Bioscience at a Crossroads:

Access and Benefit Sharing in a Time of Scientific, Technological and Industry Change:

The Pharmaceutical Industry

CBD

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Access and Benefit Sharing in a Time of Scientific, Technological and Industry Change: The Pharmaceutical Industry

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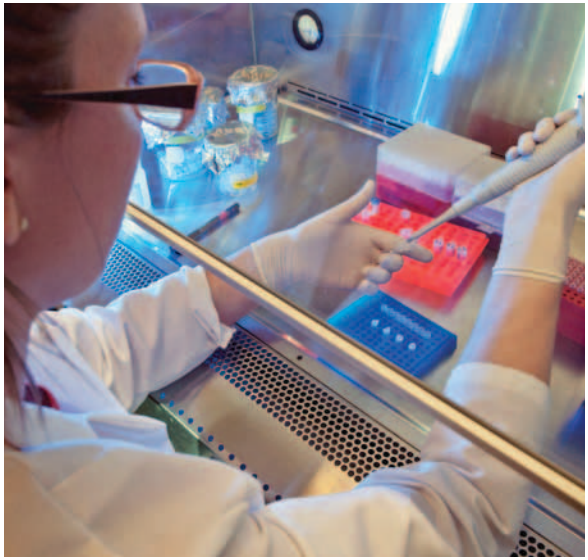
The focus of this brief is on the pharmaceutical industry, with additional policy briefs available on the agricultural, cosmetics, botanicals, industrial biotechnology, and food and beverage sectors. The reader is also referred to the overview brief in this series: Laird, S. and Wynberg, R. 2012. *Bioscience at a crossroads: Implementing the Nagoya Protocol on Access and Benefit Sharing in a Time of Scientific, Technological and Industry Change*. Secretariat of the Convention on Biological Diversity, Montreal. The overview and other industry briefs are available at http://www.cbd.int/abs.

INTRODUCTION

The global pharmaceutical industry is in a time of dramatic transition. Downward pressure on prices from many governments has increased due to the global economic crisis. At the same time, the "patent cliff" has arrived, with patents on many of the most profitable products in all the major companies recently expired or expiring in the next few years. Demand from emerging markets, in particular China, India and Brazil, is expanding and industry revenues continue to grow, but in recent years new drug launches on the market have declined. Leads and synergies promised by consolidation over the last few decades have failed to materialize, and many believe that decades of mergers and acquisitions have in fact hurt the industry's competitiveness and ability to innovate.

Large companies have also re-organized their research and development (R&D) strategies, and are now often buyers of innovation through external alliances and partnerships. The trend for many years has been towards reduced internal basic research in large companies and more discovery taking place in smaller venture capital and government-funded biotech companies, and academia. Large companies now license in compounds of interest, and partner with or acquire smaller groups that have discovered those compounds. They undertake development work on promising drug candidates, but are increasingly less likely to do discovery, particularly natural products discovery.

Natural products research has received increasingly less R&D funding and support in recent years, and most internal programs within large companies have closed over the last decade. This is due to both the business environment and the fact that natural products are largely out of fashion within industry. In recent years, however, scientific and technological advances have transformed our understanding of the natural world and our ability to study it, and the pace of these advances is so rapid that each year brings new insights and tools that could revolutionize natural products research. Already, blockages associated with screening natural product samples, isolating active compounds, and scaling up raw material supply are falling away, and natural products research is quicker, cheaper, and easier than even five years ago.



Business, scientific and technological advances mean that the ways companies and researchers demand access to genetic resources has also transformed. Companies are primarily interested in genetic material today, rather than organisms. What is accessed is often smaller, more difficult to track and monitor, and may not require re-supply. The timing of the Nagoya Protocol to adapt to these new realities, and incorporate lessons learned from the last 20 years of access and benefit-sharing under the Convention on Biological Diversity (CBD), could not be better. Following is a review of some of the business, scientific and technological advances that shape the world in which the Nagoya Protocol will be implemented.

MARKET AND BUSINESS TRENDS

Following is a review of the market and business environment that impacts pharmaceutical R&D and ultimately demand for natural products, including the following elements: global markets and growth, top companies, patent expirations, and industry consolidation.

