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Recent Trends in the Biological Prospecting

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1. Introduction

ATCM XXVIII considered biological prospecting in Antarctica under item 18 of its agenda. The Meeting approved Resolution 7 (2005) Biological Prospecting in Antarctica, which recommended that “their governments continue to keep under review the question of biological prospecting in the Antarctic Treaty Area, and exchange on an annual basis information and views relating to that question as appropriate.” The meeting also included as “Item 18. Biological Prospecting in Antarctica”, in the Preliminary Agenda for ATCM XXIX.

This paper seeks to assist Parties keep under review the question on biological prospecting by providing an overview of recent trends in biological prospecting. The paper expands upon and updates information provided previously to ATCMs, in particular, Information Paper 106 Industry Involvement in Antarctic Bioprospecting, prepared for ATCM XXVII and Information Paper 75 Bioprospecting, prepared for ATCM XXVI.

Commercial interest in Antarctica stems from two reasons. First, the lack of knowledge surrounding Antarctic biota provides an opportunity to discover novel organisms of potential use. Second, Antarctica’s environmental extremes, such as cold temperatures and extreme aridity and salinity, present conditions in which biota have evolved unique characteristics for survival.

As has been previously outlined there is continued and growing interest in conducting further research into commercially useful genetic resources and biochemical processes in Antarctica. For example many of the newly discovered Antarctic Actinobacteria species, including *Streptomyces*, *Nocardia* and *Micromonospora*, belong to genera with strong track records for producing pharmaceutically active compounds. Also the production of polyunsaturated fatty acids (PUFA) and of cold-active enzymes by bacteria inhabiting Antarctic ice has also excited widespread interest amongst academics and commercial interests. Other potentially commercial uses that are being explored include: research into glycoprotein to increase the freeze tolerance of commercial plants or extend the shelf-life of frozen food or improve surgery involving the freezing of tissues (cryosurgery) or enhance the preservation of tissues to be transplanted; research into cold-active enzymes by bacteria inhabiting Antarctic ice for better detergents and cleaning agents and new heat resistant dyes.

A recent example of a commercially useful compound derived from Antarctica is a New Zealand company ZyGEM's products forensicGEM (to extract human DNA from crime scene samples) phytoGEM (plants) and prepGEM (animals). Future uses are expected to include human DNA disease diagnostics, bio security (to quickly extract RNA, for example, from strains of avian or a pandemic flu virus) and crop genetic screening.

These products are all based on an enzyme derived from a microorganism found in a volcanic vent in Antarctica by New Zealand scientists. ZyGEM Corporation claims their new reagent extracts DNA from smaller samples three times faster and at greatly lower cost than other existing extraction methods. The DNA extraction market is worth an estimated billion dollars per year globally. Several major DNA extraction companies in the United States, European Union and New Zealand, have now signed to use the new reagent and process in evaluation trials.

The purpose of this paper is to provide an overview of trends in markets, research and development, and demand for biological compounds and genetic resources in two key sectors that have undertaken research on Antarctic genetic resources, the pharmaceutical and biotechnology industries. Drawing on perspectives from a broader range of industries - including the cosmetic and personal care, botanical, fragrance, and food and beverage – the paper then reviews trends in benefit-sharing across sectors.

2.1 The Pharmaceutical Industry

2.1.1 Market Trends

Pharmaceutical industry global revenues in 2004 topped \$500 billion, dominated by sales in North America, Europe and Japan (Table 1). The industry is also concentrated in the US and Europe (Table 3), followed by Japan. Despite poor research and development productivity, the loss of patent protection for some major products in recent years, and pressures for containment of drug costs, the industry grew around 9% in 2004 (Class, 2004). Companies are adapting to changes in the market and regulatory environment in a number of ways, including moving away from the ‘blockbuster’ model to smaller niche markets with still significant sales, although 85 blockbusters are expected to account for 30% of global sales in 2005, up from 69 in 1993 (Lewis et al, 2005).

The top 10 companies in 2003 accounted for half of all worldwide sales, but their relative contribution to overall industry growth declined to 41% in 2003 from 53% in 2001. The greatest rates of growth were seen in generic and biotechnology companies (Class, 2004). Biotechnology products account for an increasing share of the market, with 17% growth in 2004. Eighty percent of the biotechnology market was held by just ten firms, with Amgen the leading player (Lewis et al, 2005).¹

There is continued consolidation in the pharmaceutical industry, although the rate of mergers and acquisitions has slowed in the last few years. Recent ‘megamergers’ have produced mixed results, with many of the top companies having lower actual market shares in 2003 than the sum of their components in 1998 (Table 2).

¹ In 2004 Amgen saw 30% growth and has five of the ten biotechnology blockbusters – Epogen (erythropoietin), Aranesp (darbepoietin alpha), Enbrel (etanercept), Neulasta (pegfilgrastim), and Neupogen (filgrastim) (Lewis et al, 2005).

2.1.2 Trends in Research and Development

Despite continual increases in R&D expenditures, including the highest-ever investment in R&D in 2004², pharmaceutical industry productivity is significantly lower than in recent years. The number of new chemical entities (NCEs) launched worldwide in 2004 was the lowest for 10 years (Lewis et al, 2005). Of the New Drug Applications approved by the FDA in 2002, only 22% were for NCEs, with the majority being ‘me-too’ drugs that are new formulations or line extensions of existing products.

Biotechnology is making an increasing contribution to the industry’s bottom line, and biotechnology research tools and techniques are central features of pharmaceutical discovery and development today. Eight of the thirty NCEs launched in 2003 were biotechnology-derived, and 27% of active compounds in industry’s pipeline were biotechnology-based³ (Class, 2004).

Advances in molecular biology, cellular biology and genomics in the 1990s deconstructed disease pathways and processes into their molecular and genetic components to identify the exact point of malfunction, and the point in need of therapeutic intervention. The result was an increase of molecular targets that may be applied to the discovery of novel tools for the diagnosis, prevention and treatment of human diseases from approximately 500 to more than 10,000 targets (Class, 2004; Newman et al, 2003; Bio, 2005).

The development of high-throughput screens based on molecular targets led to demand for large libraries of compounds that might inhibit or activate a specific biological target, such as a cell-surface receptor or enzyme. For much of the 1990s, scientists thought the best way to generate compounds for the screens was through mass-produced combinatorial libraries (Newman et al, 2003; Koehn and Carter, 2005). The importance of natural products as a source of molecular diversity for drug discovery and development was overshadowed by chemical approaches that use combinatorial chemistry and biological approaches such as the manipulation of biosynthetic pathways of microbial metabolites through combinatorial biosynthetic techniques (Cragg et al, 2005). Natural products were considered too slow, too costly, and too problematic from both a scientific perspective (for example, the additional steps needed to identify and isolate active components in mixtures), and for the legal and public relations uncertainties associated with gaining access to genetic resources as a result of the Convention on Biological Diversity.

² 2004 R&D investment was \$49.3 billion for PhRMA member companies alone (www.PhRMA.org).

³ Biotechnology is transforming drug discovery and development, including high-throughput screening that has revolutionized the process of target identification, DNA sequencing machines that shaved years off the mapping of the human genome, and monoclonal antibodies that transformed the diagnostics industry and are now used in treatments (Ernst and Young, 2005). Biotechnology techniques used in drug discovery and development include: bioprocessing (using living cells to manufacture products such as human insulin); monoclonal antibody technology (using immune system cells that make antibodies to target treatments to specific cells); molecular cloning (creating genetically identical DNA molecules); and recombinant DNA technology (combining and modifying genes to create new therapies) (PhRMA, 2005).

Despite the contributions of natural products to industry's bottom line⁴ (see Chart 1), particularly in categories like infectious disease and cancer⁵, natural products experienced a slow decline over the past two decades due to both scientific and commercial considerations (Koehn and Carter, 2005). Disease categories for which natural products are well suited – in particular infectious disease – lost ground within companies (Koehn and Carter, 2005; Handelsman, 2005). The US pharmaceutical industry essentially abandoned antibiotic discovery around 1990, even as resistance problems were emerging. Antibiotics have limited profitability (compared with those taken over long periods of time for chronic conditions) and there was a misplaced belief of having conquered infectious diseases. Wyeth's tigecycline released in 2005 is the first new class of antibiotics to be introduced to the market in 20 years (Handelsman, 2005).

