals, reagents, equipment and other products that are provided by specialised chemical companies. There could be close to 1 million laboratories around the world requiring a host of fine chemicals and related products. Successful promotion and distribution is a key business success factor. Bioactives suppliers can use fine chemical companies as a distribution channel to reach millions of potential customers. Fine chemical suppliers include: Sigma-Aldrich Canada; BDH; Fisher Scientific and PPG Fine Chemicals.

3.3 Bioactives in Nutraceuticals

Nutraceuticals contain bioactives that have the purpose of providing a physiological benefit or protection against disease. They can be taken as dietary supplements or contained in products such as foods (i.e., functional foods) and cosmetics (i.e., cosmeceuticals). A functional food is similar in appearance to a conventional food and is consumed as part of the usual diet.[15]

Table 9: Size and Growth of North American Nutritional Products Market

(Consumer Sales)

Product Area	**Average Annual Growth 1996 to 2000**	**Consumer Sales 2000**	**Growth Projection**	**Year 2005 Projected Sales**
	(per year)	(C$ billion)	(per year)	(C$ billion)
Vitamins	9%	10.3	+5%	13.4
Herbs/Botanicals	15%	7.9	-7%	5.3
Sports Nutrition	15%	2.8	+7%	4.0
Minerals	12%	2.1	+12*	3.9
Meal Supplements	7%	1.2	+2%	1.4
Specialty dietary supplements, Other	14%	2.3	+11%	4.0
Total		**26.6**	**3.8%**	**32.0**

Source: Chemical Marketing Reporter based on Health Business Partners[16]
* Industry sources contacted in this study claim this is too high.

The dietary supplements segment of the broad nutrition products market can be considered representative of the core of the nutraceuticals business (in that it excludes functional foods). In the year 2000, the market for dietary supplements was estimated at C$ 27 billion in North America, at the consumer level.[17] The nutraceuticals market grew rapidly, with an average annual growth rate of 12% per year between 1996 and 2000. In Canada, annual sales of nutraceuticals have been estimated at 10% of the U.S. market or about C$ 2 billion per year in

15 Saskatchewan Nutraceutical Network, Nutraceutical Market & Industry Information, http://www.mutranet.org/subpages/markets.htm, 05/02/01.
16 Schnell Publishing Co., Chemical Marketing Reporter, August 27, 2000. Based on Health Business Partners.
17 Schnell Publishing Co., Chemical Marketing Reporter, September 25, 2000.

consumer sales.[18] The value of nutraceutical bioactives contained in products sold in Canada is estimated at $200 to $300 million (i.e., 10 to 15% of $2 billion in total sales).[19]

3.3.1 Growth in Nutraceuticals

The value of demand for the total nutrition products market is anticipated to continue to grow at nearly 4% per year. In comparison, the conventional food business is growing at a yearly rate of only 2 to 3%.[20] Consumer demand for some nutraceuticals has declined, largely as a result of negative perceptions of product safety and/or efficacy. Herbal supplements are projected to post declines of 7 to 8% per year.[21] However, specialty dietary supplements, which are derived from marine and plant bioresources are projected to maintain high growth rates at approximately 11% per annum.

Table 10: Estimated North American Demand for Specialty Dietary Supplements

(C$ Million)

Major Specialty Supplements	**1995**	**1996**	**1997**	**1998**	**1999**	**2000P**
Melatonin	123	143	125	119	114	109
Probiotics	102	109	125	141	156	171
DHEA	55	68	76	74	74	74
Essential fatty acids, fish oils	110	125	174	223	279	322
Glucosamines (& chondroitins)	95	141	207	409	594	711
Bee products (e.g., bee pollen, royal jelly)	55	71	80	94	103	110
Co-enzyme Q10	79	125	175	239	263	334
5-HTP	7	30	42	52	59	62
SAMe	0	0	0	18	200	262
Homeopathics	347	369	414	503	545	575
Others (e.g., enzymes, etc.)	102	83	72	82	99	124
Total Specialty Dietary Supplements	1,075	1,265	1,488	1,954	2,487	2,853
Overall Growth		18%	18%	31%	27%	15%

Source: Chemical Marketing Reporter, based on NBJ[22]

18 Saskatchewan Nutraceutical Network - personal conversation with Kelly Fitzpatrick. Other industry sources. Detailed Canadian market segmentation is not available.

19 See below for basis of estimate.

20 Nutrition Business Journal

21 Schnell Publishing Co., Chemical Marketing Reporter, August 27, 2000. Based on Health Business Partners, Nutrition Business Journal.

22 Schnell Publishing Co., Chemical Marketing Reporter, August 27, 2000.

Two major products within the specialty dietary supplements segment are already being derived from marine bioresources, although there are alternative sources (e.g., livestock animals). Sales of glucosamines, which can be derived from the shells of crustacea, have grown substantially since 1995. Similarly, essential fatty acids (EFAs) such as omega-3 and 6, some of which are derived from fish oils have also seen high growth rates. In 2000, total North American market for EFAs was estimated at C$ 320 million.[23] Ocean Nutrition Canada of Bedford, NS is an important supplier of glucosamines and EFAs, derived from marine bioresources.

A key feature of the dietary supplements nutraceutical market is that some products come to market and achieve explosive growth over a short period of time. Notable example of this phenomena are SAMe, 5-HTP, Co-enzyme Q10, glucosamines and essential fatty acids. This presents opportunity for new entrants that can provide new products that are perceived as safe and effective. However, another feature of the market is the potential for decline in product demand over a short period when perceptions of safety and effectiveness turn negative. It therefore becomes vital in the nutraceutical business to develop and maintain standards of safety and efficacy, and ethical behaviour.

3.3.1.1 The Cosmeceuticals Segment

Cosmeceuticals represent an important and growing market for nutraceuticals. Cosmeceuticals are a subset of the broader group of products comprising cosmetics (e.g., facial cremes), personal care (e.g., toothpaste) and toiletry items (e.g., shampoos). What makes cosmeceuticals unique is that they are products that aim to provide some positive therapeutic function or health benefit such as 'anti-aging' effects, or nutrition for the skin, healthier hair and other such benefits. Often this functionality is provided by bioactive nutraceutical or pharmaceutical ingredients (e.g., essential fatty acids, vitamins, amino acids) contained in the cosmeceutical products.

The global market for cosmetics and personal care products is estimated at C$ 265 billion in retail sales for the year 2000.[24] The global retail market for cosmeceuticals is a minor portion of this total, estimated at approximately C$ 33 billion or 12% of the total market for cosmetics and personal care products.[25] Using approximate regional market share information, the North American market for cosmeceuticals is very roughly estimated at 23% of the global market, or C$ 8 billion in retail sales. The market for cosmetics has been growing at 6% per year over the last five years.

23 ibid

[24] Schnell Publishing, Chemical Marketing Reporter, Cosmetics/Personal Care 2001, May 14, 2001.

[25] Technology Catalysts: http://www.technology-catalysts.com/Conumer_care/cosmerpt.htm

Cosmeceuticals are expected grow faster than the overall cosmetics market. The cosmeceuticals segment of the cosmetics and personal care business industry features some of the fastest growing products. In particular, cosmeceuticals are the fastest growing products in the skin, body and hair care segments of the market. Consumer demand for cosmeceuticals is strong due to the additional functionality offered by these products versus traditional products. Demand is also being 'pushed' by cosmeceutical suppliers as well as their ingredient suppliers, since these products offer highly attractive margins.[26] Therefore, they can tolerate higher promotional expenditures. Nutraceuticals, such as vitamins, coenzyme Q10, flavinoids and other bioactives being, incorporated in cosmetic formulations, are providing suppliers with innovative products to promote.

Key market trends, some that relate to research and technology development requirements are:

- need for enhanced delivery technologies for cosmeceuticals;
- shift away from livestock animal-based products to botanical based products; and
- product innovations/enhancements to continue.

The shift away from animal based raw materials has been a result of concerns related to BSE and foot and mouth disease. This trend has resulted in a greater interest in the use of raw materials derived from botanical sources. While botanical sources may increase in demand, synthetic products are likely to see an increase in demand as well.

3.3.2 Value of Nutraceuticals

The values of bioactives in nutraceuticals are very high and approach pharmaceuticals in some cases. The unit value of nutraceuticals contained in consumer retail products can be in the tens of thousands or even million of dollars per tonne of nutraceutical-contained. The margins in the nutraceutical industry are also relatively high. As a rule of thumb the value of products sold to consumers are approximately double the price paid by the retailers from the wholesaler or packager. Therefore, if a product is sold for $10 per package to consumers, the package was purchased at $5. Few other products categories sold through retail outlets can achieve these margin levels, which compare to cosmetics and perfumes.[27]

The packager works with similar gross margins. That is, if the product is sold to the retailer at $5, the cost to the packager would be approximately $2.50 per package. Raw materials (the value of the actual nutraceutical) contained in the product can between 20% to 90% of the packaging costs (or 5% to 30% of the retail price). Overall the value of the active nutraceutical is roughly 10 to 15% of the final product. Therefore the value of nutraceuticals (bioactives) in

[26] Schnell Publishing, Chemical Marketing Reporter, Cosmetics/Personal Care 2001, May 14, 2001.
27 Anecdotal information from Shoppers Drug retail store Owner/Manager.

Canada can be estimated at over $200 to $300 million (i.e., 10 to 15% of $2 billion in total sales).

3.3.3 Bioactives Customers and Distribution Channels

There are more than 300 companies in Canada now engaged in the nutraceutical industry, which represent the market for bioresources containing bioactives, as well as the bioactives themselves. Assuming there are 10 to 15 times that number of companies in the United, States, the total customer base for nutraceutical bioactives could number in the range of 3,300 to 5,000 in North America. Multiplying this number by 3 to 4 would provide an order-of-magnitude estimate for the number of potential nutraceutical firms in the world.

This total includes growers of nutraceutical containing crops, raw materials preparation, blenders, packagers and wholesalers. There are about 50 companies in Atlantic Canada, employing nearly 1,250 people already involved in the nutraceuticals industry. Two thirds of these companies have been founded in the past decade. This excludes many more thousands of nutraceutical product retailers.[28]

The majority of nutraceutical (as well as cosmeceutical) products are sold through retail outlets including: supermarkets; drug stores (pharmacies); mass merchandisers; large chain natural products supermarkets; large and small independent natural/healthfood stores. A portion of the sales is also carried out over the internet.

Selling though retail outlets requires access to retail shelf space, which may involve promotional costs. New nutraceutical products require major investments to establish name recognition and sufficient retail presence to attract consumers. Prominent marketers of nutraceuticals are some of the major pharmaceutical companies, which have traditionally had a range of packaged health products to sell, including over-the-counter therapeutics and prescription drugs. Therefore, companies such as Bayer, McNeill, Whitehall-Robbins, and Abbott Laboratories are prominent nutraceutical suppliers, at least in the U.S. market. In Canada, companies such as Jamieson Vitamins and Swiss Herbal Remedies, and Natural Factors seem to have important retail presence selling. They sell a broad set of nutraceutical products, as well as vitamins. There are a host of other firms involved in the making and selling of products. In the vitamins segment, these firms compete with Hoffman-LaRoche, Cognis, Takeda, Whitehall-Robbins, and other global suppliers.

Some of the larger nutraceutical suppliers such as Jamieson Laboratories formulate and package their own products, while others may rely on custom manufacturers. For example, Swiss Herbal

[28] The accompanying report: *Background and Industry Overview to PEI Bioresources-Based Technology Cluster Roadmapping Process",* lists 61 companies engaged in Canadian nutraceuticals industry.

Remedies uses contract blending and packaging companies. Consumer nutraceutical firms include: Quest (Vancouver, BC), Cisu (Vancouver, BC), Vitahealth (Winnipeg, MB), Pharmetic (Quebec), Frega (Quebec City, QU), Trillium Health (Brockville, ON) and Pangea (Quebec).

3.4 Market and Other Drivers of Technology Innovation

There are various general market factors and other drivers that are likely to influence technology innovation in the bioactives industry. Organisations involved in the bioactives industry need to be consider the opportunities and challenges presented by the following:

- Social benefits of bioactives and reduction of healthcare costs;
- Mapping of the human genome;
- Regulations and ethics;
- Environment and sustainability;
- Size and complexity;
- Investments and risks; and
- Attracting human resources.

3.4.1 Social Benefits and Healthcare Costs

In the pharmaceuticals market, the pressure to reduce the cost of healthcare products and services in many countries is an important driver for the identification and manufacture of effective bioactives. This pressure drives a need for many technology innovations that can reduce the costs of researching as well as manufacturing bioactives. For example, biotechnology is one of the technology areas that offers potential for lowering the costs of bioactives manufacturing. There are also many other bioactives prospecting and manufacturing technologies that offer the opportunity to lower the costs of pharmaceuticals. In the market trends, which will relate to technology requirements for the industry, are:

- desire to find new products;
- desire to find new lower cost sources of existing products;
- improved standards and enforcement of existing standards for products;
- desire for suppliers to differentiate products through multi-ingredient formulation;
- desire for increased purity and concentration of active ingredients;
- desire to differentiate products through demonstration of superior efficacy;
- desire to reduce the price and costs of products;
- improvements in product stability; and
- trend toward incorporating nutraceuticals in foods and drinks.

Examples of prospecting and bioscreening technologies that will be influenced by market trends include: analytical technologies (such as X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, mass spectroscopy, chromatography; bioactivity analysis technologies (such as high-throughput bio-assays, laser-based single cell metabolic interrogation); bio-informatics (biochips, lab-on-a-chip, modelling & databases, in silico analyses). Manufacturing technologies include: separation and purification (such as solvent extraction, use of supercritical gases, ion-exchange and membranes).

3.4.2 Mapping of the Human Genome

With the completion of the mapping of the human genome, interest in protein interactions (proteomics) as well as other bioactives, has emerged as a discipline to not only increase the fundamental understanding of living processes, but also to provide the potential to improve human health to an unprecedented extent. Previously, for example, the understanding of interactions with the potential to lead to disease conditions was limited to approximately 400 to 600 target systems. It is expected that proteomics will reveal up to 6,000 to 10,000 (varying estimates from different experts and literature sources) targets where intervention may be beneficial to address disease and/or improve nutritional conditions.

The huge growth in target biological systems, coupled with advances in the related sciences bodes well for the growth in bioactives demand, especially proteins and peptides (short proteins - say up to 50 - amino acids). With more biological sites to target, greater demand for bioactives for use in pharmaceuticals and nutraceuticals is expected. It is predicted that by 2008, leading biopharmaceutical companies will expect an increase of 65% in the number of bioactives that their discovery organisations send into development.[29] The explosive growth in knowledge and the market pull to develop new bioactives for a greater number of target biological systems translates into a growing requirement for new products and technology innovations. Innovations to lower the cost and improve the efficiency of bioactives identification (e.g., bioprospecting and bioscreening) as well as innovations in other technology areas of the value-adding process will be required. The actual innovations will be quite technology-specific and will require expertise to identify, develop and commercialise.

Many of the products that will be developed to meet this increase in demand will come from synthetic processes (e.g., synthetic production of peptides) as well as biotechnology sources. Natural plant and marine sources are likely to make up the minor portion of the new demands.

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29 http://www.drugdisc.com/stuttgart/

3.4.3 Regulations and Ethics

Government regulations and ethics can be important market drivers, which can translate into new technology requirements and business changes. Governments play an important regulatory role with respect to the production and use of bioactives, whether they are contained in pharmaceuticals or nutraceuticals. The role of government affects the business dynamic and technology developments. Government involvement covers patents, approvals for use in humans and animals, labelling, and even sustainable use of bioresources.