GLOBAL MARKETS

The global pharmaceutical industry had revenues estimated at $955.5 billion in 2011, with the North American market the world's largest at 41.8%, followed by Europe at 26.8%.[1] Growth in the largest pharmaceutical markets – the US, Europe, and Japan – has slowed significantly in recent years due to numerous patent expirations and generic competition, price cuts in the Japanese and European markets, and the effects of the economic downturn on government spending.[2]

TABLE 1. Total unaudited and audited global pharmaceutical markets by region

REGION	2011 REVENUES (US$ billions)	GROWTH over previous year
North America	347.1	3.0%
Europe	265.4	2.4 %
Asia/Africa/Australia	165.2	13.1 %
Japan	111.2	5.6 %
Latin America	66.7	8.9 %

Source: IMS Health, 2012

In contrast, there is rapid growth in emerging economies such as Brazil, China and India. In 2011, Brazilian and Chinese markets grew more than 20%. Emerging markets

are expected to grow 10-13% through 2016, while major developed markets will grow between 1-4%. Within the next decade, Asia is expected to overtake Europe in pharmaceutical sales, and spending in emerging economies will reach 30% of global expenditures on medicines. When all factors are considered, global spending on medicines will continue to rise, and is estimated to reach $1.2 trillion by 2016.[3]

TOP COMPANIES

US and European companies continue to dominate the pharmaceutical industry, with 5 of the top 10 companies coming from the US, and the other 5 from Europe (Table

"Many observers believe the traditional pharmaceutical company model is broken. As patents expire, pharmaceutical companies are having an increasingly difficult time filling their product pipelines with new blockbuster drugs. Firms are cutting back on the number of research programs they pursue and the number of researchers that pursue them. They are trying simpler internal structures and more complex external alliances. Results, however, are slow in coming."[4]

1). The top 10 companies account for $352.5 billion in sales, which is 59.40% of total revenues of the top 50 companies.[5] However, domestic companies outside Europe, Japan and the US are undergoing rapid expansion, with many in countries like China and India reporting sales in excess of a billion dollars.

TABLE 2. Top Ten Pharmaceutical Companies, 2011

	COMPANIES	SALES (US$ billions)	COUNTRY
1	Pfizer	$58.5	USA
2	Novartis	42	Switzerland
3	Sanofi-Aventis	40.3	France
4	Merck	39.8	USA
5	Roche	39.1	Switzerland
6	GlaxoSmithKline	36.2	UK
7	AstraZeneca	33.3	Sweden/UK
8	Johnson & Johnson	22.4	USA
9	Eli Lilly	21.1	USA
10	Abbott	19.9	USA

Source: PharmExec, 2011

THE 'PATENT CLIFF'

A major cause of decreased growth in revenues in the pharmaceutical industry is the recent spate of patent expirations, and the absence of new blockbusters in product pipelines to take their place. Finding new drugs that work better than what is available today is difficult, and the next generation of targets are more complex and far more expensive to do R&D on.[6] In 2011, the long-feared 'patent cliff' also arrived, with drugs worth $12 billion going off patent, and in 2012 the figure ballooned to around $30 billion in annual sales.[7] By 2015, $200-250 billion worth of branded medicines will have lost patent protection.[8] The result is a likely shift in companies' portfolios from a top end of 3-4 drugs with revenues of many billions of dollars, to 10-12 drugs with revenues of $500-800 million.[9]

INDUSTRY CONSOLIDATION

For the last few decades, industry acquired new technologies and novel drug candidates through mergers and acquisitions, which boosted short term revenues and a company's stock price. Over the past 30 years, 34 companies consolidated into 7 very large companies.[10] However, promised gains in productivity failed to materialize. As John LaMatinna, former president of Pfizer Global R&D said, mergers and acquisitions have instead been "a major factor in the decline in R&D productivity… the fact is that, due to industry consolidation as well as some companies dropping their pharmaceutical R&D, there is far less competition in this industry than there was a decade ago." Fewer companies also mean fewer researchers working to discover new drug candidates; overall employment in pharmaceutical R&D has been creeping down since 2009.[11]

IMPLICATIONS FOR ABS AND THE NAGOYA PROTOCOL

Implications of these market and business trends for policy on access to genetic resources and benefit-sharing (ABS) are multifaceted. Unlike twenty years ago, large companies are no longer demanding access to genetic resources on any scale. Most have closed their internal natural products programs, and what natural products

"A confluence of internal and external factors is now transforming the landscape for discovering, developing, commercialising, and marketing pharmaceuticals, and the old rules simply no longer apply to an industry now facing (1) pressure to increase sales, (2) pressure to decrease development time and cost, (3) competition from smaller companies, (4) looming patent expirations, (5) increased regulatory scrutiny, and (6) unparalleled pricing pressures"

– Phil Kearney, Director of Licensing and External Research, Merck Sharp & Dohme (2011).

discovery exists is largely undertaken through external collaborations. R&D budgets across industry are shrinking, which means that industry's modest interest in access to genetic resources for natural products research is further reduced. As a result, inappropriate policy regimes could have a real and lasting impact on natural products research, which must compete with other research programs for support within companies.