After a multi-billion dollar investment in combinatorial chemistry since the late 1980s, however, large pharmaceutical companies have found very little in the way of new structurally diverse entities, and their pipelines are all but empty. The percentage of synthetics as new chemical entities (NCEs) has remained roughly the same (see Chart 2; Newman, 2005). It is now widely agreed that while combinatorial chemistry is a valuable development tool for optimization of leads, including those from natural products, it does not yield much in the way of new molecular diversity.

At the same time the limitations of combinatorial chemistry have become evident, breakthroughs in technologies (eg in separation and structure-determination) have made screening mixtures of structurally complex natural product molecules easier, and have expanded the potential role of natural chemical diversity in the drug discovery process (Koehn and Carter, 2005). Expanded understanding of the genes involved in secondary metabolite biosynthesis also mean that researchers can now discern the complex chemical structure of a secondary metabolite which will result from the enzymes produced following expression of a particular set of genomic sequences. This makes "genome mining" of even well-known natural products a potentially powerful new approach to natural product discovery (McAlpine et al, 2005). Advances in synthetic chemistry have revolutionized the process of material supply, making it possible to recreate almost any compound in the laboratory, and addressing one of the fundamental concerns in natural product discovery, the 'supply issue' (Koehn and Carter, 2005). The result of these developments is renewed interest in natural products as a source of chemical diversity and lead generation, and a view of natural products and combinatorial synthesis as complementary rather than stand-alone approaches (Koehn and Carter, 2005).⁶

⁴ See, for example, Newman et al, 2003; Newman, 2005; Newman and Laird, 1999.

⁵ In addition to infectious diseases, cancer drugs draw heavily upon natural products, and companies with aggressive oncology programs, like Novartis and Bristol Myers Squibb, maintain natural products R&D programs in this area. Newman et al (2003) undertook a study of natural products as sources of new drugs from 1981-2002 and found drugs of natural origin predominate in certain disease categories like cancer and infectious disease, despite the expansion of combinatorial chemistry in the 1990s.

⁶ Newman et al (2003) suggest the best solution to the current productivity crisis is "...a multidisciplinary approach to drug discovery that involves the generation of truly novel molecular diversity from natural product sources, combined with total and combinatorial synthetic methodologies, and including the manipulation of biosynthetic pathways (so-called combinatorial biosynthesis)." (p 1036).

It has become evident that mergers can actually have a negative impact on R&D productivity, previously cited as a one of the main drivers of mergers and acquisitions. Many analysts now believe that the optimal number of scientists for a successful R&D program is 300-800, with any more being unmanageable. Large companies like Glaxo SmithKline and Lilly are breaking their research teams into therapy areas to promote an 'independent, entrepreneurial spirit' (Class, 2004).

Targeted acquisitions of small biotechnology firms to gain access to a specific product or technology are increasing in importance, as are licensing deals, to make up for unproductive R&D programs in large companies. In 2001, in-licensed products accounted for 16-20% of the top 20 companies' revenue; by 2007 this figure is expected to reach 40%. Some predict that the industry will divide into two, with small R&D boutiques providing candidates for large companies that focus on development, sales and marketing (Class, 2004). This means that smaller companies may be more likely than the largest to seek access to genetic resources for their discovery programs, and that promising compounds will then be licensed to the larger companies for development.

2.1.3 Demand for Natural Compounds and Genetic Resources

Despite renewed interest in natural products, most large companies are not at present expanding their in-house natural products programs, but they are licensing in, or forming partnerships, with small companies and universities that generate interesting leads from natural products discovery research. However, the same technological and scientific developments that make natural products more interesting again, also mean that a great deal of research can be done in laboratories or on a computer looking at the genomes of already known organisms. Analysis, using new scientific and technological tools, of the genome of the well-characterized microorganism *Streptomyces aizunensis*, for example, produced novel and highly defined structures (McAlpine et al, 2005). Demand for access to 'new' natural products is therefore different in approach and character to that of previous cycles of natural products research.

Most of the major changes and areas of interest emphasize the importance, potential and utility of research undertaken on the biota of Antarctica.

2.1.3.1 Microorganisms

While plants, insects, marine and other organisms are still of interest to natural products researchers, the trend over the last 5-10 years is towards microorganisms. Metagenomic technology allows researchers to extract DNA directly from microorganisms found in environmental samples, making available the 99% of microbial diversity previously inaccessible through traditional cultures, while at the same time discovering a far greater number of secondary metabolites in a given organism by genome mining (Handelsman, 2005; McAlpine et al, 2005). The genomes of microorganisms can be more easily sequenced than those of plants or insects, and can be grown in culture, rather than collected (eg plants), which makes it easier for companies to deal with supply issues as research progresses (although synthetic chemistry is making it possible to produce most compounds in the laboratory).

2.1.3.2 Marine organisms

The last 10 years have also seen a surge of interest in marine organisms. Marine chemistry is new to natural products chemists, but already approximately 20 marine natural products are in clinical trials, and 34 of the 36 phyla of our planet's biodiversity is found in oceans (only 17 are found on land) (William Fenical, SCRIPPS, pers.comm., 2005). The US National Cancer Institute has reduced its interest in plants and is now focusing its collections on marine organisms. Although plants can still provide invaluable leads for other disease categories, they have not been as promising for anti-cancer agents. Marine organisms live in extremely hostile environments, and in a perpetual state of 'chemical warfare' that produces potent toxins, and a number of novel compounds that work in a way similar to existing anti-cancer agents have been found (David Newman, NCI, pers comm., 2005).

2.1.3.3 Complex associations between organisms

It is also increasingly recognized that distinctions between organisms – plant, marine, invertebrate, microorganism – are not always clear-cut, and that promising compounds may in fact be produced by symbiotic microbial species (Cragg et al, 2005). For example, in 1972 researchers working with the US National Cancer Institute isolated maytansines from an extract of *Maytenus serrata* collected in Ethiopia, and subsequently found them in other *Maytenus* and *Putterlickia* species. However, recollections of the plants, cell cultures, and greenhouse-grown plants did not yield the active compounds. In recent years, it was found that microorganisms isolated from the rhizosphere appear to be responsible for producing the active compounds, perhaps with plants playing a role in determining the final chemical structures (Yu and Floss, 2005). Toxins in birds feathers or secreted by reptiles have been found to originate in insects they eat; promising compounds from insects are traced back to the microorganisms living in their gut; and marine invertebrates have been found to undertake the bulk of the chemistry that produces an interesting compound, which is then modified by associated microorganisms, or vice-versa. Through co-evolution a spectrum of complex community associations, rather than single organisms, appear to be the source of many promising compounds.

2.1.3.4 Demand for diversity

These associations get to the heart of another on-going discussion within natural products research: the need for accessing 'new' biological diversity to fuel discovery. New research tools mean that diversity found in one's 'backyard', particularly that found in the previously inaccessible genomes of microorganisms, and even those of known microorganisms (eg McAlpine et al, 2005), can keep researchers busy. A number of researchers feel that for microorganisms "every species is everywhere" and that there is enough at home, or in a few provider countries, to fuel research for many years to come. But as Jo Handelsman of the University of Wisconsin-Madison put it (pers.comm., 2005): "Until very recently I used to think that 'everything is everywhere', and it is true that going into any backyard is like going to Mars. But even if every species is everywhere, members of the same species will produce different secondary metabolites in different places, and I think it is unlikely that all species are indeed everywhere. Insects, for example, have highly specific associations with microorganisms, with some

microorganisms known only to exist inside one species of insect. No one would argue that insect diversity in the tropics is not unique, so if macrodiversity is unique, it is likely that the associated microdiversity is as well. We really don't know, and it is premature to make those judgements, because we are so far from having a complete census of the microbial world. It is very possible that most microorganism species are everywhere, but that the most interesting strains are not." The same advances in science and technology that currently make many research programs focus on existing collections or materials easily available at home, may very well lead to expanded interest once again in a broader range of biological diversity.