Health Canada and the U.S. Food & Drug Administration administer the relevant regulations pertaining to the pharmaceutical industry in North America. Among other objectives, regulations protect the public against products that are unsafe or do not function properly. Developing new drugs and obtaining approvals for new drugs is a time consuming and expensive process. Estimates are that it takes between C$ 200 to $400 million to develop a new drug that has been approved for use. Approximately $10 to $40 million of that may be required to support the process of getting new products approved by regulatory authorities. Regulations therefore present major investment requirements for suppliers.

In the nutraceutical industry, perception of safety and efficacy are paramount. If the perception of consumers turns negative, sales can plummet. A minor portion of suppliers can present issues of safety or efficacy for the nutraceutical industry as a whole. Some claims for the efficacy of products may be scientifically defensible (e.g., in some cases by suppliers selling over the Internet.). In addition, a lack of knowledge of the physiological effects of some bioactives may yield human health problems or a realisation that the products simply may not work. There are also issues that can potentially arise from the interaction of various combined nutraceuticals or the interaction of pharmaceuticals and nutraceuticals, when taken together.

Given potential health concerns and the potential for unethical business behaviour, regulatory considerations are likely to continue to be important to the nutraceuticals industry. In Canada, new proposed regulations pertaining to nutraceuticals have been development by Health Canada and the subject of consultations with stakeholders. Canada's Health Minister recently announced a series of measures aimed at nutraceutical industry. The measures include proposed regulations, improved labelling, research and public awareness activities. The proposed Regulations feature improvements in a number of areas including product licensing and good manufacturing practices, which will ensure the safety, effectiveness and high quality of natural health products marketed in Canada.[30]

In the United States the greater enforcement of FDA regulations covering nutraceutical claims will result in a requirement for suppliers to ensure their products are safe and can provide the

[30] Canada Gazette, Part I, December 22, 2001

benefits claimed. This will increase demand for research and development for larger companies with the resources to carry out this investment. Smaller companies may find they cannot invest in safety and efficacy testing and may be forced out of business, or may need to find other ways to participate.

3.4.4 Environment and Sustainability[31]

Generally, environment and sustainability become economic drivers when the scale of economic activity and its associated population shows evidence of overloading the carrying capacity of the local natural environment. The issue then becomes a constraint on economic growth or a driver for more environmentally-friendly or sustainable technologies and business practices. The visible evidence of an environmental constraint may come from any number of directions – availability of clean drinking water, urban air quality, fish kills, limitations on solid waste disposal. The management tools are usually regulatory intervention by government (using a variety of options) or, less frequently the exercise of consumer preferences.

Any region where tourism or the exploitation of bioresources is a major contributor to the economy would potentially be particularly sensitive to environmental issues and this is certainly the case in the Atlantic Provinces. The development of innovation clusters also requires the attraction of new employees and families to the region. This can be a challenge if the area has to contend with significant environmental constraints since these are seen as detrimental to a good "quality-of-life".

Evidence of sustainability constraints on economic growth is somewhat different and is often less visible to the general population. It appears, for example, as the economic need to destroy natural habitat, loss of wild populations of economic species, insufficient land, soil loss, insufficient water. In PEI, economic growth is currently limited by sustainability of fish stocks and water and land availability.

It would appear that, in general, sustainability rather than environmental constraints are currently the key drivers affecting economic development of the Atlantic Region and particularly PEI. It could affect the ability to exploit the growth opportunities associated with bioactives in the Region.

3.4.5 Challenge: Size and Complexity

[31] For a comprehensive description of the environment and sustainability analysis developed by Dr. David Minns, please see accompanying documents on the roadmap website at http://www.nrc.ca/atlantic/pei/reports.html.

The bioactives field is very large and complex, involving thousands of products currently under research and development. This research and development is being carried out by hundreds of universities, pharmaceutical companies, biotechnology companies, nutraceutical companies, suppliers, bioactives discovery firms, government research groups and others. A minor portion of the cluster activity is involved with using plant, animal and microbial species to find new bioactives as well as therapeutics that have already been approved or available in the nutraceutical and pharmaceutical markets.

3.4.6 Challenge: Investments and Risks

The bioactives cluster involves considerable financial risk since a very small portion of products and services under investigation can be commercialised. Industry experts engaged in the bioactives field and literature sources point out the requirements of success and the risks of participating in the cluster. The following summarises important considerations communicated by cluster participants:

- To take a drug from "bench-to-bottle" costs between C$ 200 million to $900 million and can take up to 12 years. 75% of the costs of drugs are attributed to failures.
- Less than 5% of "hits" (i.e., molecules with potentially useful bioactivity) identified in drug discovery enter pre-clinical studies. Of these less than 2% become medicines.[32]

3.4.7 Challenge: Attracting Human Resources

The technical core competence of many organisations involved in the high value bioactives cluster resides in their scientists possessing doctoral (Ph.D.) degrees. Employees with Masters degrees and undergraduate degrees in chemistry, genetics, biology, biochemistry, pharmacology, engineering and similar science fields are also necessary to the cluster.

In a recent study of one portion of the bioactives cluster, namely Canada's intermediate pharmaceutical suppliers, it was found that the overall percentage of the workforce with doctoral degrees was approximately 8%.[33] This percentage of employees with doctoral degrees is higher than most other chemical products businesses, where 0 to 3% of the staff are likely to have doctoral degrees. Talented scientists are required to envision innovative solutions and develop unique technologies to meet market requirements.

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32 http://www.drugdisc.com/stuttgart/

33 Cheminfo Services, Investment Opportunities and Challenges in the Canadian Intermediate Chemicals Industry, For Industry Canada, March 2001

A major challenge for Atlantic Canada and PEI (as well as the Canadian) bioactives cluster is the ability to find suitable new employees. It can be difficult to attract Canadian university graduates to small Canadian companies featured in this cluster and it is even more difficult to recruit talented U.S. graduates, so that the pool of suitable graduates available to the cluster is relatively small, according to duster participants. Part of the problem is Canada's larger and rapidly growing biotechnology sector, which is attracting personnel. Graduates are more interested in working for large established organisations with strong financial capabilities, including access to funds for research and growth.

It is also a challenge to retain high quality staff. The salaries and promotion opportunities for scientists are much better in the United States, according to industry sources. Employment opportunities in the United States are also more plentiful, especially for employees with doctoral degrees. American organisations pay close to 50% more, after taking into account the exchange rate.

Atlantic Canada and PEI are attractive locations for people with a preference for the region's natural beauty. In addition, many scientists born or educated in the region are likely to have interest for family or cultural reasons to locate in Atlantic Canada. The challenge will be to find and sell the merits of the region to prospective scientists, managers and employees.

3.5 Bioresources

There is a great diversity of marine and plant species available in Atlantic Canada. Marine bioresources present a special and unique opportunity for the region. A recent analysis of bioresources available in PEI along with ingredients that they contain found many bioactives, many with established commercial values.[34] The table below lists some of the major bioresources identified in PEI alone.

Organisations in Atlantic Canada are only beginning to realise the potential of the bioresources available in the region for production of bioactives. A notable example, is Ocean Nutrition Canada of Bedford, Nova Scotia, which has been successful in making nutraceutical products from bioresources available in the region (as well as other sources). Ocean Nutrition Canada makes high purity essential fatty acids (EFAs) such as omega-3 and 6 oils from fish. It also makes glucosamines for the nutraceutical market. Glucosamines are made from the chitin contained in crustacea shells (e.g., lobster) that would alternatively be sent to waste.

34 Food Technology Centre, PEI Bioresources Inventory, December 2001.

Table 11: Sample of Diversity of Bioresources Available in PEI and Atlantic Canada

Marine	Plants
Algae	Blueberries
Clams	Broccoli
Cod	Cranberries
Dogfish	Echinacea
Eels	Ground hemlock
Flounder	Hawthorn
Herring	Hemp
Jelly fish	Irish moss
Lobster	Lady's slipper
Mackerel	Potatoes
Mussels	Red Elderberry
Salmon, Salmonoids	Running clubmoss
Sea urchin	St. John's Wort
Shrimp	
Snow crab	

Some of the species available in the Atlantic Canada region are known to contain bioactives that are already in commercial pharmaceutical use. For example, ground hemlock (Taxus *canadensis)* is a known source of taxanes. Taxanes have been approved by regulatory authorities for use in the treatment for certain forms of cancer. The total taxanes market value at the wholesale level (i.e., sales by pharmaceutical suppliers to pharmacies, etc.) for the year 2000 is estimated at C$ 2 billion. The value of bulk intermediate bioactive taxanes sold to pharmaceutical companies is estimated at $50 million for the year 2000. There are likely to be many more marine and plant species in Atlantic Canada from which bioactives could be derived. The challenge is to identify the bioactives that are effective and have commercial value.

4. Technology Challenges and Priorities

4.1 Introduction

The relevant technologies in the bioresources and bioactives areas can be grouped in four categories related to progressive stages of the value-adding chain.

- Identification of the bioactives;
- Production in bioresource;
- Processing bioresources; and
- Utilisation of bioactives.

Value Adding Process

Another category of technologies, of importance to this roadmap report, are those involved with operationalising or further developing the sustainable development framework, described above. Technologies in this group are cross-cutting with the various technologies in the value-adding process.

The rest of this section of the report explores these technology fields, related barriers and some of the potential priorities for technology advancement. Taxane, a bioactive derived from bioresources, is highlighted as a case study. Technology considerations related to sustainable development are analysed in the last part of this section.

4.2 Technologies and Barriers

Bioresource-based bioactive development and exploitation is predicated on a widely accepted view that there must be an increase in the use of renewable resources. Today, most bioactives are synthesised by chemists in the laboratory, and are generally better controlled than those occurring naturally. To utilise natural sources, large quantities of feedstock need to be processed to final specifications. The bioactives field, oriented to providing final products that are derived from natural sources, encompasses a great many individual technologies and many areas that are under research and development. Due to the present relatively low use of renewable feedstocks and taking into account today's accepted value chain of manufacture of bioactives, it is useful to segment the significant barriers into key groupings (see table below).

Table 12: Barriers to Bioresource-Based Bioactive Development

Identification	Production	Processing	Utilisation
• Bioprospecting • Bioactivity • Bio-informatics • Molecular modelling	• Yield • Costs • Consistency • Genomics • Sustainability • Bioresource Management	• Extraction • Separations • Conversion • Purification • Refining • Control	• Efficacy • Marketing • Regulation • Ethics • Standards
Education, Training, Infrastructure, Sustainability and Rural Development			

In addition to the individual barrier groupings there is a large degree of interaction among the areas, shown in the above table, which suggests an overall dynamic which is viewed to be essential to understand and a significant barrier to overcome. For example, sustainability will play an essential role in regulatory approval of newly identified biological entities. In turn, a sustainability analysis will impact on the choices of production and processing technologies. The required and under-pinning infrastructure to support this practise will require the appropriate training of students and practitioners in various related disciplines such as regulation, manufacturing practice and sustainability analysis in addition to scientific and technical methodologies.

Illustrative of the management of this interactive system is the methodology developed by the pharmaceutical industry. From idea to production, the development of a new drug can take up to ten years and cost hundreds of millions of dollars. Once a new substance has been determined to have bioactive value, an elaborate testing program begins that recognises the strict regulatory practices of government agencies. In parallel with laboratory and clinical trials, manufacturing processes must be developed that in turn recognise strict manufacturing practice. Out of 10,000 chemicals tested in a laboratory, only one may eventually become a drug. Recent advances in gene splicing or recombinant DNA have led to technologies that promise to speed the advance of drug discovery and processing with associated positive effects on the economy.

For each of the identified barrier topic areas, examples of technical challenges for an expanded use of bioresource-based bioactives are discussed below.

4.3 Bioactives Identification

Expertise in the discovery arena is vital for organisations aiming to find or produce bioactives or their precursors that can be used in pharmaceutical or nutraceuticals. While a certain level of in-house expertise is generally deemed essential, discovery service companies have also emerged and are able to provide solutions to bioactive suppliers in often expensive and highly specialised services such as high throughput assays. In addition service providers are also targetting the newly emerging bio-chip and bio-informatics approaches. Prioritising and synthesising appropriate compounds for pharmaceutical companies is a critical component for drug discovery service organisations. These companies can offer customised expertise to provide the most consistent delivery of appropriate compounds to help build their customers' development pipelines.

Examples of specific technologies applied and under development include:

- **Bioprospecting (or Screening)**
    - *X-ray crystallography*
    - *Nuclear magnetic resonance (NMR) - spectroscopy*
    - *Mass spectroscopy*
    - *Gas chromatography*
    - *High Performance Liquid Chromatography (HPLC)*
- **Bioactivity Analysis**
    - *High-throughput bio-assays*
    - *Laser-based single cell metabolic interrogation*
- **Bio-informatics**
    - *Modelling & Databases*
    - *Biochips, Lab-on-a-chip*
    - *In silico analyses*

Three key research activity areas are identified as:

- protein characterisation;
- development of bio-informatics and molecular modelling approaches;
- improved functionality of screening systems.

4.3.1 Protein Characterisation

Early in the drug discovery process, proteins, which can be extracted from bioresources, are screened as possible drug targets. Proteomics, the study of all of the proteins in a biological system, is a rapidly developing field where matrix-assisted laser-desorption ionisation time-of-flight (MALDI/TOF)[35] instruments and ion traps have taken the lead. Proteins are typically separated by 2-D gel electrophoresis and then digested using trypsin. A mass map generated from a mass spectrum of the peptide fragments is ultimately used to query a protein database using a search engine.

Data interpretation is highly automated using search engines. With some knowledge of the chemistry involved, the technology need is to manually deduce partial sequences (tags) and perform a homology search tool such as BLAST (Basic Local Alignment Search Tool) which can be found on the National Center for Biotechnology Information's Web site at www.ncbi.nlm.nih.gov.

The challenge for MS instrument manufacturers is to devise a platform flexible enough to meet the ever-evolving needs of researchers, at a cost that can be justified on the basis of throughput and results.

4.3.2 Informatics: Protein Modelling[36]

The linear code of the human genome promises to empower drug discovery efforts. However, since most drugs act at the level of proteins, researchers have to add another dimension to the code. Structural genomics, enabled by technologies such as high-throughput X-ray crystallography, powerful nuclear magnetic resonance (NMR), and mass spectroscopy, are focused on the experimental protein structure determination. The goals of the public and private structural genomics efforts are challenged with determining the 3-D structure of any given protein in a costly and time-consuming endeavour. Technology innovations are therefore required to reduce costs, financial risks, and time in making determinations of protein structures. Advanced protein modelling software can help to provide quick and accurate approximation of the protein structure and even determine the likely inhibitors through in silico ligand docking.

The use of protein modelling has doubled in the last five years, according to industry sources and most of the growth occurred in the last two years as the genome efforts begun to bear fruit. As modelling algorithms become more powerful and automated, protein modelling will emerge

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[35] Time of flight (TOF) refers the use of time as part of the mechanism used to differentiate the mass of ionized molecules travelling in an electric field.

[36] Largely borrowed from: Boguslavsky, Julia, Protein-structure modelling and in silico docking tools accelerate drug discovery and development, Drug Discovery Magazine November/December 2001

as an indispensable tool in drug discovery research. The three general approaches to modelling protein structure include the *ab initio* method, homology modelling, and threading.