Smaller discovery companies and academic research laboratories, often funded primarily by government, undertake the bulk of natural products research today, but as we will discuss below, few undertake collections overseas. Large pharmaceutical companies are well-informed of the CBD and avoid collections that do not have necessary approvals from provider country governments. Smaller companies and academics, however, tend to be more inconsistently informed about the CBD, and are more numerous and dispersed, and therefore difficult to monitor.

Governments could undertake outreach programmes to educate and build capacity in academia and smaller companies; could raise awareness in all user groups about their obligations under the Nagoya Protocol; and could draw a larger pool of individuals from academia and industry into national and international policy processes to contribute views and experiences, and strengthen the effectiveness of ABS measures.

RESEARCH AND DEVELOPMENT TRENDS

The impact on pharmaceutical R&D of these business developments is significant. Although still the most R&D-intensive sector,[12] well above the high-tech and manufacturing industries, pharmaceutical R&D budgets are contracting. In 2011, for example, Pfizer made deep spending cuts in its R&D budget of $1.5 billion[13] and Sanofi recently cut R&D by 12% from 2008 levels to about $1.1 billion.[14] The number of R&D programs and researchers across industry has shrunk significantly in recent years. At the same time industry support for R&D has declined, government funds for basic research and the discovery stage of pharmaceutical development have decreased due to the economic crisis. Some estimate that in countries with significant pharmaceutical R&D, government's contribution to discovery is 84% of that spent by the sector[15], and all agree it is a large part of early stage research, so reduced government expenditures have a very negative impact on R&D overall.

Pharmaceutical R&D in Europe, USA, and Japan ($bnUS) 1990-2011

	USA	EUROPE	JAPAN
2011	$38.5 (est)	$27.5 (est)	n.a.
2010	$40.7	$27.8	$12.8
2005	$31	$22	$10.5
2000	$21.3	$17.8	$7.5
1995	$11.9	$11.4	$6.4
1990	$7.8	$6.8	$5.1

Source: EFPIA, 2012

DECLINE IN INDUSTRY NATURAL PRODUCTS PROGRAMS

Many large companies with active natural products programs in the 1990s and 2000s, and associated bioprospecting efforts overseas, have closed their programs. This includes Merck, Bristol Myers-Squibb, AstraZeneca, GlaxoSmithKline, and Monsanto. Natural products research is more commonly found today in smaller discovery companies, semi-governmental or governmental entities, and universities around the world. Elements of large pharmaceutical natural products programs were spun off into non-profits, or semi-governmental entities (particularly in Europe), and compound libraries were given away or sold off cheaply. In 2011, for example, Merck gave its library of natural compounds to a non-profit, including 100,000 extracts representing 60% of all known plant genera.[16]

The few remaining large companies with internal natural products programs include Novartis, Pfizer (from its acquisition of Wyeth), and Takeda, however many of the large companies with shuttered natural products programs still participate in ad hoc and more involved external partnerships. Many large companies also have natural product drug candidates in their pipelines from earlier research efforts, and these continue to emerge on to the market and contribute significantly to their bottom lines (Newman and Cragg, 2012).[17]

Reductions in natural products research in large companies have not been balanced by growth in smaller companies and academia. These groups are impacted by the global economy as governments in financial straits cut research funds, as well as by research fads that impact private sector funding. Venture capital funds are scarce, funding for biotech companies is increasingly skewed towards larger companies, and support is increasingly for products well into development rather than early stage discovery.[18] Today, many smaller companies and academic research labs are having a hard time finding money.

In addition to natural products serving as the starting point for drug development, they are also elements of vaccines, inactive parts of final products, tools in the research process, and tools in the production process.[19]

"One of the biggest changes in natural products discovery is that of scale. We no longer have to collect large quantities of an organism and return it to a lab and work on it. We can work with much less material and often still get the same answer. Biological assays are much more powerful, and we can also use chemical synthesis – which has also improved in recent years – to supply large screening programs... The power of genetics has also changed dramatically. With a miniscule amount of any material, we can get the genetic material out, sequence it, and learn how those chemicals might be programmed genetically to see if we can engineer it easily in the laboratory. Genetic information is now loaded onto public websites and even if the organism was collected from a remote location, once released publicly it is out there for anyone to see and use."