2.1.3.5 Supply issues

A decade ago, the unknown associations between organisms created issues with re-supply, and researchers at times faced difficulties re-locating individual plants or marine organisms that produced the active compounds. However, today DNA is isolated and expressed in an external host for mass production, so this circumvents that element of the supply issue. The technology is still developing, and all genes cannot be expressed in this way, so there is still some demand for re-supply along a continuum from full synthesis, to semi-synthesis from a precursor taken from the raw material produced in culture, and so on. However, the need for re-supply of material for research and development, and in some cases commercialization, was until recently an important component of the relationship between providers and users, and served as a useful incentive for users to establish solid partnerships with providers. While advances in technologies also make it easier to trace plant, marine and other compounds back to the source, it is much more difficult to do this with microorganisms. The need for providers and users to develop strong partnerships as a way of monitoring development of natural product compounds is far greater today than even a few years ago, and will continue to grow in importance.

2.2 The Biotechnology Industry

The biotechnology industry spans a wide range of sectors, including industrial, agricultural, and healthcare. Health care biotechnology is the largest and most profitable sector, comprising 51% of European and 60% of US biotechnology companies, and accounting for a majority of industry revenues (EuropaBio, 2005). Following a discussion of market trends for all elements of the biotechnology industry, this section focuses on industrial biotechnology, which uses living cells like moulds, yeasts or bacteria, as well as enzymes, to produce goods and services. Industrial biotechnology applications may create more efficient and cost-effective industrial processes that produce less waste, and use less energy and water in such sectors as chemicals, pulp and paper, textiles, food, energy, and metals and minerals (Bio, 2005; EuropaBio, 2005). In some cases, environmental biotechnology products make it possible to clean up hazardous waste more efficiently by harnessing pollution-eating microbes without the use of caustic chemicals. (Bio, 2005).⁷

⁷ Industrial and specialty enzymes produced an estimated \$3.6 billion in revenue in 2000 (www.Diversa.org, 2005).

2.2.1 Market Trends

The global biotechnology industry had revenues of \$54.6 billion in 2004, a 17% increase over 2003. The US dominates the industry, accounting for 78% of global public company revenues, followed by Europe at 14%, Canada at 4% and the Asia-Pacific region at 4% (Ernst and Young, 2005; Table 4). In 2005, the top 12 biotechnology countries, ranked by number of biotechnology companies (private and public), were: the US, Canada, Germany, UK, Australia, France, Sweden, Israel, China and Hong King, Switzerland, India and The Netherlands (Ernst and Young, 2005). The largest companies are primarily found in the US (see Table 5).

Biotechnology firms vary greatly in size and scope, ranging from small, dedicated biotechnology companies that are R&D-intensive to large, diversified companies that have greater in-house resources and well-established production and distribution systems. In a survey undertaken of the US biotechnology industry, 90% of firms had 500 or fewer employees, and only 19 (2%) had more than 15,000 (US Department of Commerce, 2003).

The majority of biotechnology companies operate primarily on venture capital, grants, initial public offerings and collaborative agreements, and the state of this research-intensive industry depends heavily upon the availability of these forms of financing (US Department of Commerce, 2003). Biotechnology companies need external capital to act as a catalyst for growth in early years, fund R&D, and allow them to build on their intellectual property without the need to develop a separate infrastructure to generate revenues to fuel the business (EuropaBio, 2005).⁸

After the collapse of the boom market for biotechnology companies in 2001, the investment cycle entered a 'bust' phase and investors stayed away from the sector. Companies responded by restructuring, spinning off assets, reducing cash burn rates, refocusing their business models to place more emphasis on product development and commercialization and less on technology platforms, and forming alliances with other companies (EuropaBio, 2005; Ernst and Young, 2005).⁹ By 2004, a surge of products in the late-stage pipeline and product approvals¹⁰, as well as better-articulated company

⁸ A study by EuropaBio found that the biggest barrier to development of the European biotechnology industry was the lack of a suitable financial infrastructure later in the business cycle. While US companies raised \$2.4 billion in venture capital in 2004, sold an additional \$3.3 billion worth of equity in 2004, and raised a further \$3.3 billion in debt in 2004, European companies raised \$771 million in venture capital, \$1.3 billion through equity, and \$820 million in debt financing in the same year (EuropaBio, 2005).

⁹ Examples of biotechnology/biotechnology deals includes Idec Pharmaceuticals \$4.2 billion all-share merger with Biogen, Amgen's \$7.8 billion acquisition of Immunex, and the range of acquisitions made by Genzyme Corp in recent years. Pharmaceutical giants such as Novartis, Pfizer and Johnson & Johnson have also acquired biotechnology companies in recent years, but the most common relationship between pharmaceutical and biotechnology companies remains discreet biopartnerships (EuropaBio, 2005).

¹⁰ In the US, 365 products were in Phase II clinical trials in December 2004, compared with 290 the previous year, and as of early 2005 there were 55 new drug application submissions under review at the FDA. European companies brought 9 products to market in 2004, compared with 6 in 2003 (Ernst and Young, 2005).

paths to products and profitability, had drawn investors back to what is now considered a more mature industry (Ernst and Young, 2005).¹¹ At the same time, partnerships between biotechnology companies, and between biotechnology and pharmaceutical companies, continue. Biotechnology companies need capital and pharmaceutical companies, concerned about the effect their innovation deficits will have on future earnings, need products (EuropaBio, 2005).

2.2.2 Trends in Research and Development

Biotechnology is one of the most research-intensive industries in the world. In the US, biotechnology-related R&D accounted for roughly 10% of all US industry R&D in 2001 (US Department of Commerce, 2003). New biotechnology research tools have enabled researchers to tease apart cellular and genetic processes, and to understand biological systems at the molecular level. Biotechnology research tools have changed the research questions scientists ask, the problems they tackle, and the methods they use to get answers (Bio, 2005). Biotechnology includes bioprocessing technology, monoclonal antibodies, cell culture, recombinant DNA technology, cloning, protein engineering, biosensors, nanobiotechnology, and microarrays. The need to integrate the pieces of data generated by biotechnology into an understanding of whole systems and organisms has given rise to other new information technologies called the “omics” - genomics, proteomics, metabolomics, immunomics, and transcriptomics. At the same time, new bioinformatics technology uses computational tools provided by the information technology revolution - such as statistical software, graphics simulation, algorithms and database management – to consistently organize, access, process, and integrate data from different sources (Bio, 2005).¹²

These new technologies have changed new product discovery, and identified new uses for existing products, by helping researchers understand the basic biology of the processes they want to control or change, and manage vast quantities of data. They have also made product development quicker and often cheaper. For example, pharmaceutical companies can better identify molecular targets, pinpoint winning compounds far earlier in the discovery process, and use cell culture and microarray technology to test the safety and efficacy of drugs and observe adverse side effects early in the drug development process; agricultural biotechnology companies developing insect-resistant plants can measure the amount of protective protein that a plant cell produces and avoid having to raise the plants to maturity (Bio, 2005). Combined, these technologies are leading to synthesis of living organisms from scratch. Venter (2005) notes how science is moving from “reading the genetic code to writing it”, predicting that within 2 years it will be possible to synthesize bacteria, and within 10 years single-cell eukaryotes. Increasingly,

¹¹ The global biotechnology industry raised \$21.2 billion in venture capital in 2004, a 15% increase over the capital raised in 2003, and IPOs raised \$2 billion in the US, Europe, and Canada in 2004, compared with \$450 million in 2003. Asia-Pacific companies raised about \$500 million through Initial Public Offerings in 2004, led by offerings in Australia, Japan, and India (Ernst and Young, 2005).

¹² For a full description of these technologies and their applications, see: *Guide to Biotechnology*, Biotechnology Industry Association, www.bio.org, 2005.

technological changes are enabling biological materials to exist in a 'virtual' as well as an actual state (Parry, 2004).

The ways biotechnology companies use genetic resources vary significantly by sector. Some companies develop specialty enzymes, enhanced genes, or small molecules for use in crop protection and drug development. Others develop enzymes that act as biological catalysts in the production of polymers and specialty chemicals, or for use in industrial processing; and others might insert genes that impart desirable traits into crops. The pharmaceutical, crop protection, and seed industries are dealt with in other sections. The remaining biotechnology market is primarily focused on the use of enzymes, which we will review here.

Enzymes are proteins found in every living organism and are the 'tools of nature', i.e. they cut and paste products and speed up vital biological processes in cells. They have been used for more than 60 years by textile, detergent, food, feed and other industries, to make higher-quality products and make production processes more cost-effective and efficient, and therefore more environmentally-sound by minimizing the use of water, raw materials and energy. Since they are biodegradable, enzymes are also a more environmentally-sound substitute for synthetic chemicals (Novozymes.org, 2005).