The *ab initio* method generates a 3-D structure from the amino acid sequence based on physical and statistical principles. This method is time-consuming and can only be practically applied to small sequences. Within the next decade--as more protein structures are solved at a constantly accelerating pace-- *ab initio* modelling will probably be overshadowed by homology modelling methods.

Homology modelling and threading are both based on an assumption that proteins with similar structure or function share common structural elements and folding patterns, probably due to their common evolutionary origin. The threading method is similar to homology modelling, but in addition to comparing the sequence of related proteins, it also compares their structure.

While homology modelling is a very powerful technology, it still has limitations, being addressed through research. The quality of the model is directly related to the quality of the sequence alignment used to generate that model. For example, at 30% sequence identity, there may be a 25% error in sequence alignment. The key area of improvement in homology modelling is optimising sequence alignment for remotely related protein sequences.

4.3.3 In silico Screening

To capitalise on the growing number of protein structures, pharmaceutical companies are increasingly adopting in silico ligand screening to cut the experimental expenditures associated with combinatorial library production and screening and to speed up time-to-market. In silico screening is expected to be a key component of the drug discovery process in the next five years, according to industry sources.[37]

Major challenges are that: proteins are flexible; there are solvent effects that do not necessarily model very well; and there are very many compounds with different chemistry that need to be represented. There are also multiple functions required to score the compound conformations. It is a very large multidimensional problem, requiring significant resources and talent to address. It is a problem that has yet to be solved because one cannot accurately represent what is going on in the system fast enough to screen millions of compounds in a short time. Current algorithms focus on optimising the problem and taking shortcuts.

[37] Accelrys Inc. (Edwards) from Drug Discovery Magazine November/December 2001.

4.4 Bioactives Production

Commercial bioactives need to be produced in sufficient quantities to serve market demands. Technologies are required to enhance sustainable development and economic growth as well as the harvest of animals or plants.

Examples of important technologies are:

- **Constituent and yield improvements**
  - *Consistency of plant components*
  - *Plant engineering to overcome adverse environmental stress*
  - *Plant engineering to produce components of interest*
  - *Yield improvement via plant productivity and harvestable parts*
  - *Bioactive preservation systems*
  - *Genomics*
- **Agriculture and aquaculture optimisation**
  - *Aquaculture production via new environmentally-friendly, intensive methods*
  - *Aquaculture species fishpen design*
  - *Agronomic optimisation technologies for materials of interest*
  - *Harvesting machinery for biomass collection*
  - *Marginal land use*
  - *Sustainability and environmental monitoring and modelling*
  - *Information technologies (databases, models, information exchange)*
  - *Genomics*
- **Bioresources management**
  - *Technologies that assist in quantifying availability, growth and depletion in large regions*
- **Sustainability and environmental science**
  - *Sustainability and environmental monitoring and modelling*

Many of these technologies are already the subject of research and advancement in PEI, other Atlantic Canada provinces, as well as in many other regions where agriculture and aquaculture enhancement is required. The bulk of the technology advancement is oriented to sustaining and enhancing traditional food crops and fish, not necessarily focused on bioactives that may be contained in them.

The applicable technologies related to bioresource growing and harvesting will be bioactive-specific as well as bioresource/species-specific. However, a general description of cultivation and harvesting technologies is provided below. These are more applicable to plants rather than marine animals or livestock, which would involve a different set of technologies. This analysis excludes genomics technologies, which may be important depending on the bioactive and alternative bioresources from which it could be derived.

Most of the plants used for nutraceuticals or medicinal purposes are cultivated, that is, grown on farms. Some, however, may be collected from the wild. The following section discusses some of the technologies involved in obtaining bioactives from plants.

Cultivation allows producers to have more control over quality and purity than does collecting plants from the wild. Cultivars (cultivated varieties) of a number of medicinal plant species have been developed to produce high yields of the desired constituents. Some plants that are grown commercially for medicinal purposes are propagated vegetatively. (This means that new plants are grown from cuttings of old plants. Plants grown in this way are genetically identical to the parent plant.) Some medicinal plants are grown from selectively bred hybrid seeds, while others are varieties of plants that are unchanged from their natural form.[38]

A number of medicinal plants are cultivated for use by the pharmaceutical industry. Some examples include yams, which are used in the production of steroids; foxglove, which is used for digitalis; belladona, which is used for atropine; and opium, which is used to make morphine. There are many plants that are cultivated for pharmaceutical and nutraceutical use. Many are listed in the section of Bioresource Inventory.

Many countries commercially cultivate and trade in substantial quantities of plants used for production of bioactives. Countries include United States, China, India, Thailand, South Korea, Brazil, Mexico, Egypt, Indonesia, Nepal, the Philippines, Canada, and Kenya. More recently, eastern European countries have become involved in the cultivation and trade of plants containing bioactives. Many of these countries offer low costs for harvesting, much of which can be labour intensive.

As for any agricultural crop, producers of medicinal plants must provide plants with adequate moisture and nutrients and must control pests and diseases. Pesticides must be used cautiously to reduce the risk of harmful residues on plants (List and Schmidt, 1989). Production of medicinal plants is generally labour intensive. In many cases, only the portions of the plant that contain the active ingredients - not the whole plant- are used. Harvesting often involves picking leaves and flowers by hand. In the future, tissue culture may be used for producing plant material. These issues combine to suggest that the development of novel harvesting technologies will play a role in bioactives production.[39]

[38] Wijesekera, R.O.B., The Medicinal Plant Industry. Boca Raton: CRC Press. ISBN 0-8493-6669-0. From Virginia Commonwealth University Libraries, 1991.

[39] List, P.H., and P.C. Schmidt. Phytopharmaceutical Technology. Boca Raton, FL: CRC Press, 1989.

4.5 Bioactives Processing

Separation and purification technologies for isolating often dilute components from natural feedstocks represents a critical technology barrier for developing a bioresource-based bioactives industry. The major and ongoing technology challenge is to extract, isolate and concentrate the bioactive ingredients economically. The innovation process in these technology fields is therefore often focused on reducing capital and operating costs, minimising raw materials requirements, increasing purity and minimising wastes. The scale-up of laboratory techniques to economical continuous processes remains as a critical challenge.

Originally, bioactive compounds including those used in nutraceuticals and pharmaceuticals were isolated largely from natural sources. However, over time, synthetic routes become predominant. For example, vitamins were originally derived from plants and animals. Vitamins A and D were originally isolated from fish liver oil; vitamin E from wheat germ oil; vitamin K from alfalfa; vitamins B_1 and B_6 from rice; vitamin B_2 from eggs; and vitamin B_12, niacin, folic acid, pantothenic acid, and biotin from liver. Although it is possible to extract all vitamins from natural products, it is generally infeasible for commercial reasons. There are exceptions, and possible opportunities for marketers interested in the "totally-natural" segment of the broad market. For example, small quantities of vitamins A and D are extracted from fish oils.

The most important technologies involved with processing and production of bioactives from bioresources are separation and purification technologies, which include:

- **Separation and purification**
    - ***Aqueous extraction techniques***
    - ***Organic hydrocarbon solvent extraction***
        - Maceration, Percolation, Countercurrent extraction
    - ***Purification and concentration***
        - Decanting, Filtration, Sedimentation, Centrifuging, Heating, Adsorption, Precipitation, Ion exchange
    - ***Supercritical fluid extraction***
        - Carbon dioxide, Nitrogen, Ethane, Nitrous oxide, Sulfur dioxide, Ammonia, Chlorofluorocarbons, Sulfur hexafluoride
    - ***Steam distillation***
    - ***Pressing, enfleurage***
    - ***Ion-exchange***
    - ***Membranes***

Nutraceuticals and pharmaceuticals can be produced from fresh, dried or otherwise preserved plants or parts of plants. For nutraceuticals, bioactive ingredients may not be completely isolated but rather are obtained along with other naturally occurring components of the plant. For bioactives used in pharmaceuticals, the required purity of the bioactive may be very high.

Increasing the purity of the bioactive compound may be carried out by at different value-adding stages in different organisations. Other components can influence the efficacy of the active ingredient. Sometimes the bioactive ingredients are concentrated, and undesirable substances such as chlorophyll, tannins, or resins, are removed.

An additional significant and well recognised barrier to the development of processing natural based products is the current lack of trained practitioners. The present focus of chemical engineers and technologists on traditional chemical manufacturing principles and lack of biochemical process subject matter in most curriculums must be altered to provide the necessary trained workforce. Illustrative of this need is the serious lack of scientists, engineers and technologists trained in c-GMP knowledge.

Key research areas identified for bioactive processing are:

- Chromatographic technologies
- Separation Membranes
- Synthetic Modifications of Post-Extracted Bioactives

4.5.1 Chromatography[40]

Ion exchange chromatography (IEC) is applicable to the separation of almost any type of charged molecule, from large proteins to small nucleotides and amino acids. It is very frequently used for proteins and peptides, under widely varying conditions. However, for amino acids standardised conditions are used. In protein structural work the consecutive use of gel permeation chromatography (GPC) and IEC is quite common.

Reversed phase-fast performance liquid chromatography (FPLC) is employed in biochemistry to separate low molecular weight compounds according to their hydrophobicity. Examples of biochemical samples are peptides, amino acids, and nucleic acid components. Due to the very small sizes of the particles employed as the stationary phase, very narrow peaks are obtained.

The challenge remains to develop continuous – high throughput processes based on these techniques. Simulated moving-bed technology, a continuous chromatographic technology, is a recent development being used to scale up conventional chromatographic techniques.

[40] Natural Toxins Research Center, Texas A&M University- Kingsville. http://ntri.tamuk.edu/fplc/ion.html

4.5.2 Membrane Separation[41, 42]

An ideal method for separation would be a barrier that allows the desired substance to pass while restraining other materials. Semipermeable membranes meet this ideal by having pores through which one substance can pass while others cannot. In nature such membranes enclose living cells; nutrients enter while wastes escape, and some substances are transported against their concentration gradients by energetic mechanisms. Synthetic membranes are available with a wide range of pore sizes. Very minute pores allow only molecules of gases or water to pass, intermediate sizes of pores discriminate between molecules such as different proteins, and larger pores may be just fine enough to prevent passage of particles and cells such as microorganisms.

Pressure-driven synthetic membrane processes are being increasingly integrated into existing reaction and recovery schemes for the production of valuable chemical and biological molecules. Membrane systems offer the following operational advantages: no phase change; no temperature excursion from ambient; no need for additives and feature with relatively low energy consumption. Another advantage over the popular purification method - chromatography - is that a membrane separation process can be run in a continuous fashion.

While not in commercial use today, membrane reactor systems are gaining attention in the research community. By combining catalysts and membranes into one device, production and separation can be accomplished simultaneously. Also in the development phase are membrane based systems for the separation of chiral compounds (compounds differing in spatial arrangement with practically identical physical properties but often differing physiological effects) such as liquid membrane systems and micelle-enhanced ultrafiltration.

Membranes research and development is proceeding to overcome technical problems in achieving faster throughputs, more complete separations and lower costs (e.g., cost of membrane replacements) for market users of the technology. Some of the developments include research on: backpulsing; membrane surface modification and membrane reactors (e.g., plasma treatment, chemical modification).[43]

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[41] Aufderheide., B adapted from "*Evaluation of Cwall Control Parameters for a BSA Ultrafiltration Process*" by Ralf Kuriel, et al, Bioprocess Division, Millipore Corporation, 80 Ashby Rd., Bedford MA 01730. http://www.eng.rpi.edu/dept/chem-eng/Biotech-Environ/rssep/Purification/Membranes/membrane2.html

[42] Hegener, P., Protein Fouling of Microfiltration and Ultrafiltration Membranes, Rensselaer Polytechnic Institute, July, 2001

[43] 2000 by SRI Consulting, Explorer, Membrane Separations

4.5.3 Synthetic Modifications of Bioactives

Chemical substances or pre-bioactives derived from bioresources often require synthetic modifications to make them effective and/or safe for application. Synthetic modification may occur at the pharmaceutical companies or at companies that support the pharmaceutical industry with synthesis services. These companies, referred to as intermediate pharmaceutical suppliers, apply a range of chemical and biotechnologies to make or "tweek" bioactives.

An emerging technology being applied is in many sectors is biocatalyst technology; including the food, materials processing, pharmaceutical, and chemical industries. Biocatalysis[44] is a process that uses biological mechanisms to catalyze chemical reactions. Within these industries, biocatalysts have many applications, ranging from product synthesis (for example, amino acid manufacture) through use as active agents in products (for example, in biological washing powders) to use in diagnostic testing equipment and as therapeutic agents.

Of particular interest, is the emerging appeal of plant based production systems for producing complex proteins. The need for lower-cost manufacturing methods is very apparent in the production of monoclonal antibodies for therapeutic applications. Current technology for the production of monoclonals generates product costs of $100 to $1000 per gram. At this price, the cost of treatment may exceed $100 000 per patient and is much too high for nontherapeutic applications (that is, catalytic antibodies). This high cost (as well as companies' desire to manufacture products that do not provoke severe immune reactions) explains why companies are turning to plant-based production systems. Scientists use two basic strategies to produce proteins in plants: generation of a transgenic plant through stable integration of the desired gene into the plant genome and transient expression of the desired gene using a plant virus as a vector. Each of these approaches is currently finding use in protein production.

With the successful demonstration of high-yield protein production in plants, many companies have shown significant interest in the production of chemicals and therapeutics in plants. Further development of plant-based production systems by plant biotechnology companies, including the engineering of metabolic pathways, will allow plants to synthesise many products efficiently.

[44] 2000 by SRI Consulting, Explorer, Biocatalysis

4.6 Bioactives Utilisation

Bioactives must meet general market and customer requirements when in use. Technologies are therefore required to ensure that the products are functional, stable, and safe. Examples of technology fields include:

- **Bioactive Functionality**
  - Material functional properties
  - Chemical/molecular functional formu lations
  - Structure-function relationship development
- **Dosage and packaging**
  - Formulation, flavouring
  - Biomaterials/biopolymers
  - Packaging design
  - Labelling
  - Time release
- **Safety and efficacy**
  - Animal testing
  - Human clinical trials
  - Standards and metrology

4.6.1 Bioactive Efficacy

Nutraceutical and pharmaceutical companies are heavily engaged in technologies forward in the value-adding chain. That is, pharmaceutical companies incur the necessary and large investments to obtain government regulatory approval from drugs containing the bioactives. There is a very large body of research occurring with respect to developing ever better knowledge of how bioactives (contained in nutraceuticals or pharmaceuticals) work in the human body to treat disease or provide nutrient value. In many cases, the same technologies involved in identifying bioactives are also applied to understanding how they function in humans and animals, as nutraceuticals and pharmaceuticals.

Ultimately, animal and human testing are required to ascertain whether the bioactive is indeed safe and useful. There is expertise involved in human as well as animal testing and clinical trials that are usually the domain of the pharmaceutical companies. The required expertise involves experimental design, tissue analysis, pathology, and statistics.

Associated with functionality or efficacy and regulation is the development of methodologies for metrology. This is a particular concern in dealing with natural based products where production standards may require greater development.

4.6.2 Final Dosage Forms and Packaging

The final dosage forms of many nutraceuticals and pharmaceuticals are similar in many cases. Some of the important technologies involved at this stage of the value-adding process include:

- Ingredient formulation;
- Coatings technologies;
- Biomaterials/Biopolymers used for time release.
- Packaging materials and design;
- Label design;
- Dosage and packaging equipment and process (filling, etc.);
- Consumer testing.