Enzymes used by industry are usually found in microorganisms, in particular bacteria and fungi. Microorganisms are the world's most genetically diverse organisms, and include bacteria, archae, fungi, yeasts, and viruses. Through billions of years of natural selection in dissimilar environments, microbes have developed broader and more varied characteristics than those observed in plants or animals, while silently enabling and supporting life for larger plants and animals (Mathur et al, 2004).

Extremophile microorganisms are of particular interest to researchers today because they live in environments similar to those required by industrial processes, and reflect the necessary range of conditions - for example, extreme hot or cold temperatures, or acidic or salty conditions. For example, starch and baking require high temperatures and low pH; textiles, pulp and paper, and detergents a high temperature and high pH; and dairy and food a low temperature and low pH (Lange, 2004). As technologies to collect and study extremophiles advance, commercialization of processes and products derived from extremophiles is likely to increase (Arico and Salpin, 2005).

Recent advances in bio- and information technologies allow target compounds from environmental samples to be identified much more rapidly. Microorganisms were traditionally isolated and cultured in laboratories, a process that requires scientists to recreate the environments in which the target microbe lives, and as a result less than 1% of the billion plus microbial species have been studied (Mathur et al, 2004). Today, using metagenomics - the culture-independent analysis of assemblages of uncultured microorganisms - DNA is extracted directly from a soil, water or other environmental sample, it is cut with restriction enzymes, and cloned into a culturable host such as *Escherichia coli* (Handelsman, 2005). The host organism will then produce the

biochemicals from which commercially valuable enzymes and other biomolecules are developed.

Using computer-assisted techniques such as massive parallelism and randomness, genome sequencing can now occur at a speed previously unheard of. In 1995, for example the first genome sequence was described (for *E. coli*) – a task that then took 15 years and today could be done in less than a day (Venter, 2005). Since September of 2003 the number of genome mapping projects registered with the Genomes Online Database (GOLD) increased from 803 to 1951 projects. This represents a 2.5 times increase in the number of mapping projects. These trends are likely to accelerate with the completion of additional genome maps which will provide the foundation for unlocking the genomes of other organisms and technological developments such as the “whole genome chip”.

Patent demand has seen a similar growth with 188,213 biotech patents being issued in 1990 rising to a preliminary total of 299,163 patents by the end of 2003.

2.2.3 Demand for Genetic Resources

A striking trend over the past five years has been the vigorous attention given to microorganisms. The astounding numbers and diversity of microbes, combined with their all-pervasive existence – from thermal vents to Antarctica – and advances in technological development, have led to renewed interest in their use for energy saving, climate control, pollution control, biomaterials, and many other applications.

Biotechnology companies continue to seek access to genetic resources, which are either collected from nature or acquired through external collections. Microorganism samples needed for biotechnology research tend to be small – typically a few grams of soil or milliliters of water - and recollection is not usually necessary. The majority of companies and research institutes maintain in-house collections of genetic resources, including microorganisms, plants, insects, human genetic material, animals, fungi, bacteria, and derivatives of these resources such as enzymes, purified compounds, and extracts. Researchers access *ex situ* materials from the collections of companies, universities, national culture collections, and international collections (e.g. the International Mycological Institute) (ten Kate, 1999).

Most collections made by biotechnology companies outside of pharmaceuticals and agriculture are microorganisms. Insects, plants, animals, marine organisms and others continue to hold interest, although often for their associated microorganisms (Lange, 2004; Mathur, 2004).

When collecting from nature, companies are interested in samples from diverse and extreme environments and ecological niches (eg salt lakes, deserts, caves, hydrothermal vents, cold seeps in the deep seabed), as well as areas with microbial diversity associated with endemic flora (eg epiphytes, endophytes and pathogens) and fauna (eg insects, pathogens and endosymbionts) (Lange, 2004; Arico and Salpin, 2005). The objective of

micro-organism collection is *biochemical* diversity, which can be found not only by collecting in areas with high species diversity, but also in extreme environments or unique ecological niches (Lange, 2004). To access regions high in microbial diversity, for example, Diversa, a publicly traded US biotechnology company whose business involves the discovery and evolution of novel genes and genetic pathways from unique environmental sources, has entered into 18 partnerships with groups providing access to genetic resources in 10 countries across six continents, and to all international waters around the world (Diversa, 2005).

The Venter Institute has likewise, through ‘Sorcerer II’, embarked upon a global expedition to sample microbial abundance and diversity in marine and coastal environments describing, in its initial findings a situation where 85% of data collected is unique to each site. Findings from the Sorcerer II’s voyage will be used, among other things, to: design and engineer species to replace petro-chemicals; better understand reef health; analyze drinking water and air quality; track and avoid emerging viruses; and understand the effects of ballast water, where ships flush micro-organisms from one part of the world into the seas of another (Venter, 2005). The related ‘Air Genome Project’ of the Venter Institute aims to determine the numbers of new protein families from air-borne bacteria. Initiatives such as these throw up a host of new questions and challenges with regard to access and benefit-sharing, in particular relating to the sovereignty of microbes and the difficulties of ascribing ownership.

While initiatives such as these signify an accelerated increase in collecting microbes at a global scale, there are also companies that believe that new scientific and technological developments, coupled with the astounding diversity often found in their own ‘backyards’ or in existing collections, do not necessitate prospecting overseas.

Recent trends in science and technology have affected demand for genetic resources from nature in both positive and negative ways. The poor showing of combinatorial chemistry and synthetic compounds over the last decade, limitations to protein engineering, and a realization that natural solutions to the pressures of evolution have come up with things that could not be engineered in the laboratory, have made genetic resources in nature more attractive candidates for discovery. The ability to isolate DNA directly from samples, without resorting to culturing, also means that the vast genetic diversity in microorganisms can be accessed. At the same time, however, new scientific and technological developments mean that more diversity can be generated in the laboratory through molecular biology, shuffling, and protein evolution, and tools like bioinformatics allow researchers to hunt, not in nature, but in existing genome sequences and databases, for novel proteins and enzymes. Bioinformatics and sophisticated molecular biology tools also mean that for each sample collected, a great deal more information is gleaned, and so only a few strains are needed to keep research programs busy in a given year.

Novozymes, the leader in biotechnology-based enzymes and microorganisms, with more than 700 different products, net turnover of DKK 6,024 million in 2004, and 4,000 employees, has long-standing partnerships in Thailand and other countries for sample collection (novozymes.org, 2005; Lange, 2004). Although patents have been filed on

interesting developments, no new products have been developed from collections made since the CBD entered into force. The 5-6 new products that come out each year primarily derive from a handful of well-known strains that continue to yield valuable products (Lange, pers. comm., 2005).

Diversa, on the other hand, has developed a number of new products from its collections undertaken with partners overseas. For example, Luminase - which enhances the reactivity of pulp fiber to bleaching chemicals and reduces the need for chlorine dioxide and the cost of pulp processing - was developed from a microbe discovered in a thermal feature in Kamchatka, as part of a research partnership between the company and the Center for Ecological Research and BioResources Development (CERBRD) in Russia. Diversa estimates the potential market for Luminase at \$200 million. Another Diversa product, Cottonase, reduces the use of harsh chemicals, extreme temperatures and large volumes of water in cotton scouring (diversa.com, 2005).¹³

3. Trends in benefit-sharing and partnerships

The issue of benefit sharing is still relatively immature. Experience, perceptions, practices are rapidly evolving. Whereas early experiences in this area have generally been negative, a more realistic, pragmatic and less divisive intercourse is developing. Previous papers have mapped out the wider policy developments that reflect this evolution. This section provides an overview of the evolving industry practices of particular relevance to Antarctica.

Industry and researcher perceptions of the CBD, and ABS in particular, have been mixed. Some continue to cite the positive role the CBD can play in promoting equitable relationships, conservation and best practices in industry, others consider the negative impacts to outweigh the positive. In 1999, ten Kate and Laird reported that over the course of the previous two years of their study many of the companies they interviewed had come to believe that implementation of the CBD had a largely negative affect of their use of genetic resources and natural products. They cited lack of clarity in the regulatory framework; bureaucracy and delays in receiving permits; lack of understanding of business; confusion about national focal points; unrealistic expectations and transaction costs; restriction of scientific traditions of collaboration and exchange; and the pressures these new regulatory frameworks place on already taxed natural product research programs (ten Kate and Laird, 1999, p296).

These concerns remain widespread today, but increasingly, more and more companies are finding that a greater sophistication in the providers and regulators, along with advances in the technology described above, is changing the situation for the better.

The following highlights areas of interest and concern to industry generally. As part of the research for this paper, approximately 40 interviews were undertaken in 2005 with a wide range of academic and industry researchers, as well as company executives,

¹³ Cottonase grew from the companies' collaboration with the National Institute of Biodiversity (InBio) in Costa Rica (Leif Christofferson, pers. comm., 2005).

government officials, and individuals working on ABS issues for NGOs and other groups. The breakdown of interviews with researchers and industry representatives by sector is as follows: pharmaceuticals: 7; biotechnology: 4 ; seed and crop protection: 5; horticulture: 3; personal care and cosmetic (including fragrance): 4; botanicals: 4; food and beverage: 1.

3.1 Benefit-sharing as standard practice in industry

Benefit sharing varies by sector, but standards for best practice in benefit-sharing have become widely accepted. Although unscrupulous and ill-informed companies continue to by-pass these standards, the larger or more socially responsible companies today would not consider genetic resources freely available, or the ‘common heritage of mankind’. The package of benefits typically includes a mix of monetary benefits like fees per sample, milestone payments, royalties on net sales, and licensing agreements, as well as non-monetary benefits like training, capacity-building, research exchanges, supply of equipment, technology transfer¹⁴, and joint publications¹⁵. Groups with the most experience in benefit-sharing generally emphasize the importance of non-monetary benefits and ‘front-loading’ benefit-sharing packages. ‘Front-loading’ benefit-sharing packages ensures that provider countries receive a stream of benefits through the discovery and development phases, given the small odds of any one partnership yielding a commercial product and the fact that all products will not necessarily be billion-dollar ‘blockbusters’, generating large royalties, or that in most industries products rarely, if ever, achieve this status¹⁶.

Concerns continue to be raised about the quality of prior informed consent and benefit-sharing arrangements in particular cases, and there are many companies and indeed some sectors (eg cosmetic, fragrance, botanical, horticulture) that have not fully grasped the new legal and ethical obligations that arise from the Convention on Biological Diversity. In general, however, companies now see benefit-sharing as a necessary business practice associated with accessing genetic resources. For example, the European biotechnology firm Novozymes has developed a partnership with BIOTEC, Bangkok. BIOTEC collects, isolates, identifies and screens samples, with Novozymes sponsoring the research and providing training at BIOTEC, while transferring enzyme technologies and libraries, bioinformatics, providing training, and royalties if products are commercialized (Lange, 2004). A three year access and benefit sharing partnership between Syngenta and the

¹⁴ The International Seed Federation (ISF), for example, reports that technology transfer as it relates to the maintenance of plant genetic resources for food and agriculture is common practice, with more than 40% of ISF members granting licenses free of charge to developing countries and some members also participating in programmes for technology transfer (International Seed Federation, 2005b).

¹⁵ As part of their roughly 125 agreements since 1993, the ICBGS have provided formal training for 2,800 individuals from 12 countries, with 90% of these from developing countries. Associated with training and research efforts, a substantial amount of equipment and infrastructure enhancement for both US and developing country institutions is carried out, and capacity-building to undertake research. Other benefits address the direct needs of collaborating communities, and include water tanks, fencing for gardens, shade cloth, boats, and refrigerators (Rosenthal and Katz, 2004).

¹⁶ As noted in Section 2.1, even within the pharmaceutical industry, companies are moving away from the ‘blockbuster’ model to smaller niche markets with still significant sales (Lewis et al, 2005).

Hubei Biopesticide Engineering Research Centre in China aims to discover natural chemicals that can be used as starting points for the development of novel crop protection agents. Under the terms of this agreement, HBERC will collect micro-organisms from natural habitats in China, screen them for interesting biological activity and produce information on their chemical properties. Syngenta will provide technological and financial support and will pay HBERC royalties on any products derived from the research (Syngenta, 2005).

Horticulture is a sector characterized by ignorance of the CBD, but even here new access and benefit-sharing agreements have been developed. A Research and Licensing Agreement between the Chicago-based Ball Horticulture and the South African-based National Botanical Institute (NBI; now the South African National Biodiversity Institute), was entered into in 1999. The five-year agreement, which is the first North-South bioprospecting agreement in the horti- and flori-culture sector, involved the NBI using its expertise to select South African plants of horticultural interest for Ball, both from its living collections and from the wild. Thus far three varieties have been introduced, based on South African species, although royalties, despite being substantial, have yet to surpass costs of the project (Brian Corr, Ball Horticulture, pers. comm., 2005). While the agreement has raised concerns about the adequacy of benefits and the role of public institutions (Wynberg, 2003), the process of negotiation and revision in response to public concerns has helped to refine expectations and stimulate discussion about standards for benefit-sharing within South Africa, which will eventually be incorporated in a re-negotiated contract between the parties.

3.2 Lack of resolution on appropriate monetary benefits

While responsible users of genetic resources understand that benefit need to be shared, the scale of those benefits remains unresolved in some cases. Non-monetary benefits are not generally a source of much controversy or confusion, although some provider countries appear to undervalue the importance of this type of benefit for their scientific and technological institutions and domestic industry. There remains much concern on the part of both providers and users, however, about appropriate monetary benefits, in particular up front payments and royalties. For the most part, companies are reluctant to provide significant advance benefits unless they are attached to an agreed workplan. Fees for samples and milestone payments, attached to progress in the research collaboration and a product's development, are familiar components of most industry R&D programs. Royalties are also standard practice, and the vast majority of companies agree that should a product be commercialized, provider countries should receive financial benefits, but the scale and nature of these benefits is often in dispute.

The greatest controversy remains the appropriate range for royalty rates. At the heart of this debate are different concepts of the value of genetic resources to commercial product discovery and development. A regular feature in current industry commentary on these issues is the need to match expectations of value with commercial realities, and to appropriately value genetic resources in negotiations with companies. Lange (2004) refers to this as a 'mismatch of expectations' which she says grows from provider country

inexperience with industry, and a lack of awareness on the part of national focal points and negotiators about the higher risks and costs involved in development, compared with discovery. In the absence of information on possible commercial values for genetic resources, providers make the assumption that genetic and biochemical resources have significant value for companies.

Companies feel that the different research and development approaches and profit margins of industries, and existing practices in paying royalties for samples or leads, must inform the negotiation of royalties for genetic resources. The relative contribution of the partners to discovery and development, the information provided with samples, the degree of derivation of the final product from the original sample, and the novelty or rarity of samples all affect where in an established industry range a royalty rate will fall.¹⁷

In addition, providers should consider the time and cost it takes to develop a product; the volumes sold and average profit; and the likelihood that a product will be developed from a given collaboration. For example, industrial enzymes have a much lower profit margin than pharmaceuticals, and generally a lower royalty range (0.5 – 2% compared with 3-5%), but they cost between \$2 – 20 million to develop compared with around \$1 billion, and can yield commercial products in half or less the time (3-5 years compared with 10-15 years, with markets of \$200 million compared with possibly \$1 billion) (ten Kate, 1999; Laird and ten Kate, 1999; Ernst and Young, 2005).

A debate also exists about when royalty negotiations should take place. Cragg et al (in press) propose a two phase process of agreements between providers and users based on their experience with drug discovery and development at the US National Cancer Institute. The first stage is a research agreement that covers the discovery phase, and the second a commercial agreement that includes benefits related to drug development and royalties, triggered by a patent or selection of an agent for Phase II development. They feel that negotiation of these latter types of benefits are better left to the second stage, once a promising drug candidate has been identified and fully characterized, the breadth of any intellectual property determination is made, the disease category with known markets is clear, and resulting appropriate levels of benefit-sharing can more reasonably be discussed. It is not common practice within industry to lock down these terms in the earliest stages of a research collaboration, and they feel that requiring this serves to dampen demand for access. However, in industries where the likelihood of commercial product development is high, such as horticulture, it is common practice to merge discovery and commercial agreements, and in such cases royalties may be specified.¹⁸

The stakes for coming to agreement on the ways genetic resources are valued as part of commercial product discovery and development are quite high. A significant number of companies in the pharmaceutical, biotechnology, seed and other industries voiced the opinion that if provider countries set the bar too high, for example demanding royalties well outside of what is considered standard commercial practice, companies will

¹⁷ See ten Kate and Laird (1999) for a review of the factors influencing royalties for genetic resources.