The following describes some of the technology considerations involved with putting nutraceuticals and pharmaceuticals into the final form in which they are purchased by consumers.

For many years, formulation has been an important technology with respect to bioactives dosage and delivery systems. Gelatin capsules were formulated in the 1830s by a pharmacist who wanted to make unpalatable medicines easier to swallow. Both hard and soft capsules have similar ingredients, which include gelatin and water, and possibly colorants, preservatives, opacifying agents, flavours, and sweeteners. Soft capsules also contain plasticisers such as glycerin or sorbitol to keep them pliable.

Tablets are a solid dosage form that come in various shapes, sizes and formulas. They are formed by compression and generally contain additives to aid in their manufacture, as well as various colorants and coatings. Once tablets are formed, they may be coated with a sugar, film, or enteric coating. Sugar coatings protect the active ingredients in the tablet from air and humidity and cover bad flavours. They also can be used to make tablets larger and easier to handle. Film-coated tablets are covered with a thin layer of a polymer that protects the tablet and makes it easier to swallow. This film breaks apart in the stomach. Enteric coatings remain intact until the tablet reaches the intestines. Chewable tablets, which have no coating, are also made by compression. This type of tablet is commonly used for children's vitamins. They are generally made from a mannitol base with added colours and flavours.[45]

Other dosage forms include liquids and powder. Formulation technologies are similarly important for these dosage forms. Formulators are typically involved with developing new

[45] Ansel, Howard C., Nicholas G. Popovich, and Loyd V. Allen, Pharmaceutical Dosage Forms and Drug Delivery, 1995.
Systems. Sixth edition. Baltimore: Williams and Wilkins.

products by working with quite a variety of ingredients. Typical ingredients include: sugar or a sugar substitute, flavourings, colourings, preservatives solvents, solubilising agents, thickeners, stabilisers and alcohol. These ingredients which provide specific function in the dosage form must also be compatible with active ingredients, and the container packaging.

4.6.3 Biomaterials/Biopolymers Used for Drug Delivery Systems[46]

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under- and overdosing. Other advantages of using controlled-delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance.

While the above advantages can be significant, being addressed through research and development include: the possible toxicity or nonbiocompatibility of the materials used; undesirable by-products of degradation; any surgery required to implant or remove the system; the chance of patient discomfort from the delivery device; and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations.

4.6.4 Packaging and Labelling

The purpose of packaging is to provide protection, presentation, identification, information and convenience from the tie a product is manufactured until it is consumed. The type of packaging used will depend on the characteristics of the product or bioactive, such as its sensitivity to moisture, oxygen, or light as will as its reactivity with the packaging material. The form of the product is also important. Whether the product is a tablet, capsule, liquid, or granule will determine the appropriate packaging. Plastic bottles and jars are commonly used to package nutraceutical and pharmaceutical products. Other types of packaging include glass bottles, jars, vials, and ampules, as well as bags or pouches made of specialised plastic films, laminates and papers. Some types of packaging such as blister packs, are a combination of several materials.

Suppliers of nutraceuticals and pharmaceuticals are always seeking to optimise appeal, functionality and cost. For some products, packaging involve complex material science (e.g.

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[46] Brannon-Peppas, Polymers in Controlled Drug Delivery Medical Plastics and Biomaterials Magazine, November 1997
http://www.eng.rpi.edu/dept/chem-eng/Biotech-Environ/rssep/Drug_Delivery/drug_delivery.html

CHEMINFO

polymer, gas barrier technologies, bonding, reactivity.) Packaging design is therefore often performed or assisted by organisations specialised in packaging design. Some of these organisations are integrated to making packages and even filling products for customers (which may include nutraceutical and pharmaceutical suppliers).

4.7 Key Research and Development Actions

The key research and development actions required to overcome barriers were identified in a similar roadmap process undertaken by the U.S. Department of Energy (DOE) in their Technology Roadmap for Plant/Crop-Based Renewable Resources 2020. Some of the findings of contained in that research map have been borrowed and modified taking into consideration the findings of this roadmapping process, and the product is shown in the Table below. The key activities have been ranked from top to bottom in order of priority for impact on the development of bioresource-based bioactives.

Table 13: Key Research and Development Activities

Identification	Production	Processing	Utilisation
Develop analytical tools for compounds of interest, and functionality screening systems.	Agronomic/aquaculture optimisation technologies for materials of interest.	Develop new separation methods.	Develop better understanding of structure-function relationships.
Development of bio-informatics and molecular modelling approaches	Yield improvement via plant productivity and harvestable parts	Develop improved conversion methods.	Study sustainability of infrastructure to optimise impact on rural economies.
Develop improved functionality of screening systems.	Sustainability and environmental monitoring and modelling	Develop/optimise enzymes.	Develop standards and methods to support product quality.
	Develop technologies that assist in quantifying availability, growth and depletion in large regions	Develop hybrid bio and chemical systems	Materials development for controlled bioactives delivery.
	Harvesting machinery for biomass collection	Develop new reactor methodology	Develop packaging and labelling formats.
		Explore reactive enzymes within plants.	

4.7.1 Example: Taxanes

Attention will now focus on determining the specific research priorities required for the development of an identified example project. Illustrative of such an analysis, and to test the robustness of the key research actions map is an investigation of taxane based products. This case study is useful in that it illustrates how market needs and technologies are interwoven.

Taxanes are a group of drugs used in the treatment of some forms of cancer, which are derived from processed biomass associated with yews. (A more in-depth analysis of taxane markets and barriers is contained in the Appendix.) Technical barriers to market growth are focussed in the production, processing and utilisation groups where significant sustainability issues are associated with the exploitation of natural resource - yews - which needs to be better understood. Projects are underway to improve crop yields and in biotechnology routes to produce taxanes. Due to the dilute concentration of the bioactive taxane in the target species, novel separation methods will play a significant role in product economics.

Table 14: Taxane Development Mapped Onto the Research and Development Activities Map

Identification	Production	Processing	Utilisation
Develop analytical tools for compounds of interest, and functionality screening systems.	Agronomic/ aquaculture optimisation technologies for materials of interest.	Develop new separation methods.	Develop better understanding of structure-function relationships.
Development of bio-informatics and molecular modelling approaches	Yield improvement via plant productivity and harvestable parts	Develop improved conversion methods.	Study sustainability of infrastructure to optimise impact on rural economies.
Develop improved functionality of screening systems.	Sustainability and environmental monitoring and modelling	Develop/optimise enzymes.	Develop standards and methods to support product quality.
	Develop technologies that assist in quantifying availability, growth and depletion in large regions	Develop hybrid bio and chemical systems	Materials development for controlled bioactives delivery.
	Harvesting machinery for biomass collection	Develop new reactor methodology	Develop packaging and labelling formats.
		Explore reactive enzymes within plants.	

4.8 Sustainability Technology Considerations [47]

Bioactives are present in small concentrations in plants and animals. Echinacea is a well-known example. Echinacea is also an example of how popular demand can threaten natural populations even for a relatively common species. There are many examples where commercial demand for a bioresource has outstripped supply threatening populations and causing local extinction or extirpation. This is one of the essential sustainability challenges of a bioresource-based industry such as that being considered here. To preserve and protect natural populations, farming or synthesis may be possible alternatives to meeting demand.

4.8.1 Technologies for Measuring of Impact

Quantifying and verifying the impact on the indicators of sustainable development and eco-efficiency requires a comprehensive measurement and analysis approach. This could have implications with respect to, for example, sensor development, use of wireless technologies, modelling and database management.

Measurement needs fall into two categories

4.8.1.1 Technologies for Assessing Systems Performance

The intent here is to characterise the system and its sustainability. Systems measurements are generally distributed in space and would be mapped using methods such as GIS. Methods used range from:

a) survey methods (such as field monitoring for biodiversity) but also use of information and communication technologies (ICT) for surveying public or consumer opinions and preferences. The GB-Quest initiative described in the chapter on SEMF elsewhere in this report is an illustration of new techniques being developed in this field;
b) sampling and chemical analysis or sensing of air and water (toxic pollutants, particulates, BOD, COD, GHG gases);
c) use of remote sensing methods such as LIDAR or IR for climate change gases and urban air quality;
d) recording of weather (temperature, humidity, wind velocity, precipitation, etc),
e) soil sampling and analysis, and
f) measurements of the distribution of resources such as the quantity of groundwater using geophysical measurement techniques.

[47] For a comprehensive description of sustainability issues and technology developed by Dr. David Minns, please see accompanying documents on the roadmap website at http://www.nrc.ca/atlantic/pei/reports.html.

4.8.1.2 Technologies for Assessing Emissions and Use

This is essentially measuring inputs to the system (waste, heat, pollutants, etc) and outputs (withdrawals) from the system (water, energy, materials) such that these can be linked to changes in systems performance and sustainability. Some of these are measured at the process scale (e.g. toxic air emissions, effluent water quality, use of groundwater, use of energy, etc.), some at the scale of the system of interest (e.g. imports and exports of materials, tourist trade, demographics and population changes) and some on the global scale using life-cycle assessment methods.

For all categories the variable of interest should be measured over time using time intervals that allow the tracking of the dynamic change in system performance resulting from a change in inputs or outputs. Knowledge of this time response relationship is fundamental to the development of stable management and control strategies and could involve sampling frequencies of <1 second, to hours, days or years depending on the nature of the system and the component interaction being investigated. It is a preferred approach to link such measurement with a modelling and analysis program. Besides laying the foundation for effective decision-making, modelling also helps determine the best locations or targets for sampling.

4.8.2 Technology Development Options to Enhance Sustainability

The following options have been identified during the sustainability and eco-efficiency assessment process.

(a) Technologies to preserve bioactivity in feedstock during harvesting and storage. This would reduce unnecessary wastage.
(b) New bioprospecting technologies that demand limited samples to reduce threat to rare or endangered species.
(c) Bioprospect for bioactives in waste materials from existing bioresources based production such as food processing.
(d) Find other uses for the waste from bioactives production. Possibilities are a) feedstock for the production of biocataysts and commercial enzymes; and b) small scale energy production (which could be used by local industry).
(e) Design production processes to reduce water or other solvent intensity.
(f) Design production processes to reduce energy intensity.
(g) Develop benign synthetic processes for the production of bioactives to relieve load on natural bioresource production.
(h) Develop packaging and/or just-in-time delivery processing technologies to preserve bioactivity at the point of application. Effort should be made to reduce the amount of packing required and to make it recyclable. Can packaging be produced from biopolymers?

4.8.3 Sustainable Technology Grouping

Some of the technologies noted above can be combined to create a Technology Grouping that collectively has a chance of operating sustainably where any single technology likely will not. An example might be:

Use waste from other processes as feedstock, recover energy from manufacturing and feedback to the manufacturing process, use waste from manufacturing process as feedstock for other products (e.g. enzyme production), use renewable forms for process energy (e.g., wind power, solar or biomass), use biopolymers for packaging, recover and recycle process water.

Such a grouping could be established through the design and operation of an "eco-industrial" park.

4.8.4 Sustainable and Environmental Modelling Framework (SEMF)

Economic growth in PEI is constrained by limited land availability, limited water supply and the often negative interactions between the commercial strengths of its economy: tourism, agriculture and aquaculture. Continued economic development must occur within the physical constraints of the Island. The bioresource industry will need to grow within the environmental and social context of these constraints.

Given the complexity of sustainability, PEI offers a practical opportunity for advancing our understanding of sustainable development and establishing a Sustainable and Environmental Modelling Framework (SEMF) on a scale that is tractable and relevant for the continued economic development of bioresources. Although PEI is well positioned to be the focus for research and demonstration of the SEMF and be an early beneficiary of its application, much broader applications and outcomes can be expected. In particular, the development of the SEMF would firmly establish considerations of sustainability within a management and decision-making framework for technology development and innovation in bioresources and provide the basic management framework for the development of the bioeconomy in Canada. The research supporting the development of the SEMF would be closely linked with initiatives to develop indicators of sustainability.

Currently, there are no scientific research initiatives or National Centres of Excellence (NCE) focussed on a comprehensive modelling of the indicators of sustainability for decision-making though there are several that are working in related fields. Most major Canadian universities now offer both undergraduate and graduate studies in environmental science and/or environmental engineering. Some universities and other research organisations are developing more specific initiatives in the field as illustrated by the following:

The **Institute Of Island Studies** is a research, education and public policy institute based at the University of Prince Edward Island, Charlottetown, Canada. With an emphasis always on Prince Edward Island, the work of the Institute focuses on the culture, environment and economy of small islands.

University of New Brunswick, Environment and Sustainable Development Research Centre

GPI Atlantic is a non-profit research group, founded in 1997, to develop an index of sustainable development and well being - the Genuine Progress Index. Application of the Genuine Progress Index to Nova Scotia is serving as a pilot project for Canada. To that end, Statistics Canada is providing in-kind support in the form of data access, ongoing advice and consultation, and review of drafts. Wide interest in the GPI reports to date has led to projects developing Genuine Progress indicators at the community level.

Sustainable Technology Office, NRC-ICPET has a capability in systems analysis, LCA and process design for improving the performance of technologies at the concept stage and for assessing their contribution to sustainable development using the WhatIf™ platform.

Office of Energy Efficiency, NRCan has developed very detailed models based on the WhatIf™ platform along with its own LCA model to evaluate energy technologies.

The **Sustainable Development Research Institute** of UBC is the co-ordinator of The Georgia Basin Futures Project. This is a five-year research project that combines expert knowledge and considered public opinion to explore pathways to sustainability. Georgia Basin QUEST is a key component of the Georgia Basin Futures Project. It is an interactive user-friendly game that allows one to develop "what if?" scenarios for the future of the region. The scenario that one creates is saved and forms part of a larger research question that seeks to understand how one can meet society's needs within the limits of the environment in the Georgia Basin. GB-QUEST is available for public participation at Vancouver's Science World in the Weyerhaeuser Science Theatre.

There is also a "sustainable city" project being conceived in **Regina** with the University in consultation with NRC which conceptually also is focussed on developing an understanding of the interrelationships of sustainability indicators for decision-making but focussed on urban issues.

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As noted earlier, internationally, key research and expertise resides at **IIASA** in Austria and at **CSIRO** in Australia.

Complementary to the modelling expertise is that required for experimental work and field studies. Strength exists in Atlantic Canada in this regard in organisations such as AVC, AAFC, Environment Canada, DFO, NRC-IMB and the Provincial laboratories and in the science and engineering departments of universities.

There are also industrial players in Canada, primarily in the environmental consulting business, who use sophisticated analysis and modelling in for example site environmental risk assessment, groundwater management and urban air-quality modelling. These organisations use modelling tools such as CFD and GIS. Examples of companies involved in such activity are:

- **Jacques-Whitford**, a world-wide environmental services company with a strong presence in Atlantic Canada.
- **RWDI** of Guelph, Ontario with strength in CFD and international reputation in determining wind stresses on tall buildings and, in collaboration with NRC-ICPET, an advanced capability in urban airshed modelling.
- **SNC-Lavalin Environment Inc**, a large engineering services company based in Montreal, that offers consulting services in areas such as environmental studies, environmental management, waste management, contaminated sites, and air quality.

5. Strengths and Gaps in PEI, Atlantic Canada's Bioactives Cluster

The full North American bioactives/bioresource sector embraces quite a number and variety of organisations that support as well as compete with one another. Customers in the cluster define market needs that are addressed by their suppliers. Suppliers include those organisations that provide raw materials, R&D services, equipment, consulting services, and a source of suitably educated and trained personnel. This drives technology innovations to meet evolving market needs. Governments and regulatory authorities that represent general public interests can also play supporting as well as regulatory roles.