¹⁸ For example, see the Ball-NBI agreement in South Africa.

withdraw from collection and research partnerships. Even if higher than normal royalties are agreed upon, some in industry feel that products with these conditions attached would fare poorly within the company and would not be developed. Products derived from genetic resources must compete with those originating from other research programs for development support, and they may look less financially promising if attached to large financial obligations.

3.3 Benefit-sharing in sectors that consume large quantities of raw material

An important trend observed is that many companies in sectors reliant on bulk trading of raw material (rather than genetic resources) are becoming more socially and environmentally responsible and are considering benefit-sharing measures. The nature of benefits reflects the different research and business practices of particular industries. For example, in ornamental horticulture a vast amount of material is already in the public domain, but many developing countries do not have the funds to develop cultivars for IPR registration, the primary mechanism for benefit-sharing (Coetzee, 2002). An alternative approach proposed for generating benefits for local communities and rural producers is to promote fair trade certified horticultural products¹⁹. Socially-responsible personal care and cosmetic, and botanical companies, similarly emphasize a range of benefits associated with raw material sourcing following product development. Aveda, for example, seeks to develop sourcing partnerships with local groups that include long term agreements and fair prices, as well as contributions to community development funds, bringing in certifiers to broaden the market appeal of the products, and helping communities link with other buyers (Waddington and Laird, 1999; David Hircock, Aveda, pers.comm., 2005). But it takes a great deal of time and money to do this, including staff dedicated to following and monitoring these activities, so most companies do not invest in these activities.

3.4 The importance of partnerships

Many companies seek the benefits of better-developed and longer-term partnerships with source institutions. Partnerships allow companies to access local expertise and resources in areas of interest, and in some cases companies build research capacity to undertake a greater share of discovery, more affordably, in provider countries. Partnerships also provide more insurance to companies that the resources they access are legally obtained. Because these more involved partnerships require a large investment of time and resources, however, companies tend to work in fewer countries than in earlier years, a trend further encouraged by developments associated with the CBD and ABS measures.

The US biotechnology company Diversa has developed criteria by which it selects partners that include: the legal framework and political will within a country to support research and commercial activities; the scientific and institutional strength of potential partners; and the presence of unique and protected habitats (Mathur et al, 2004).

¹⁹ For example, Fair Trade certified cut flowers were launched in 2001, and are now sold widely in European supermarkets. Fair trade roses have since gained a market share of 8% of imported roses (Jorgensen, 2004; Lawrence, 2005).

Partnerships also enhance the benefits accruing to provider countries and their institutions, particularly those that build the scientific and technological capacity of countries to undertake research on their own biological diversity²⁰. Because provider country scientists play a larger role in discovery when part of partnerships, it also means that financial benefits derived from any commercial product will be more significant. Better-established partnerships also help provider countries monitor the ways samples are collected and used. This is of increasing importance as microorganisms come to dominate many natural products research programs, re-collection of samples becomes unnecessary with expression of DNA in the laboratory, and improvements in synthetic chemistry make it possible to create almost any compound in the laboratory (Koehn and Carter, 2005; Bull, 2004). As one US academic researcher that has brokered access and benefit sharing agreements in a number of countries put it: “This highlights again the value and importance of partnerships – for the benefit of everybody. People need to develop relationships so that they are comfortable working with each other. This kind of research is a difficult thing to regulate, and is becoming more so. Trust is a huge issue, and paramount to the process working. It is not enough to get a permit from a government agency that doesn’t really know what the research is about - it is much better for all involved to also have full partnerships.”

3.5 Charges of biopiracy and ‘image problems’

As a result of an environment characterized by misunderstanding and mistrust, in recent years researchers and companies have become increasingly concerned about negative attacks and bad press associated with accessing genetic resources. In addition to the practical hurdles of gaining access, companies and researchers now consider the threat of ‘biopiracy’ charges a serious impediment to research (this concern did not feature prominently in the study undertaken by ten Kate and Laird (1999) in the late 1990s). One problem regularly cited is the broad definition of ‘biopiracy’. Whereas its initial meaning focused on the patenting of genetic resources based on traditional knowledge without the consent of the knowledge holders, today it is popularly used to describe any commercial activity associated with genetic resources.

In a study of German companies using genetic resources, it was found that ‘image’ problems associated with accessing genetic resources were a major concern for companies from a range of sectors, and influenced their decision-making about whether and how to undertake collections (Holm-Muller et al, 2005). An academic researcher in the US said that both academic researchers and companies today are reluctant to access genetic resources overseas for fear of “...becoming part of a very dangerous socio-political environment in which anyone can claim they are biopirates at any time, and slander them without any legal recourse.” An executive at a cosmetics and personal care company in the US similarly characterized research on ‘new’ ingredients or products as

²⁰ For example, Diversa’s 18 partners have received more than \$2 million in financial payments and \$2 million in third-party grants to support research collaborations. Diversa has also supplied a range of non-monetary benefits, including training more than 100 scientists and students, and providing equipment and infrastructure improvements (Mathur et al, 2004).

“very dangerous”, and in the on-going absence of solid laws they currently avoid this research.

The rise in concerns about biopiracy is occurring at the same time most in industry have come to accept the need to negotiate access and benefit-sharing agreements. As one biotechnology company executive put it: “ The agreements are not onerous; they [companies] can afford royalties. Furthermore, the parties to the CBD can seek some form of reprisal with any firm they feel has gathered samples without permission... I can't imagine any reasonably sized company trying to build a business on hidden material.”

Leif Christofferson of Diversa notes that attacks on companies for ‘biopiracy’ almost always focus on the companies that are most transparent, which has the effect of encouraging greater secrecy on the part of industry. He cites the case of Diversa in Yellowstone National Park in the US, because in this case both the Park and the company felt that their agreement was a ‘win-win’ and presented it to the public with the expectation that others would share their views. The firestorm that erupted and put their collaboration on hold for many years has served as a warning to other companies, he says.

Rosenthal and Katz (2004), reporting on the work of the ICBGs, note: “Sometimes, regardless of how thoughtfully, transparently, or collaboratively a collection-based project and its approach to ABS are formulated, the political context in which it operates may ultimately make certain partnerships controversial. This is particularly the case when working with indigenous peoples.”

3.6 The Impact of Intellectual Property Rights

There are sharp differences in perspective between groups about the positive and negative impacts of intellectual property rights (IPRs), and as a result this issue has been found at the center of much of the ABS dialogue. In particular, there are divergent perceptions about the role of intellectual property protection in stimulating innovation and revenue; the ethics of patenting life; and the effects of intellectual property protection on food security, and health service provision (CIPR, 2002; Oldham, 2004; GRAIN, 2005). Ongoing efforts to introduce ‘disclosure of origin’ requirements for IPR applications, the lodging of multi-genome patent claims, and differences of opinion as to the placement of genetic information in public databases have been three recent debates that illustrate these divergences.

The possibility of requiring applicants for patents or other IPRs to declare if any genetic resources or traditional knowledge have been utilized in their applications has been brought into focus in recent years. Although a number of countries have adopted these disclosures of origin measures, there are conflicting opinions about their introduction at the international level, with some making a strong calls for patents to be granted only on evidence of PIC and benefit-sharing, and others arguing that a contract-based system suffices for securing the ABS objectives of the CBD. An industry-wide survey in

Germany revealed wide support for disclosure requirements amongst users, predominantly Holm-Muller et al (2005) remark because the requirement is without prejudice to the processing of patent applications or the validity of rights arising from granted patents. Although the debate has predominantly focused on moral and ethical issues, Tobin (2005) notes an important shift in focus towards the use of disclosure as an economic tool to promote facilitated access, reduced transaction costs for ABS and legal certainty. This could go a long way to resolving the ‘biopiracy’ claims described earlier.