A cluster functions best when there is close collaboration as well as competition occurring among participants. Atlantic Canada, similar to any geographic region has certain strengths as well as gaps with respect to all components of the cluster. Regions therefore need to leverage their strengths and address their gaps to the degree possible. Often new participants in a specific region must adopt focus-type strategies to provide high quality, specialised niche products or services to participate effectively in the cluster. Atlantic Canada's key strengths and gaps in the context of the bioactives market segments can be summarised as follows:

Key Strengths

- marine bioresources locally available;
- plant bioresources available for selected bioactives (e.g., blueberries, ground hemlock);
- universities and government research organisations with strengths in marine bioresources, agriculture, and some aspects of bioactives;
- growth of companies in processing of bioresources for high value products;
- provincial priority on sustainable development of bioresources;
- proximity to a large number of major cluster participants in northeast portion of North America;

Gaps

- bioactives discovery organisations with knowledge based on local marine and plant species;
- research organisations specifically focused on deriving bioactives from local bioresources.
- pharmaceutical companies and supporting products and service suppliers in the field of bioactives;

A number of conclusions can be derived from the analysis conducted in the roadmap exercise. The sustainable development of the bioresources industry in Atlantic Canada, and particularly in PEI, implicates focusing on high value-added components of the bioresources supply chain, moving from "once-through" to recycling of resources, and moving away from commodity products. Consistent with these considerations is the selection of bioactives as a high value bioresource opportunity and its development in a sustainable manner, requiring a better understanding of the environmental, social and economic systems of the region.

The ready availability of marine sources of bioresource-based bioactives provides Atlantic Canada with an advantage not available to other regions, while links to other centres of bioactive development could complement local strengths. The Atlantic region's resource base is complemented with research strengths in marine biosciences, sustainable agriculture, food science, and nutraceuticals, along with emerging growth of companies in high value added bioresource products.

A cursory analysis of the sustainability issues surrounding bioactives indicates the need to manage populations of natural feedstock, large amounts of waste biomass, and energy requirements for processing. PEI offers a unique opportunity to conduct comprehensive experimental studies and modeling of the bioactives (and other) systems to provide an integrated approach to developing bioresources sustainably, which could be transferred to other sectors and regions. Building capacity in modeling would complement existing strengths in experimental data from agriculture and marine bioresource sectors and of environmental quality.

The set of diagrams that follow show the cluster participant groups (Figure 2), key linkages and the important strengths and gaps in Canada (Figure 3). These strengths and weakness are also applicable to Atlantic Canada.

Figure 2: Participants and Key Linkages in Bioactives/Bioresources Cluster

(Simplified Material and Service Flows)

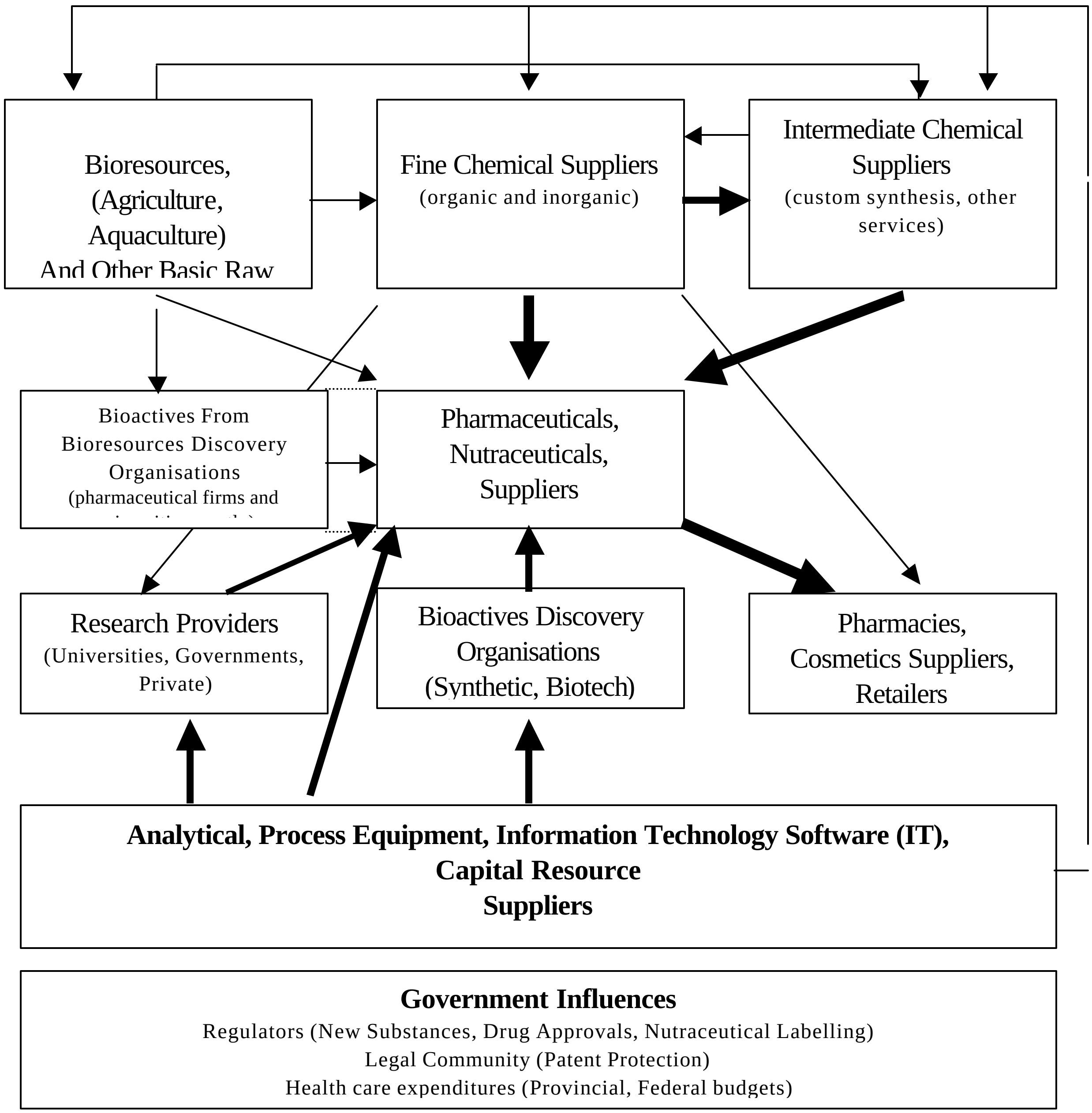
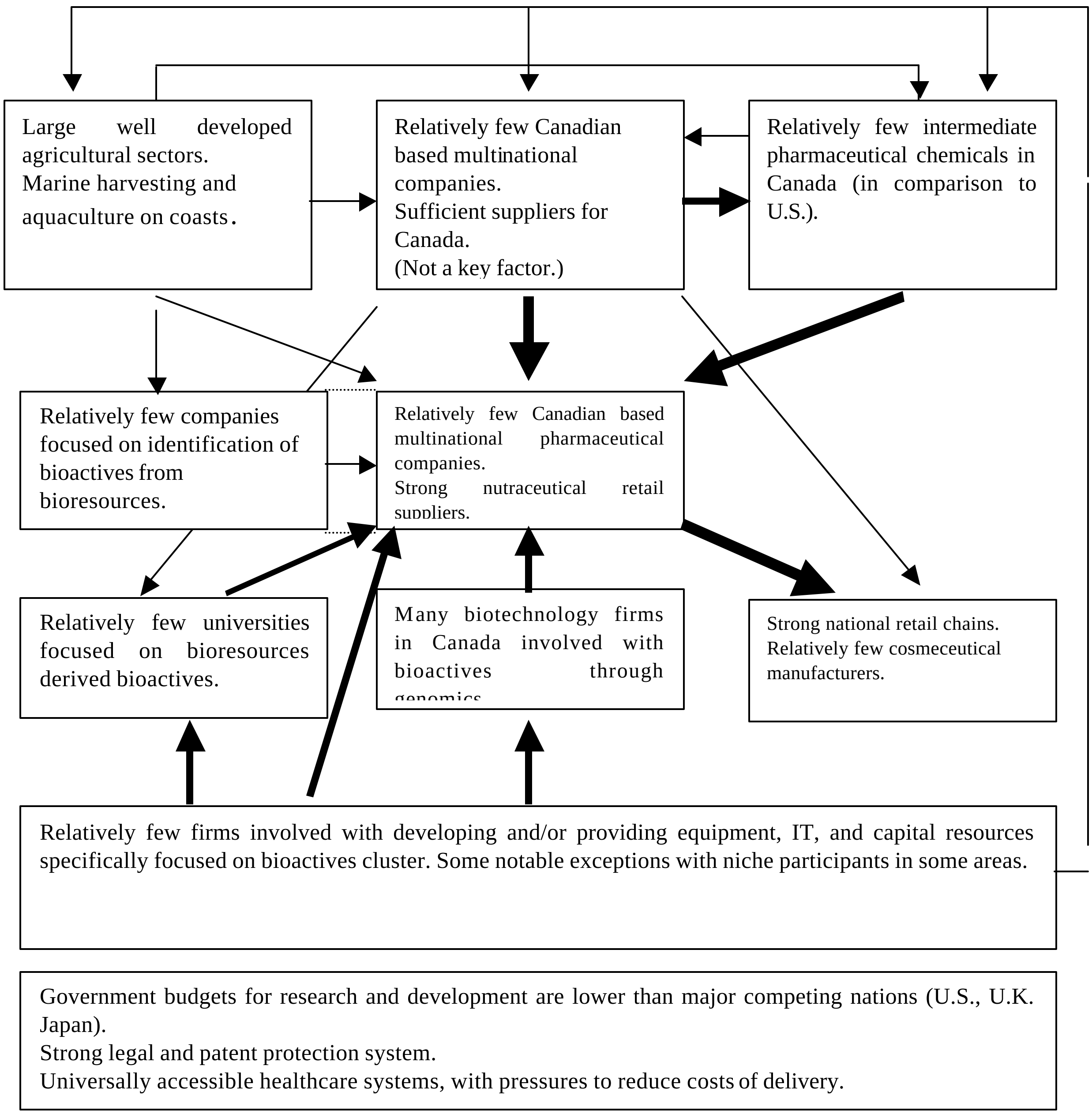


Figure 3: Key Strengths and Gaps in Canada's and Atlantic Canada's Bioactives/Bioresources Cluster

(Simplified Material and Service Flows)



Critical infrastructure requirements for the bioactives cluster relate to the understanding of how bioactives function and the knowledge of the relevant technology fields applied to identifying bioactives, growing and harvesting bioresources, manufacturing bioactives and marketing. Therefore infrastructure components required to support the bioactives field are universities, colleges and government organisations that research services as well as professionals educated and trained for the cluster.

Atlantic Canada and PEI possess various components of these important infrastructure elements, These considered as mini-clusters of expertise, which need to be further developed so that they mutually support each other to enhance the bioactives cluster. In addition, existing Atlantic Canada and PEI bioactives industry and infrastructure components will need to establish close links for the purpose of collaboration with many other bioactives infrastructure participants in the bioactives cluster elsewhere in Canada and internationally. Some of the government and university research infrastructure participants in the bioactives/bioresources cluster in Atlantic Canada and the rest of Canada are listed in the Appendix to this report.

In general, with respect to cluster technologies, Atlantic Canada and PEI's infrastructure strengths are better developed in the fields of:

- growing and harvesting of marine and plant bioresources (especially marine);
- processing and purification technologies; and
- market and utilisation technologies.

Some of the key organisations involved with these technology fields and which could be considered as mini-cluster in the region, include:

- University of Prince Edward Island (including the Atlantic Veterinary College);
- Food Technology Centre (FTC);
- University of Moncton;
- University of New Brunswick;
- Dalhousie University; and
- Memorial University.

The region's infrastructure in the technology fields relating to marine and plant bioactives identification (i.e., bioprospecting and bioinformation) is generally weaker and requires further development. There is already a nucleus of participation in these technology fields that is focused on specific bioresources and specific bioactives. For example, research is being conducted on bioactives contained in blueberries, taxanes contained in Taxus species (ground hemlock or Eastern yew) and essential fatty acids found in marine fish species. The further development of infrastructure organisations working in the fields of bioactives identification should take into consideration the experiences and successes of these and other groups.

6. Appendix

6.1 Introduction

This appendix contains:

- An overview of the roadmapping process;
- A description of the roadmapping process as applied by the BTCRM Steering Committee
- A case study of bioactives from bioresources: Taxanes (referred to in Technology Challenges and Priorities);
- A bibliography;
- Websites and other sources of information used in the preparation of this report;
- A glossary of abbreviations and terms; and
- Acknowledgements to those that assisted in the preparation of this report.

6.2 Overview of the Roadmapping Process

Technology roadmapping is a systematic planning process oriented to take advantage of future market needs. A main feature of the roadmapping process is that it engages leaders, experts and other stakeholders who will ultimately be responsible for implementing strategies and action plans. In this way roadmaps can serve various entities in the business system, including: technology researchers and developers; raw material suppliers; current and potential manufacturers; government groups; financial resource providers; customers; entrepreneurs and others.

Roadmapping should not be considered as a static or short-term process. It involves a long term and dynamic process. Champions, leaders and stakeholders interested in moving forward along the many possible paths in the roadmap are responsible for its implementation, as well as its evolution. They may need to create improved visions and goals in context of achievements realised or future challenges that need to be addressed. Changing business conditions, new technologies and/or new government regulations or priorities require flexible strategies that can be adapted to meet dynamic business environments. Ideally, there is no final step in a roadmap process. This is especially the case when the subject of the roadmap is broad, such as bioactives derived from bioresources.

The purpose of the roadmap report is to provide public and private sector participants with information regarding current and future market driven technology needs and to facilitate related investment, training, etc, as well as to guide the industry's and other stakeholders' research agenda. In other words the roadmap aims to help the industry to become a leader in the field and be able to respond to future market needs48 (in the broad field bioactives from bioresources, and sustainable development).

The roadmap report describes a large portion of the landscape through which the industry and government participants, champions, leaders and other stakeholders can travel in reaching the vision articulated by the BTCRM SC. In the broad fields selected, there are a great many small and detailed paths that could be further explored. Further exploration and analysis of certain areas in the roadmap may be required in progressing the roadmap beyond this stage. Further research and analysis will likely be required, since this is a general roadmap. Any further research and analysis, and additional resources applied need to be considered in context of specific priorities and specific objectives of those wishing to travel within this landscape.

6.3 Roadmapping Process Applied by BTCRM SC

The Bioresources Technology Roadmap Steering Committee (BTCRM SC) was created, in part, to develop a roadmap report for the development of bioresources available to Prince Edward Island. The BTCRM SC is composed on industry leaders, government representatives, academic experts and other stakeholders. Senior managers from the National Research Council (NRC) of Canada, the Atlantic Canada Opportunities Agency (ACOA) and the PEI provincial government are represented on the BTCRM SC. Cheminfo Services Inc., Inverizon International and PPM & Associates were retained by the BTCRM SC[49] to assist in the creation of a roadmap report. The key steps in the development of the roadmap included:

- Identification and recruitment of nearly 280 participants in the roadmap process;
- Input received from these participants to identify nearly 100 opportunity areas (OPAs) that could be further pursued by the BTCRM SC[50];
- Selection of 10 OPAs by the SC that offered the best potential for further development;
- Research, analysis and preparation of a profile for each of the 10 OPAs by the consulting team;
- Selection of "bioactives" as the cross-cutting "product" field of interest by the BTCRM SC (encompassing nutraceuticals, pharmaceuticals as main market opportunity areas);
- Creation and adoption of a vision by the BTCRM SC;
- Development of a draft roadmap report by the consulting team; and
- Review of the draft roadmap report by the BTCRM SC and participants at a workshop in PEI.

48 BTCRM SC summary of November 27, 2001 meeting, (Goals of the roadmap).
49 Cheminfo Services (as project lead) was retained following a competitive open bidding process.
50 Opportunity areas identified in this process.

6.3.1 100 Opportunity Areas Identified in Roadmapping Process

The following table lists approximately 100 bioresource-based opportunity areas. An accompanying report entitled, *Bioresource Opportunity Areas*[51] provides brief articulations for the opportunity areas. The report is available at the following web site:

www.nrc.ca/atlantic/PEI/

The opportunity areas were grouped into categories, namely:

- Research Centre Concepts;
- Genomics;
- Nutraceuticals and Cosmeceuticals;
- Services; and
- Miscellaneous.

The opportunity area concepts were developed by bioresource roadmapping process participants, members of the BTCRM Steering Committee as well as the project consulting team of Cheminfo Services, Inverizon International and PPM & Associates. The purpose of developing a long list of opportunity areas was to ensure that opportunities that were of interest to some roadmapping participants were not overlooked.
The BTRCM SC applied input from the many roadmapping participants, its own expertise and knowledge, applied selection criteria and identifies 10 areas that they believed represented the best opportunity for PEI. (see below)

Table 15: Approximately 100 Opportunity Areas Considered in Roadmapping Process

1.0	RESEARCH CENTRE CONCEPTS
1.1	AQUACULTURE RESEARCH & DEVELOPMENT CENTRE
1.2	AQUACULTURE RESEARCH CENTRE FOR EXTRACTIVES FOR PHARMACEUTICALS, ETC.
1.3	BIOFUELS RESEARCH CENTRE
1.4	BIORESOURCE BUSINESS CENTRE
1.5	BIORESOURCE RESEARCH AND BUSINESS OPPORTUNITIES CENTRE
1.6	ECOTOXICOLOGY/AGRICULTURAL/ENVIRONMENTAL RESEARCH CENTRE
1.7	ENVIRONMENTAL MONITORING, DATA STORAGE AND ANALYSIS TECHNOLOGIES
1.8	FUNCTIONAL FOODS: THE THIRD HEALTH FOOD GENERATION UTILIZING BIORESOURCE EXTRACTS

51 Cheminfo Services, *Bioresource Opportunity Areas*, October 3, 2001.

1.9	HR TRAINING CENTRE FOR BIORESOURCES EXPERTISE AND SKILLS DEVELOPMENT
1.10	MARINE GENOMICS RESEARCH CENTRE
1.11	NUTRACEUTICALS R&D CENTRE
1.12	PEI BIORESOURCE INNOVATION CENTRE
1.13	PEI NATURAL PRODUCTS DEVELOPMENT CENTRE
1.14	PEI TEST CENTRE FOR TRANS-CANADIAN BIORESOURCE/ENVIRONMENTAL SUSTAINABILITY RESEARCH
1.15	SUSTAINABLE TECHNOLOGY ANALYSIS CENTRE
2	GENOMICS
2.1	BIOPIRACY/EQUITABLE SHARING
2.2	BIOTECHNOLOGY-BASED ANTIBODY PRODUCTION
2.3	BIOTECHNOLOGY-BASED ENHANCED COMPOSITION (E.G., ALGINATES)
2.4	BIOTECHNOLOGY-BASED ENHANCED COMPOSITION (E.G., STARCH FOR NON-FOOD USES)
2.5	BIOTECHNOLOGY-BASED ENHANCED PRODUCTION AND COMPOSITION (E.G., POTATOES)
2.6	ENZYMES FROM MARINE MICROBES
2.7	ENZYMES: EXTREMOPHILES
2.8	FISH BIOTECHNOLOGY AND IMMUNOLOGY
2.9	GENE PLATFORM (& ENZYME MOLECULAR EVOLUTION)
2.10	GENES FOR OMEGA FATTY AND OTHER ACIDS AND OILS
2.11	GENETICALLY MODIFIED CROPS
2.12	GENOMICS PLATFORM
2.13	MICROPROPAGATION OF LOCAL UNCOMMON PLANT SPECIES
2.14	MOLECULAR FARMING – RECOMBINANT PRODUCTION OF PROTEINS IN INDUSTRIAL TUBERS™ (POTATO TUBERS)
3	NUTRACEUTICALS AND COSMECEUTICALS
3.1	COSMECEUTICALS PRODUCTION
3.2	NUTRACEUTICALS FROM MARINE SOURCES
3.3	NUTRACEUTICALS PRODUCTION
3.4	NUTRACEUTICALS FROM SEAWEED
4	OTHER PRODUCTS
4.1	AGAR FROM SEAWEED
4.2	ALGINATES
4.3	ANTI-CANCER COMPOUNDS (TAXANES) FROM TAXUS CANADENSIS (EASTERN YEW)
4.4	BIO-ACTIVE COMPOUNDS
4.5	BIODIESEL
4.6	BIOFUNGICIDES
4.7	BIOMASS GASIFICATION
4.8	BIOPOLYMERS
4.9	BIOPOWER
4.10	BIO-REFINERY
4.11	BY-PRODUCT PROCESSING (POTATO PROCESSING BY-PRODUCTS/WASTES
4.12	CAROTENOIDS PRODUCTION
4.13	CARRAGEENAN FROM SEAWEED
4.14	CHEMICALS FROM ORGANIC ACIDS
4.15	CHITIN (BIOPOLYMER)
4.16	CRUCIFEROUS VEGETABLES
4.17	DRIED, HIGH QUALITY ROSE HIP POWDER FROM NATIVELY GROWN ROSES
4.18	ETHANOL

4.19	FIBER-FILLED PLASTICS
4.20	FISH OIL PRODUCTION
4.21	INDUSTRIAL FEEDSTOCKS FROM HEMP, WOOD CHIPS, STRAW
4.22	MODIFIED POTATO STARCH DERIVATIVES
4.23	MODIFIED POTATO STARCH DERIVATIVES (FOOD)
4.24	NOVEL AND SELECTED HIGH QUALITY, EFFICACIOUS PRODUCTS FROM MARINE OILS
4.25	NOVEL CHEMICALS (LOWER MOLECULAR WEIGHT MONOMERS)
4.26	NOVEL MATERIALS (BIOTECH, HIGHER MOLECULAR WEIGHT)
4.27	PAPER
4.28	PHYTOSTEROLS
4.29	POLYLACTIDES FROM STARCH
4.3	PRODUCTION OF BIOACTIVE PHYTOCHEMICALS
4.31	PRODUCTION OF NATURAL DYES FROM BLUEBERRIES, CRANBERRIES, POTATOES, CARROTS
4.32	RENEWABLE ENERGY SOURCES (WIND FARM, WAVE POWER)
4.33	UPGRADING CO-PRODUCT DDG FEED (FROM ETHANOL PRODUCTION)
4.34	UTILIZATION OF FLAX SEED OIL (OR HEMP SEED OIL)
4.35	VALUE ADDED BIO-PRODUCTS FROM HEMP
5	SERVICES
5.1	BIO TRIALS
5.2	BIORESOURCE PROCESS CHARACTERIZATION AND OPTIMIZATION
5.3	DEODORIZATION PROCESS: GENERIC RESEARCH
5.4	DEVELOP NOVEL PROCESSING TECHNOLOGIES FOR WILD BLUEBERRY EXTRACTION, TREATMENT (TO ACHIEVE SHELF STABILITY), CONCENTRATING AND DRYING
5.5	DEVELOPMENT OF BIOACTIVE COMPOUNDS
5.6	DEVELOPMENT OF PLANT PROCESSING TECHNOLOGY
5.7	EXPERTISE DEVELOPMENT IN BIOCATALYSIS
5.8	NOVEL SYSTEMS FOR AQUACULTURE
5.9	PHYTOREMEDIATION: COST EFFECTIVE ALTERNATIVE TECHNOLOGY FOR REMEDIATION AND RESTORATION OF CONTAMINATED SITES - R&D
5.10	PROCESS ENERGY SUPPLY (DIRECT USE OF BIOMASS)
5.11	RESEARCH IN PROCESS-WATER CONSERVATION
5.12	RESEARCH TO ADDRESS COMMON PROBLEMS IN BIORESOURCE UTILIZATION (PROCESSING)
5.13	TECHNOLOGY DEVELOPMENT FOR THE PRESERVA TION OF BIOMASS ACTIVE INGREDIENTS IN STORAGE AND TRANSPORTATION
5.14	TELEHEALTH SERVICES DEVELOPMENT
5.15	UTILIZATION OF MICROBES TO TREAT ORGANIC CONTAMINANTS POTENTIALLY RELEASED TO THE WATERSHEDS
5.16	WATER DESALINATION
6	MISCELLANEOUS CONCEPTS AND INPUT
6.1	ALTERNATIVE CROPS FOR INDUSTRIAL USE
6.2	ANAEROBIC MICROBES USE TO DETOXIFY HAZARDOUS MATERIALS OR PETROLEUM CONTAMINATED SOILS
6.3	CONTROLLED-RELEASE/CONTROLLED-BREAKDOWN BIO-ACTIVES
6.4	CORN USE TO PRODUCE POLYLACTIC ACID (PLA) WHICH COULD BE MADE INTO COMPOSTABLE PLASTIC PRODUCTS INCLUDING FOOD CONTAINERS AND PACKAGING.
6.5	ETHANOL OR METHANOL FROM THE FOLLOWING FEEDSTOCKS: BARLEY, MANURE,

	STRAW, WOOD WASTE, POTATO, POTATO WASTE, HEMP AND SEWAGE SLUDGE
6.6	EXTRACTION, PURIFICATION AND COMMERCIALIZATION OF ANTIOXIDANTS FROM PLANTS AND BERRIES
6.7	GRAIN HULLS USE AS A FILLER FOR REMOVING TOXIC METAL FROM INDUSTRIAL WASTEWATER.
6.8	MANURE USE AS A FEEDSTOCK TO PRODUCE COMMODITY CHEMICALS AND OTHER HIGH VALUE PRODUCTS
6.9	DEVELOPMENT OF PROCESSES TO USE FRYER FAT OR VEGETABLE OIL TO BLEND WITH DIESEL TO BE BURNED IN DIESEL ENGINES
6.10	SYNTHETIC MODIFICATIONS OF POST-EXTRACTED BIO-ACTIVES
6.11	NEW BIOPRODUCT TECHNOLOGIES AND TRAIN GRADUATE STUDENTS IN THE BIOPRODUCTS FIELD

6.3.2 Selection and Profiles for 10 Opportunity Areas

The BTRCM SC selected 10 opportunity areas that represented the best opportunity for further development for PEI. There were many considerations applied by the BTCRM SC in selecting the 10 best areas. At its meeting of October 16, 2001, the following considerations were identified by BTCRM SC members:

- Market demand;
- Competitive advantage PEI bioresources based (bioresources inventory);
- Combination of market pull and technology push;
- High-value focus (exclude commodity);
- Focus first on areas or what will be done as opposed to how;
- Look at broad aspects of marine products;
- GMO vs. genomics selection (one does not exclude the other);
- GMO – PEI advantage; should not be excluded right now; could be an opportunity 15-20 year; start with non-food crops;
- Sustainable development: sustainable enhanced bioresources; supporting role; not a stand alone activity; should come with bio-processing activities;
- Province branding: “pure products” (PEI: Science that work with nature);
- Bio-processing would be a critical element in exploiting high-value components or molecules based on PEI bioresources;
- Attract people;
- Waste from processing;
- Environment (seafood industry context, etc.);
- Receptor capacity;
- Focal point (Regional focus – National leadership);
- Long term perspective
- Gaps in research (state of the art, what is currently being done);
- Linkage to NRC research institutes (complementary area) and other research labs (Env., AAFC, etc.) – leadership and linkages; implementing NRC model; and
- Capital resources.

The BTCRM SC selected the following 10 areas.

Table 16: Opportunity Areas Selected by BTCRM SC

Nutraceuticals- marine
Nutraceuticals - plant
Pharmaceuticals- marine
Pharmaceuticals - plant
Fine chemicals from bioprocessing by-product streams
Biopolymers
Taxanes
Bioprocessing
Cosmeceuticals
Biocatalysts

The Cheminfo Services consulting team conducted research and analysis to develop profiles for the 10 opportunity areas selected. The profiles provided information on market size and growth, suppliers and competitors, technologies, bioresources, and other characteristics of each opportunity area.

6.3.3 Selection of Best Opportunity Area(s) for Moving Forward in Roadmapping Process

The roadmapping process needed to select a few opportunity areas that offered the best prospects for further development in PEI. The reason for a requirement select even fewer areas is that some of the 10 areas are quite different than others in market scope, technologies, and resources required for further development. For example, the field of Cosmeceuticals is substantially different than "Fine chemicals from bioprocessing by-product streams".

Each member of the BTCRM SC ranked the areas in order of attractiveness for further development from 10 to 1 (10 was most attractive, 1 least attractive). The ranking of the 10 opportunity areas (OPA) by each participant at the meeting produced the results presented in the table below. Nutraceuticals (marine and plants) in general turned out to be the most attractive, followed by pharmaceuticals from marine. There was general agreement that biocatalysts, biopolymers and taxanes were the least attractive and should not be the focus of the roadmap process moving forward.

Table 17: Ranking of 10 Opportunity Areas

(in descending order of attractiveness)

Opportunity Area	Score
Nutraceuticals- marine	138
Nutraceuticals - plant	106
Pharmaceuticals- marine	104
Fine chemicals from bioprocessing by-product streams	89
Pharmaceuticals - plant	83
Bioprocessing	79
Cosmeceuticals	78
Biocatalysts	72
Biopolymers	52
Taxanes	43

After the 10 OPAs were ranked, input on the vision and goals of the roadmapping process were provided by the BTCRM SC. The common themes of the vision - bioactives, bioresources and sustainable development and environmental modelling emerged.

6.4 Bioactives from Bioresource Case Study: Taxanes

Taxanes are a group of drugs that includes paclitaxel and docetaxel. They are used in the treatment of some forms of cancers.[52] Paclitaxel has the formula of $C_{47}H_{51}NO_{14}$[53], with a molecular weight of 853. Docetaxel is similar to paclitaxel. Although paclitaxel is approved for human use in approximately 50 countries, including the United States and Canada, the status of approval for use in cancer treatment may not be the same in all countries of the world.

Taxanes have a unique way of preventing the growth of cancer cells. They stabilise cell structures called microtubules, which play an important role in cell functions. In normal cell growth, microtubules are formed when a cell starts dividing. Once the cell stops dividing, the microtubules are broken down or destroyed. Taxanes stop the microtubules from breaking down; cancer cells become so clogged with microtubules that they cannot grow and divide.[54]

52 Taxol® is a registered trade name of paclitaxel used by Bristol-Meyers Squibb (BMS). Taxotere® is a trade name for Aventis' docetaxel. There are other trade names used by other suppliers.