Industry and researchers view IPRs as important elements of the research and commercialization process, but there are also differences in approaches to intellectual property protection and the publication of research findings. For example, Diversa has patented results of their research on microbial diversity, while the Venter Institute is working in similar areas and publishing a freely-shared genomics database even though this may “decrease a nation’s benefits arising from potential commercial utilization” (Biological Resources Access Agreement, 2004). In Bermuda’s Sargasso Sea, a six-year process by Diversa to develop a biodiversity research partnership with a local biological station is in contrast to the Venter Institute’s open publication of 1.2 million gene fragments from the same area. This might mean that Diversa and other companies like it may now find it harder to justify to their shareholders that they should continue to pay for something that they can now initiate for free from a public database (Diversa, 2005).

Increasingly, genome mapping with its identification of key genetic material across varieties, species, and genera, and the increasing realization of relatedness between organisms, is resulting in a surge of very broad intellectual property claims (Oldham, 2004). The existence of overlapping patents over shared DNA may generate significant negative chilling effects on future scientific research and innovation.²¹ The well know case of Syngenta’s patent over the flowering cells of rice, which in effect extended over all flowering plants, demonstrate that these issues are not simply abstract difficulties²². Allowing private ownership of this biological pathway raises some fundamental questions about the balance limits of private and public property created by the existing IPR system.

With continued scientific and technological changes, an increased ability to turn genetic resources into new informational products, and reduced dependency on wild genetic resources in certain sectors, the ground for continued contestations of IPRs is fertile.

²¹ Heller, M and Eisenberg, R (1998) ‘Can Patents Deter Innovation? The Anticommons in Biomedical Research’, *Science*, Vol. 280, 698-701. Location: <http://www.sciencemag.org/cgi/content/full/280/5364/698>.

²² In June 2002 Syngenta Participations AG (the intellectual property arm of the company) filed international Patent Cooperation Treaty application number PCT/EP02/06968. The patent claims protection for an invention that is described as follows:-

“The present invention relates to nucleic acid molecules obtainable from the rice genome that encode protein products that are involved in the development and timing of flower formation in plants and which can be used to modulate flower development, architecture and flowering time.”

3.7 Impacts of ABS policies on Science

Researchers in both academia and industry express significant concern about the negative impact ABS is having upon basic science and upon traditions of trust and collaboration among scientists. Just as scientific and technological developments have dramatically improved our ability to study and use genetic and biochemical resources, the availability of organisms to research has diminished, including in countries with extremely threatened ecosystems where the future of these organisms is uncertain. Many felt that countries were shutting themselves behind an ‘iron curtain’ and setting back their own capacity and development. Craig Venter, Director of the Venter Institute, remarked at a recent public lecture, “If Darwin were alive today, he would not have been able to have done his research.”

A marine researcher in the US feels that “... closing off collaboration and collegiality has very serious consequences for science worldwide. People don’t seem to appreciate that it isn’t just pharmaceutical companies that have an interest in natural products, it is also academic researchers. We used to work in many parts of the world from which we are now excluded, and train students from countries with which we no longer have working relationships. How is this a positive development?” (William Fenical, SCRIPPS, pers. comm., 2005). Rosenthal and Katz (2004) consider the need to develop effective models for collaboration an urgent one. They argue that the research community must “demonstrate that this work can be done in a flexible and accommodating manner that recognizes the environmental and socioeconomic context in which these organisms exist, or we will lose access to them in the near term through politics, and eventually through extinction...”.

A representative from the seed industry believes that the CBD and FAO agreements have led to a narrow band of collaboration between companies in the North who know and trust each other, and that new collaborations with new institutions are considered with increasing reluctance. The net effect is a stifling of research and innovation (Alwin Kopse, Syngenta International, pers. comm., 2005). Others have expressed concern about the effect of the CBD on collection of genetic material for agricultural genebanks, and the reduced *ex situ* conservation of agricultural diversity, as a result.

Another researcher is working on a project called “The Scent of the Vanishing Flora” as a way of educating people about the many reasons why nature conservation is important (Kaiser, 2004). A number of countries would not let him undertake research on the scents of extremely endangered species, although they were found in botanic gardens. “As soon as they know you are from industry, they become very suspicious... There are amazing things in nature, and this research should continue” (Roman Kaiser, Givaudan, pers.comm., 2005).

4. Conclusions

Two key sectors that have used Antarctic genetic resources and are likely to keep on using them are the pharmaceutical and biotechnology industries. A recent example of a

commercially useful compound is a New Zealand company ZyGEM's products forensicGEM (to extract human DNA from crime scene samples) phytoGEM (plants) and prepGEM (animals).

The use of compounds from Antarctica is likely to increase for a variety of reasons. For example, while the limitations of combinatorial chemistry have become evident, breakthroughs in technologies (eg in separation and structure-determination) have made screening mixtures of structurally complex natural product molecules easier, and have expanded the potential role of natural chemical diversity in the drug discovery process. The growing size of the biotech sector and the broadening reach of biotechnology also increase the value of the various inputs into the sector, including natural compounds coming from Antarctica.

Another trend of significance for the Antarctic Treaty System is the developing sophistication of companies approach to benefit sharing. Experience, perceptions, practices are rapidly evolving. Whereas early experiences in this area have generally been negative, a more realistic, pragmatic and less divisive intercourse is developing.

Benefit sharing varies by sector, but standards for best practice in benefit-sharing have become widely accepted. Although unscrupulous and ill-informed companies continue to by-pass these standards, the larger or more socially responsible companies today would not consider genetic resources freely available, or the 'common heritage of mankind'. Responsible companies now see benefit-sharing as a necessary business practice associated with accessing genetic resources. The package of benefits typically includes a mix of monetary benefits like fees per sample, milestone payments, royalties on net sales, and licensing agreements, as well as non-monetary benefits like training, capacity-building, research exchanges, supply of equipment, technology transfer and joint publications.

Despite this progress there are many material differences between the various stakeholders. For example, there remains a sharp difference about what are the appropriate monetary benefits. Another important difference of relevance for use of Antarctic resources what is biopiracy. In recent years researchers and companies have become increasingly concerned about negative attacks and bad press associated with accessing genetic resources. Companies and researchers now consider the threat of 'biopiracy' charges a serious impediment to research. One problem regularly cited is the broad definition of 'biopiracy'. Whereas its initial meaning focused on the patenting of genetic resources based on traditional knowledge without the consent of the knowledge holders, today it is popularly used to describe any commercial activity associated with genetic resources. Another difference of importance for the Antarctic context is the impacts of IPRs. There are divergent perceptions about the role of intellectual property protection in stimulating innovation and revenue; the ethics of patenting life; and the impact they have on research in general. A final point of note for science in Antarctica is that researchers in both academia and industry express significant concern about the negative impacts that IPRs and ABS are having upon basic science and upon traditions of trust and collaboration among scientists.

The changing nature and dynamic of research in the biotech and pharmaceutical sectors will also have an impact on the use of Antarctic compounds. The increasing role of small boutique biotech firms means that smaller companies may be more likely to seek access to genetic resources for their discovery programs. This will mean distinguishing research from development even more difficult. The increasing use of existing libraries will make the issues of access and benefit sharing even more difficult.