53 Taxanes and More, http://www.taxanes-and-more.com/bilder/f11neu.gif

54 National Cancer Institute, http://www.hersource.com/breast/04/taxanes_print.cfm

Paclitaxel has been under research dating back to at least the 1960s. In 1984, the U.S. based National Cancer Institute (NCI) began clinical trials (i.e., research studies with people) that looked at paclitaxel's safety and how well it worked to treat certain cancers. In 1989, NCI-supported researchers at The Johns Hopkins Oncology Center reported that tumors shrank or disappeared in 30% of patients who received paclitaxel for the treatment of advanced ovarian cancer. Although the responses to paclitaxel were not permanent (they lasted an average of 5 months, some up to 9 months), it was clear that advanced ovarian cancer patients could benefit from this treatment. In December 1992, the U.S. Food and Drug Administration (FDA) approved the use of paclitaxel for ovarian cancer that was resistant to treatment (refractory) with other cancer drugs. Paclitaxel was later approved as initial treatment for ovarian cancer in combination with another drug (cisplatin). Women with epithelial ovarian cancer are now generally treated with surgery followed by a taxane and a platinum compound (another type of anticancer drug).[55] Paclitaxel can also be used for other cancers, including AIDS-related Kaposi's sarcoma and lung cancer.[56]

6.4.1 Market

The market value for taxanes (paclitaxel and docetaxel) at the wholesale level (i.e., sales by pharmaceutical suppliers to pharmacies, etc.) for the year 2000 is roughly estimated at C$ 2 billion (US$ ~1.2 billion). Nearly 70% of the demand in the developed nations is in North America. Countries such as China and possibly other lesser developed nations also make and provide taxanes to patients. The total quantitative demand for year 2000 in the western market is roughly estimated at 0.2 to 0.3 tonnes (200 to 300 kilograms). The value of bulk intermediate taxanes sold to pharmaceutical companies is estimated at $50 million for the year 2000. The value of taxanes at the wholesale level has been approximately $200,000 per kilogram.[57]

The total global market of taxanes could have been as high as 0.5 to 0.8 tonnes, in 2000 if one includes the production in China, other lesser developed countries, and the amount of taxanes produced for building up the inventory in the drug distribution pipeline. Some of this product filling this pipeline may be less than 99% pure. "Crude" taxanes with lower purity levels between 30% to 70% are sold to facilities that purify the product.

Until 2001, Bristol-Meyer Squibb (BMS) and Rhone-Poulenc Rohrer accounted for practically all of the world market for Taxol and Taxotere, respectively. BMS built the market after receiving patents from the US FDA in 1992/1993. All of its sales were paclitaxel. Since NCI had discovered paclitaxel, BSM's dominance in the market was protected by patents related to

[55] National Cancer Institute, http://www.hersource.com/breast/04/taxanes_print.cfm
[56] National Cancer Institute, http://www.hersource.com/breast/04/taxanes_print.cfm
[57] Personal conversation, anonymous source. Others believe that the market for taxanes is 400 to 600 kilograms per year.

the manufacturing process and use of Taxol. It may be possible to patent derivatives of taxanes, new innovative processes for making taxanes or innovative uses.

The efficacy of paclitaxel in the treatment of some forms of cancers is expected to increase demand for these products. World consumption is projected to increase by 20% per year over the next five years on a quantitative basis.[58] Therefore, demand in the western world market could increase to 0.5 to 0.7 tonnes per year by 2005. Total global production and demand could reach 1.5 to 2.0 tonnes per year by 2005.

However, on a value basis, taxanes may exhibit slower growth (than the rate of growth in quantitative terms), or even a decline if prices for taxanes decline faster than the annual quantitative increase in consumption. Such was the case recently, with the introduction into the market of generic forms of the drug. With BMS controlling the market, the value of formulations was very approximately C$ 5 to 7 million per kilogram of taxanes-contained. The recent introduction of additional product into the market by competitors to BMS resulted in price declines. According to one source, the price of taxane formulations declined to 25%.[59] Therefore, while the amount of taxanes consumed may have increased, the value of sales will not have increased at the same rate, or possible even decreased.

There is an abundance of research occurring around the world that is investigating the use of taxanes for diseases for which taxanes are currently not approved by regulatory authorities. These new potential applications for taxanes may lead to even faster growth than 20% per year.

6.4.2 Supply

There are approximately half a dozen firms in the world making taxanes for commercial purposes. There may be a host of other companies or research organisations involved with production of small quantities in laboratory, demonstration or pilot plant facilities. The major pharmaceutical companies, such as BMS, supplying the retail market have established product supply contracts with intermediate chemical suppliers, or dedicated manufacturing firms. Generally, manufacturers are not selling their product to directly to retailers (possibly because of product approvals, patent issues and lack of access to necessary distribution channels).

There are a greater number of raw material suppliers providing bioresources or partially purified taxanes. These companies may sell fresh (wet) or dried biomass (leaves, bark), or solutions containing various concentrations of taxanes. These solutions are sold to the manufacturers, which make active ingredient with at least 99% purity. There are Canadian firms involved in the

[58] Personal conversations, industry sources and Canadian Forestry Service, November 12, 2001
[59] Personal conversation, Canadian Forestry Service, November 12, 2001

supply of raw materials and manufacturing of taxanes. The potential market opportunities have attracted new entrants, some located in Atlantic Canada.

Pharmatech Research Inc. is an example. Pharmatech Research Inc. was established in 1997 to produce paclitaxel. Pharmatech believes it is well positioned to enter the paclitaxel market as a supplier to major international pharmaceutical companies. The company has established a processing facility in Debert, Nova Scotia, which will extract and process the clinical drug paclitaxel from the needles of the eastern yew plant. Pharmatech has developed yield, quality and cost efficiencies for bulk drug ingredients that will be produced at the new facility. The company has also secured sources of raw material (needles) of the eastern yew from several areas in Atlantic Canada. Pharmatech will be offering bulk product as well as the finished clinical product to distributors directly. The firm will focus its strategy on the retail clinical paclitaxel market and has initiated registration proceedings in Canada, USA, Asia and Europe.[60] According to one source, Pharmatech is not yet making and selling taxanes.[61]

ActaMed in New Brunswick, and Bioexel Inc. and Chaichem Inc. both located in Quebec are other examples of companies attracted to the taxanes business. These companies have been working with government agencies to further develop the opportunity area. A major challenge for these companies will be the investment in manufacturing facilities that offer unique (and therefore do not infringe on others' patents) processes, with relatively large production capability that will have secure customers.

There is at least one Chinese firm providing "crude" paclitaxel, which can be further purified by cGMP suppliers. The material is 50 to 60% pure, with a value of C$ 125,000 to $160,000 per kilogram.

6.4.3 Bioresource Considerations

Paclitaxel is a compound that was originally isolated from the bark of the Pacific yew tree (Taxus brevifolia). Early research using paclitaxel was limited due to difficulties in obtaining the drug. The amount of paclitaxel in yew bark (or needles) is small, such that extracting and purifying it is an expensive process. In addition, bark collection is restricted because the Pacific yew is a limited resource located in forests that are home to the endangered spotted owl.[62] In the United States, harvesting in the U.S. was restricted by Presidential order and more recently by the US FDA because of over-harvesting.[63]

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60 http://www.lsip.ns.ca/life_sciences_directory/html/abc/abioc1.htm
61 Personal conversation, Canadian Forestry Service, November 12, 2001
62 National Cancer Institute, http://cis.nci.nih.gov/fact/7_15.htm
63 Stewart Cameron, Canadian Forestry Service, November 12, 2001

There are different estimates of the amount of biomass required to produce one kilogram of taxanes. According to the Canadian Forest Service (forwarding information from industry), the amount of fresh (water containing) biomass required to produce 1 kilogram of 99%+ taxanes is 30,000 kilograms. A typical yield from dried biomass is 1 kg for every 10,000 kg of biomass.[64] Therefore, if the western world demand for taxanes is roughly 0.3 tonnes, 9,000 tonnes of fresh (wet basis) biomass would need to be processed. That requirement could grow to 21,000 by 2005, given a 20% per year average annual growth rate for demand of the drugs.

As demand for paclitaxel grew, the U.S. NCI, in collaboration with other U.S. government agencies and the pharmaceutical company Bristol-Myers Squibb, worked to increase the availability and find other sources of paclitaxel besides the bark of the Pacific yew tree. This work led to the production of a semi-synthetic form of paclitaxel derived from the needles and twigs of the Taxus baccata (European yew), which is a renewable resource. The FDA approved the semi-synthetic form of paclitaxel in the spring of 1995. This form of paclitaxel has now replaced the drug derived from the bark of the Pacific yew tree.[65]

There are other yew species that can be harvested for the production of taxanes. One such species is Ground hemlock (Taxus canadensis) available in Canada (see below). However, suitable species are being grown in China, India, and other countries. Species can yield taxanes can also be grown in nurseries.

Ground hemlock (Taxus canadensis), also known as Canada yew or eastern yew, is a low-spreading and relatively slow-growing shrub found in northeastern North American woods. Unlike most other native evergreens, it is not used for timber or pulp. Therefore, even though it is an important food source for deer and other wildlife, the biology and general ecology of ground hemlock have not been extensively studied until fairly recently.[66]

Eastern yew can be found throughout Atlantic Canada and in much of Quebec, but often in small isolated pockets. Although yew can comprise a significant amount of the total ground cover in some areas, seldom do you find ‘stands' or, perhaps more accurately, ‘carpets' of it. Except perhaps in PEI, there are no inventories of 'growing stock'. Research is required to determined how much yew exists in Canadian forests. While some work is ongoing to answer this question, detailed information is lacking.[67]

6.4.4 Sustainability Considerations

[64] Personal conversation, Canadian Forestry Service, November 12, 2001
[65] National Cancer Institute, http://cis.nci.nih.gov/fact/7_15.htm
[66] Canadian Forestry Services, http://www.atl.cfs.nrcan.gc.ca/cfs_afc/index-e/what-e/groundhemlock-e.html
[67] Canadian Forestry Services, http://www.atl.cfs.nrcan.gc.ca/cfs_afc/index-e/what-e/groundhemlock-e.html

The harvesting of any ground hemlock (or other species) for the production of taxanes has the potential to present challenges of sustainability that would need to be addressed. Ground hemlock typically grows in the understory of mature and semi-mature forests. It can be found under most canopy types; hardwoods, softwoods, and mixed woods. The fact that it usually is found under a closed canopy does not mean that it will not grow in the open – a common misconception, resulting from the observation that often after a stand is harvested, the yew needles 'burn,' or turn brown. In fact, yew will grow more vigorously in the open than under shade.[68]

Very little has been published on the growth of eastern yew other than to describe it as a spreading, slow-growing shrub. Although it is sometimes (seldom) grown in nurseries as an ornamental, it is not know how much biomass can be produced on either a nursery or a wild plant. It is also not known how plants will respond/recover from tipping, especially severe, improperly done tipping: a 40- to 50-cm 'tip' often represents six to ten years of growth or even more when taken from a very slow-growing plant.[69]

More research would be required to determine the total supply of raw material, develop reliable estimates of how much yew can be sustainably harvested. Harvesting ground hemlock has the potential to become an extremely valuable 'renewable' natural resource for Atlantic Canada, but only if it is managed responsibly. Sustainable harvesting guidelines have been developed jointly between Canadian Forest Service - Atlantic Forestry Centre and the Prince Edward Island Department of Agriculture and Forestry.[70] Revised guidelines are currently being drafted.

6.4.5 Technologies Involved

Making and selling taxanes involves a broad set of technologies that are different along the stages of the value-adding chain. The list of some technologies in the table below is meant to provide the scope of technologies currently involved, not an exhaustive list.

[68] ibid
[69] ibid
[70] ibid

Table 18: Technologies Involved in Taxanes Value-Adding Chain

Growing and Harvesting	**Production Process Development**	**Market/Use Development**
Source identification, Bioresource inventory	Yield improvement	New formulations
Growing, nursery	Extraction, purification technologies	Efficacy testing
Harvesting	Validation and quality control technologies	New applications and treatments
Sustainability know how	Biomass waste disposition	Side effects analysis
Genomics related to bioresources	Taxane derivatives, Molecular modifications	Assessment of taxanes with other anti-cancer drugs
	Genomics related to production through trangenics or fermentation	

One important set of technology challenges relate to improvement of crop yields and thereby lowering the capital costs for new production facilities and as well as the cost of production. Phytobiotech is a Quebec company conducting Taxus cell culture work. BMS has also made large investments in biotech methods to produce taxanes. It is possible that this technology may succeed in replacing naturally harvested materials in the long run.[71]

[71] Personal correspondence, industry source, November 15, 2001.

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6.5 Bibliography

1. Abiogen Agri-Food Services, *The Bioresource Industry on PEI*, December 2001.

2. Accelrys Inc. (Edwards) from Drug Discovery Magazine November/December 2001.

3. Ansel, Howard C., Nicholas G. Popovich, and Loyd V. Allen, *Pharmaceutical Dosage Forms and Drug Delivery*, 1995.

4. Aufderheide., B adapted from "*Evaluation of Cwall Control Parameters for a BSA Ultrafiltration Process*" by Ralf Kuriel, et al, Bioprocess Division, Millipore Corporation, 80 Ashby Rd., Bedford MA 01730.
   http://www.eng.rpi.edu/dept/chem-eng/Biotech-Environ/rssep/Purification/Membranes/membrane2.html

5. B. Foran, C. Mardon "Beyond 2025: *Transitions to the biomass-alcohol economy using ethanol and methanol*", CSIRO Resource Futures Program, CSIRO Wildlife and Ecology, Gungahlin, Canberra, Australia, December 1999

6. Boguslavsky, Julia, *Protein-structure modelling and in silico docking tools accelerate drug discovery and development*, Drug Discovery Magazine November/December 2001

7. Brannon-Peppas, *Polymers in Controlled Drug Delivery Medical Plastics and Biomaterials Magazine*, November 1997

8. Canada Gazette, Part I, December 22, 2001

9. Cheminfo Services, *Investment Opportunities and Challenges in the Canadian Intermediate Chemicals Industry*, For Industry Canada, March 2001

10. D.E. Minns "*Performance Targets for Sustainable Development Technologies*" Keynote address. International Conference on Sustainable Development by Science and Technology in Greater Mekong Subregion and Related Developing Countries, Chiang Mai, Thailand, September 2001

11. Department of Trade and Industry, UK – *National Indicators and Performance for Sustainable Development*, http://www.sustainable-development.gov.uk/ann_rep/index.htm

12. Food Technology Centre, *PEI Bioresources Inventory*, December 2001.

13. Hegener, P., *Protein Fouling of Microfiltration and Ultrafiltration Membranes, Rensselaer Polytechnic Institute*, July, 2001

14. J.F. Jaworski, D.E. Minns "*Technology Innovations and Cleaner Production: possibilities and limitations*" UNEP Industry and Environment, 24 (1-2), January-June 2001, pp. 60-64

15. List, P.H., and P.C. Schmidt. *Phytopharmaceutical Technology*. Boca Raton, FL: CRC Press, 1989.

16. Pembina Institute for Appropriate Development, *Genuine Progress Indicators.*

17. Pembina Institute: *GPI Report on Alberta*.

18. PPM & Associates, *Background and Industry Overview to PEI Bioresources-Based Technology Cluster Roadmapping Process",* lists 61 companies engaged in Canadian nutraceuticals industry.

19. S. Erkman, R. Ramaswamy " *Industrial Ecology: A new cleaner production strategy*" UNEP Industry and Environment, 24 (1-2), January-June 2001, pp. 64-67

20. S. Torjman, D.E. Minns "*Sustainable Development: Innovation and the Quality of Life*", Caledon Institute of Social Policy, May 2001 http://www.caledoninst.org/

21. Schnell Publishing Co., Chemical Marketing Reporter, August 27, September 25, 2000.

22. Schnell Publishing, Chemical Marketing Reporter, Cosmetics/Personal Care 2001, May 14, 2001.

23. SRI Consulting, Explorer, Biocatalysis

24. SRI Consulting, Explorer, Membrane Separations

25. Wijesekera, R.O.B., The Medicinal Plant Industry. Boca Raton: CRC Press. ISBN 0-8493-6669-0. From Virginia Commonwealth University Libraries, 1991.

26. Williams and Wilkins, *Systems*. Sixth edition. Baltimore

27. World Business Council for Sustainable Development' http://www.wbcsd.ch/

28. World Commission on Environment and Development (WCED), Our Common Future, Oxford University Press, 1987

6.6 Websites and Other Sources of Information Used in this Report

1. Bureau of Census: www.census.gov/

2. Canadian Forestry Services, http://www.atl.cfs.nrcan.gc.ca/cfs_afc/index-e/what-e/groundhemlock-e.html

3. Drug Discovery Magazine, http://www.drugdisc.com/stuttgart/

4. Environmental Choice Program http://www.environmentalchoice.com/index_main.cfm

5. U.S. Food and Drug Administration: www.fda/

6. IMS HEALTH Global Pharma Forecast

7. Industry Canada, Strategis, http://strategis.ic.gc.ca/

8. International Institute for Applied Systems Analysis, http://www.iiasa.ac.at/Research/TED/

9. National Round Table on the Environment and the Economy, http://www.nrtee-trnee.ca/eng/programs/Current_Programs/SDIndicators/index.html

10. Natural Resources Canada, http://oee.nrcan.gc.ca/english/

11. Natural Toxins Research Center, Texas A&M University- Kingsville. http://ntri.tamuk.edu/fplc/ion.html

12. National Cancer Institute, http://cis.nci.nih.gov/fact/7_15.htm

13. Nutrition Business Journal, Various issues, San Diego, CA, www.nutrionbusiness.com

14. Patent Medicine Prices Review Board, *Annual Report 2000*, Ottawa, ON (http://www.pmprb-cepmb.gc.ca/PDF/ar00e6.pdf) based on *Scrip Magazin*e, February 2001, p.31.

15. Pembina Institute: http://pembina.org

16. Robbert Associates' http://www.robbert.ca/

17. Saskatchewan Nutraceutical Network, Nutraceutical Market & Industry Information, http://www.nutranet.org/subpages/markets.htm

18. Sustainable Development Research Institute, *Quest Model* University of British Columbia http://www.sdri.ubc.ca/ , http://www.basinfutures.net/

19. Sustainable Technology Office, National Research Council, http://www.nrc.ca/icpet/

20. Technology Catalysts: http://www.technology-catalysts.com/Conumer_care/cosmerpt.htm

21. The Factor 10 Institute: http://www.factor10-institute.org/Factor10.htm

22. UK Regional Indicators and Performance for Sustainable Development, http://www.sustainable-development.gov.uk/indicators/regional/rqol_index.htm

23. United Nations Environmental Program, Division of Technology, Industry and Economics. http://www.uneptie.org

6.7 Glossary

6.7.1 Abbreviations

AAFC	Agriculture and Agrifood Canada
AVC	Atlantic Veterinary College
BTCRM SC	Bioresources Technology Cluster Roadmap Steering Committee
CDEN	Canadian Design Engineering Network
CEC	Commission for Environmental Cooperation
CETAC	Canadian Environmental Technology Advancement Centre
CFD	Computational Fluid Dynamics
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DfE	Design for Environment
DFO	Department of Fisheries and Oceans
DHEA	Dehydroepiandrosterone.
GIS	Geographic Information System
GPI	Genuine Progress Indicator
HTD	Hydroxytryptophan.
IIASA	International Institute for Applied Systems Analysis
ISO 14000	International Standards Organisation guidelines for environmental management
LCA	Environmental life-cycle assessment
NRC	National Research Council
NRCan	Natural Resources Canada
NRC-ICPET	NRC-Institute for Chemical Process and Environmental Technology
NRC-IMB	NRC-Institute for Marine Biology
NRC-IRAP	NRC-Industrial Research Assistance Program
NRTEE	National Round Table on the Environment and the Economy
OEE	Office of Energy Efficiency, NRCan
SAME	S-Adenosyl-methionine
SEMF	Sustainability and Environmental Modelling Framework
UBC	University of British Columbia
UNEP	United Nations Environmental Program
UPEI	University of Price Edward Island

6.7.2 Glossary

This glossary is borrowed from the following source:

Drug Discovery and Development Magazine: © 2001 Cahners Business Information, a member of the Reed Elsevier plc group, 301 Gibraltar Drive, Morris Plains NJ 07950; Phone: 973-292-5100; Fax: 973-539-3476

A more extensive glossary is available at: http://www.dddmag.com/

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ADME

Procedures for evaluating the absorption, distribution, metabolism, and elimination of pharmaceuticals.

Algorithm

An explicit computational procedure that uses a precise sequence of simple operations to perform a complex operation. Bioinformatics algorithms enable processing, analysis, and visualization of sequence-related data.

Analogy

The deduction of the function of a new gene or protein by comparison with genes or proteins of known function using similarity searching and alignment.

Antioxidant

A compound that inhibits oxidation, often because it is preferentially oxidized. Antioxidants trap free radicals, breaking the chain of reactions and preventing damage to cell components.

Base pair (bp)

A unit of nucleic acid length, based on the number of paired bases (adenine and thymine, guanine and cytosine) in a DNA double helix.

Base sequence

The order of nucleotide bases in a DNA molecule.

Bead-based array

A microarray technology based on the attachment of individual probes to microbeads. The beads may be embedded in the microwells formed at the tip of a bundle of optical fibers.

Bioassay

An assay that uses a living system, such as an intact cell, as a component.

Biocatalysis

The use of biological systems or their components for chemical synthesis or transformation.

Biochips

Micro-scale systems for bioanalysis based on integrated circuit technology. Biochips include molecular microarrays (gene chips, protein chips, small molecule chips), microfluidics systems (lab-on-a-chip), and fiber-optic-based arrays.

Biocide

A compound that is toxic to living systems.

Biocombinatorial chemistry

An iterative process consisting of synthesis of combinatorial chemical libraries followed by screening in biological systems to evaluate function.

Bioconversion

The conversion of one chemical to another by a living system, such as a bacterial cell.

Biodegradable

A material that can be broken down to simpler components by a biological process.

Biodiversity

The genetic diversity of natural organisms. Collections of millions of microbial genomes harvested from global ecosystems can be the starting point for developing new processes and molecules.

Bioinformatics

Computational or algorithmic approaches to the analysis and integration of genomic, proteomic, or chemical data residing in databases. Bioinformatics includes applications for the analysis of DNA and protein sequence patterns and similarities as well as other tools

Biomass

The mass of material produced by living micoorganisms, plants, or animals.

Biomaterial

Biologically derived material that is utilized as a structural component.

Biometrics

The statistical study of biological events.

Biomimetics

The development of synthetic systems based on information from biological systems.

Biopolymer

A protein, nucleic acid, or polysaccharide molecule.

Bioprocess

A method for preparing biological products, for commercial use.

Bioprospecting

Searching for new plant and microbial strains that may serve as sources for natural products, such as phytopharmaceuticals.

Bioreactor

A container used for fermentation or enzymatic reactions. Bioreactors vary in size from benchtop fermentors to standalone units.

Bioresource

Biomass that can be used as a raw material in a manufacturing process or more generally has economic value.

Biosensor

A device that uses a biological element, such as an immobilized enzyme or cell, as a sensor.

Biosynthesis

Synthesis by a living system.

Biotechnology

Biological techniques applied to research and product development.

Biotherapy

Treatment with genetically engineered biological materials.

Building block

A reagent used in combinatorial library synthesis.

Cancer

A disease characterized by uncontrolled proliferation of cells.

Carcinogen

A molecule that can transform normal cells into cancer cells.

Cell culture

The process of growing and maintaining cells and cell lines; a form of tissue culture.

Cell mapping

The localization of proteins within organelles or protein complexes by purification of the organelle or complex followed by mass spectrometric identification of the components.

Chaperone

A protein that binds newly synthesized polypeptide chains to prevent incorrect folding during transport to protein assembly sites.

Chemical genetics

The use of small molecules to interact with proteins in order to identify the genes involved in a biochemical pathway.

Chemical genomics

The large-scale study of biological processes based on small-molecule intervention.

Chemical proteomics

A method for defining the function of proteins by screening proteins against libraries of small molecules.

Chiral synthesis

The production of one enantiomer of a chiral compound, often by stereospecific synthesis by an enzyme.

Chromatography

The separation of a mixture of substances by charge, size, or other property by allowing the mixture to partition between a moving phase and a stationary phase.

Chromosome

A structure that carries the heriditary information for an organism and consists of a long DNA molecule with associated proteins.

Cluster (as in industry cluster)

A group of supporting and competing industry organisations.

Clustering

A bioinformatics technique for visualizing patterns in experimental data.

Coenzyme

A small molecule associated with an enzyme that participates in enzymatic catalysis. (e.g., Coenzyme Q10).

Computational biology (bioinformatics)

Computational technologies for the collection, structuring, and mining of biological data that make possible prediction and knowledge discovery.

Computational chemistry

Computer-based modeling and prediction of the structure of chemical compounds most likely to bind a protein drug target. Known properties are used to calculate properties of new molecules and energy minimization is used to adjust the structure.

Data mining

The automated or semi-automated search for relationships and global patterning within data. Data mining techniques include data visualization, neural network analysis, and genetic algorithms.

Denaturation

The loss of the native 3-D structure of a molecule.

DHEA

The nutraceutical dehydroepiandrosterone.

DNA

Deoxyribonucleic acid (DNA) A long macromolecule with a duplex structure composed of complementary deoxyribonucleotide strands of opposed polarity.

DNA sequencing

The determination of DNA base sequence order.

Docking

Computational exploration of the possible binding modes of a ligand to an enzyme, receptor, or DNA.

Drug

A molecule used to diagnose, treat, mitigate, or prevent disease.

Drug delivery

The delivery of a drug to the site of action. The pharmaceutical formulation may target the molecule for transdermal, oral, or nasal/pulmonary delivery. Liposomes delivermolecules through membranes and immunotoxins target antibodies to specific tissues.

Drug discovery

Processes for the identification and development of drugs. High-throughput methods that utilize combinatorial chemistry, genomics, and proteomics information are the starting point. Additional research to characterize lead compounds is followed by clinical trials, and regulatory approval for use.

Encapsulation

A method for immobilizing cells for use in a bioreactor, usually based on the use of polysaccharides or collagen to coat cells. Also, cell encapsulation is used in tissue engineering.

Enzyme

A protein that catalyzes biochemical reactions. Substrates are bound and oriented within the active site of the enzyme in a manner that facilitates the formation of the transition state and the conversion to products.

Essential fatty acid

A polyunsaturated fatty acid that cannot be synthesized by a cell or organism and must be supplied as a nutrient.

Ex vivo

The external alteration of tissue taken from an organism and subsequently returned to the organism.

Extremophile

An organism that grows optimally in extreme conditions, including extreme temperature, pressure, pH, ionic concentration, and pressure.

Folding

The acquisition of 3-D structure by a protein; the pattern of the 3-D structure that is the result of the folding process.

Functional proteomics

The large-scale study of protein function, especially protein-protein interaction networks, biochemical pathways, and post-translational modifications.

Gene

A DNA region that corresponds to a single protein, a set of alternately spliced protein isoforms, or an RNA. The sequence of a gene consists of the entire functional unit and includes noncoding regulatory sequences and introns, as well as coding regions

Gene chip

A gene expression microarray.

Genome map

The linear arrangement of genes and markers within the chromosomes of a genome.

Genomics

The large-scale investigation of the structure and function of genes. Understanding the structure and function of genomes aids in drug discovery and development, agroscience research, and other fields.

High-throughput system,

High-throughput screening (HTS) A massively parallel screening technique for the simultaneous assay and evaluation of large numbers of samples.

Homology modeling

The use of the structural and functional characteristics of known proteins as a template for the generation of a hypothetical structure for a similar protein of unknown structure.

5-HTD

The nutraceutical 5-hydroxytryptophan.

In silico biology

The use of computational algorithms to create virtual systems that emulate molecular pathways, entire cells, or more complex living systems.

In situ oligonucleotide synthesis

On-chip synthesis of oligonucleotides or peptide nucleic acids.

In vitro

Occurring outside an organism, in culture, or in an extract.

In vivo

Occurring in a living organism.

Lab-on-a-chip

A microfabricated fluidics system designed to perform high-resolution biochemical analyses.

Laser capture microdissection

A technique for isolating single cells from tissues. Laser microdissection makes possible the collection of pure populations of cells for the analysis of molecular function.

Lead compound

A peptide or small molecule that optimally modulates the activity of a receptor or other target protein. A successful lead compound becomes a drug candidate for further development.

MALDI-TOF MS

The abbreviation for Matrix Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry, a high-throughput protein sequencing method based on embedding samples in a matrix from which they are desorbed by laser light.

Mass spectrometer (MS)

An instrument that determines the exact mass of charged particles or ions by measuring the flight path through a set of magnetic and electric fields. Mass spectrometers specialized for protein and peptide sequencing are used for high-throughput identification of bioactives.

Mass spectrometry

A method for identifying molecules based on the detection of the mass-to-charge ratio of ions generated from the molecule by vaporization and electron bombardment. Deflection of the ions through a magnetic field results in a characteristic pattern used to distinguish molecules.

Melatonin

A nutraceutical promoted as a sleep aid as well as offering other benefits.

Molecular modeling

Computational analysis and modeling of the physicochemical properties of a molecule or biomacromolecule.

Nuclear magnetic resonance (NMR)

A spectroscopic technique used to determine the 3-D structure of small- to medium-sized proteins. NMR is based on resonant absorption of electromagnetic radiation by the magnetic dipole moments of atomic nuclei in an applied magnetic field.

Nucleic acid

A polynucleotide polymer consisting of deoxyribunucleotide units (DNA) or ribonucleotide units (RNA) joined by phosphodiester bonds.

Peptide

Two or more amino acids joined by a peptide bond.

Protein

A linear biomacromolecule synthesized by ribosomes and consisting of a chain of amino acids in peptide linkage.

Protein chips

Microarrays used to identify proteins and characterize protein function.

Proteomics

Proteome-wide analysis of protein regulation, expression, structure, post-translational modification, interactions, and function. This study of proteins is important in biotechnology and drug discovery, because proteins are responsible for most tasks in cells.

Recombinant DNA

DNA molecules generated by cloning DNA fragments into vectors, transforming cells, and isolating clones that express the DNA fragment.

SAME

The nutraceutical supplement S-Adenosyl-methionine.

CHEMINFO

Structural bioinformatics

The process of predicting the 3-D structure of a protein from comparison of primary sequence alignment, secondary structure prediction, homology modeling, threading prediction, NMR data, and crystallographic data.

Target

A DNA, RNA, or protein that is involved in a disease process and is a suitable target for therapeutic compound development.

Ultra-high-throughput system(UHTS)

A high-throughput system is capable of processing 100,000 or more samples a day.

X-ray crystallography

A technique for determining the 3-D structure of a molecule, based on the diffraction of x-rays by the crystallized form of the molecule.

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