ANNEX

PHARMACEUTICAL INDUSTRY: TABLES AND CHARTS

Table 1. Top 10 Pharmaceutical Markets

	June 2003- June 2004 (\$ billions)	Share of global sales (%)	Annual change (%)
USA	228.7	46.0	10
Japan	55.4	11.1	3
Germany	27.8	5.6	6
France	26.4	5.3	7
UK	18.4	3.7	11
Italy	17.9	3.6	6
Spain	12.8	2.6	11
Canada	10.5	2.1	1
China	6.6	1.3	19
Mexico	6.3	1.3	11
Total	410.8	82.6	9

Source: IMS Health, Moving Annual Total (MAT) to September 2004

Table 2. Five year merger history of the top 10 pharmaceutical companies

	Market share (%), based on 2003 sales	Market share (%), based on 1998 sales (pro forma)	Major component companies
Pfizer	10.1	9.0	Pfizer, Pharmacia, Upjohn, Warner-Lambert, Searle
GlaxoSmithKline	6.6	7.2	Glaxo, Wellcome, SmithKline French, Beecham
Sanofi-Aventisa	5.4	5.8	Sanofi, Synthelabo, Hoechst, Rhone-Poulenc, Fisons
Merck & Co	4.8	4.2	
Johnson & Johnson	4.8	3.6	
Novartis	4.3	4.2	Ciba-Geigy, Sandoz
AstraZeneca	4.1	4.3	Astra, Zeneca
Bristol-Myers Squibb	3.4	4.2	Bristol-Myers Squibb, DuPont Pharma
Roche	3.3	3.1	
Abbott	2.8	3.3	Abbott, BASF Pharma (Knoll)
Top 10 companies	49.6	48.9	

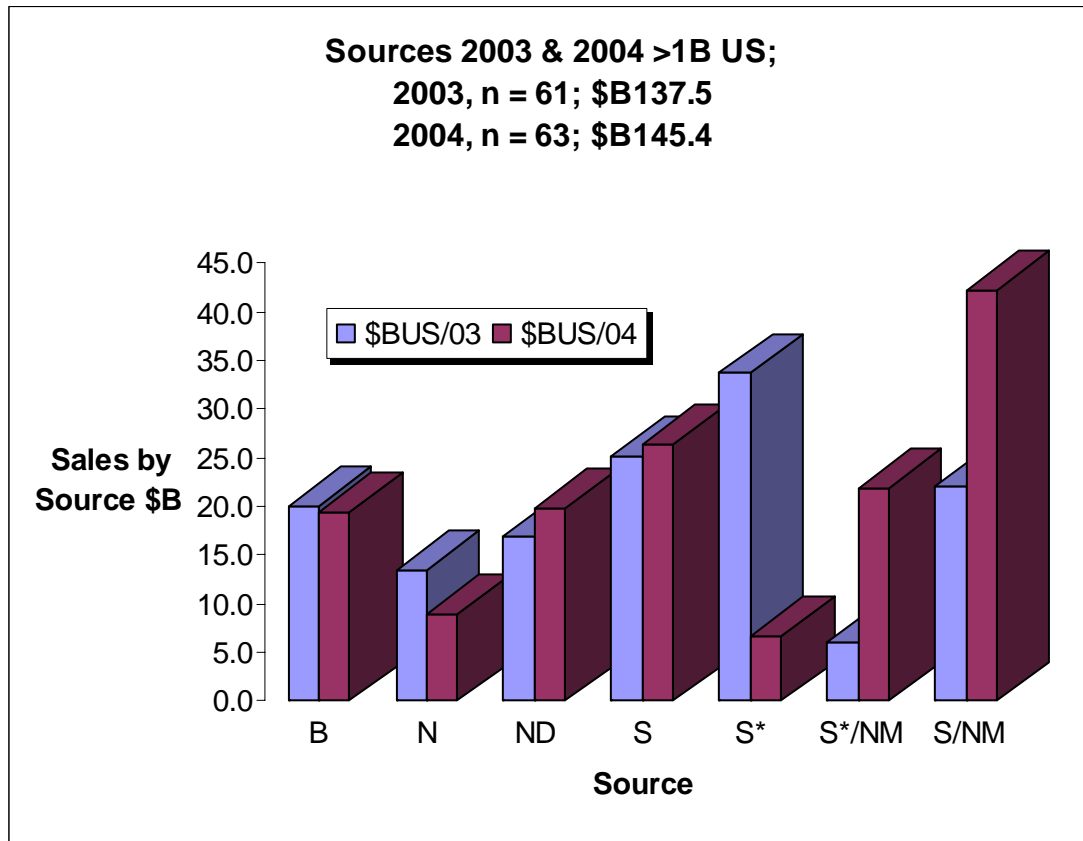
Source: IMS Health, 2004

Table 3. Top 15 pharmaceutical companies 2004

Company	Location	Healthcare revenues (\$bn)	% change from 2003
Pfizer Inc	US	52.5	17.4
Johnson & Johnson	US	47.3	13.1
GlaxoSmithKline Plc	UK	37.3	(5.1)
Sanofi-Aventis Group	France	31.6	9.0
Novartis	Switzerland	28.2	13.6
Roche	Switzerland	25.2	0.2
Merck & Co.	US	22.9	2.0
AstraZeneca Plc	UK	21.4	13.7
Abbott Laboratories	US	19.7	13.9
Bristol-Myers Squibb	US	19.4	3.9
Wyeth	US	17.4	9.5
Eli Lilly and Co.	US	13.9	10.1
Bayer	Germany	10.6	(4.4)
Amgen Inc.	US	10.6	26.3
Boehringer Ingelheim GmbH	Germany	10.1	10.5

Source: MedAd News, 2005.

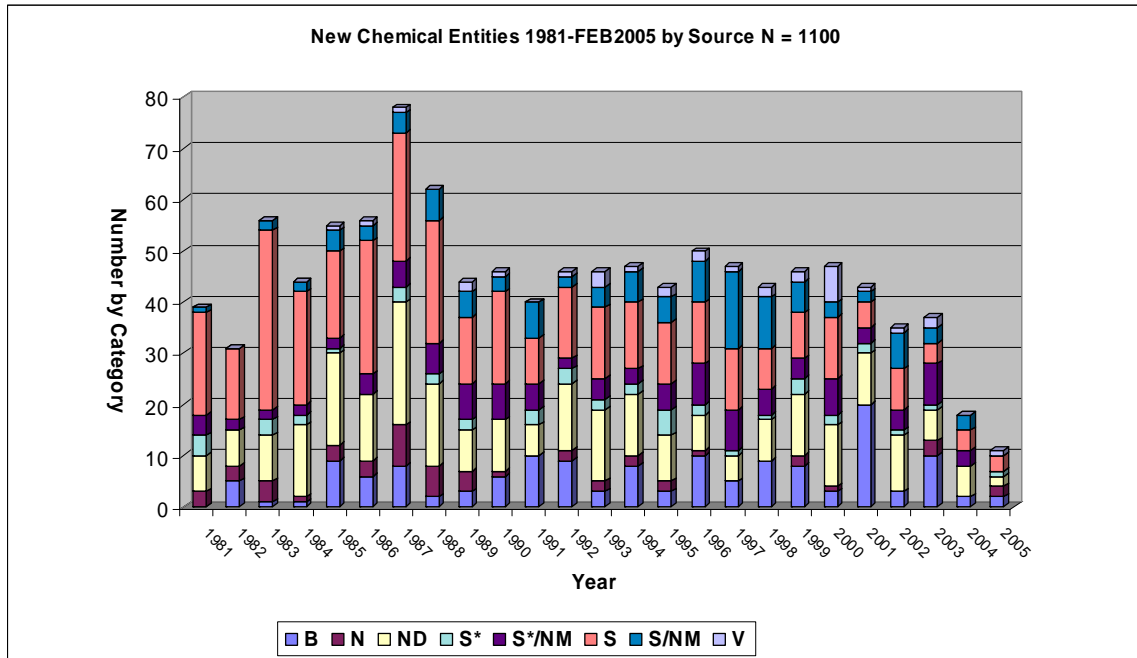
Chart 1. Sales by all categories, drugs >\$1 billion, 2003 and 2004



Source: Newman, 2005

B=biologicals; N = natural products without modification; ND = modified natural products; S= synthetic; S/NM= synthetic by natural product mimic; S*=natural product pharmacophore; S*/NM=natural product pharmacophore or mimic

Chart 2. New Chemical Entities 1981-2005



Source: Newman, 2005

BIOTECHNOLOGY INDUSTRY TABLES

Table 4. Global biotechnology at a glance in 2004

	Global	USA	Europe	Canada	Asia-Pacific
Public company data					
Revenues (\$m)	54,613	42,740	7,729	2,091	2,052
R&D expense (\$m)	20,888	15,701	4,151	782	253
Net loss (\$m)	5,304	4,317	484	408	94
Number of employees	183,820	137,400	25,640	7,370	13,410
Number of companies					
Public companies	641	330	98	82	131
Private companies	3,775	1,114	1,717	390	554
Public and private companies	4,416	1,444	1,815	472	685

Source: Ernst and Young, 2005

Table 5. World's Top 10 Biotechnology Companies

Company	2002 sales (US \$millions)
Amgen	5,523
Genentech	2,212
Amersham	2,305
Serono	1,546
Genzyme	1,329
Chiron	1,276
Biogen	1,148
MedImmune	848
Invitrogen	649
Cephalon	507

Source: ETC Group, 2003

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