– Brad Moore, SCRIPPS

Along with microorganisms, marine toxins and other agents are used in cell biology and pharmacological research, and are sold as research biochemicals.[20] In 2010, an estimated 5% of the $160 billion chemical market and 60% of all fine chemicals were produced using methods that utilize microbes.[21] These uses of natural products are more difficult to identify and track than compounds that contribute biological activity to the final product, but will likely only increase in importance in the coming years. As part of the ABS policy process, governments should clarify the products and activities that fall under the new ABS regulations, bearing in mind that, in accordance with the Nagoya Protocol (Article 2(c)),[22] "'utilization of genetic resources' means to conduct research and development on the genetic and/or biochemical composition of genetic resources...".

ADVANCES IN SCIENCE AND TECHNOLOGY

At the same time the business realities of today make it more difficult to do natural products research, significant advances in science and technology make natural products a great deal less slow, costly, and difficult to work with than previously. These scientific and technological advances address detection, characterization, purification, supply and other issues associated with small molecule natural products.[23] Over the past decade, dramatic changes have also occurred in researchers' ability to access the genome sequences that encode the enzymes responsible for the biosynthesis of secondary metabolites, or compounds of interest. Sequencing of whole genomes has become 'commonplace, rapid, and relatively inexpensive', with the number of whole bacterial genomes entering the public literature doubling every 20 months.[24] The use of "omic" approaches – genomics, proteomics, metabolomics, transcriptomics – are now regular features of natural product research.[25]

One result of new technologies is that discovery of new molecules requires only a few micrograms, a fraction of the material needed even ten years ago.[26] "In the old days, we might require a milligram of material, but today can do with a microgram and nanogram quantity" one researcher from a large company said. "The amount we used to screen 100 samples in the past can now do million sample screening." Added to this, advances in science and technology are also reducing the need to harvest or cultivate raw material for manufacture of a commercial product. This means that the need to recollect material in provider countries for further research on a promising compound, or for product manufacture – points of contact in many ABS agreements – may not arise at all.

CHANGED UNDERSTANDING OF RELATIONSHIPS BETWEEN ORGANISMS

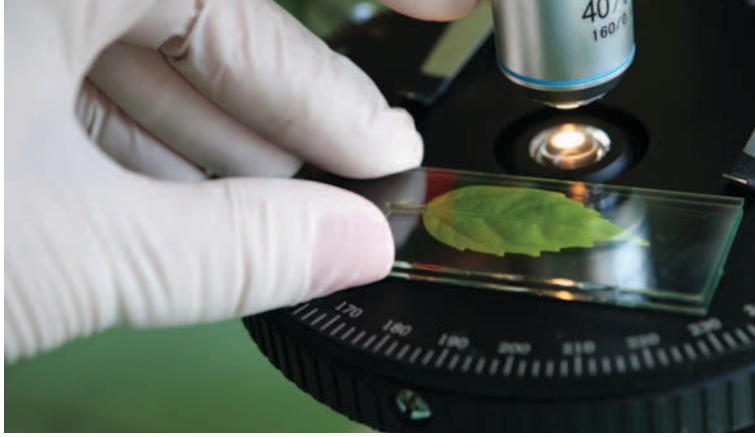
Scientific and technological advances are also dramatically expanding our understanding of the natural world, relationships between organisms, and the ways natural products can contribute to human health. It is

increasingly recognized, for example, that distinctions between organisms – e.g. plant, invertebrate, microorganism – are not always clear-cut, and that promising compounds are often produced by symbiotic microbial species.[27] Compounds from insects are traced back to the microorganisms living in their gut; marine invertebrates undertake the bulk of chemistry that produces an interesting compound, which is then modified by associated microorganisms, or vice-versa; and toxins in bird feathers or those secreted by reptiles have been found to originate in the insects they eat. Through co-evolution a spectrum of complex community associations, rather than single organisms, appear to be the source of many promising compounds.

As Gordon Cragg and David Newman of the US National Cancer Institute said: "As a result of these discoveries, it now may well become extremely difficult to follow the trail of a given producing organism, particularly since the actual producer may be commensal or epiphytic microbes that cannot be detected except in well-equipped laboratories with available experts in genomic techniques. Although there are analytical systems that might be able to differentiate between microorganisms of similar taxonomy but of different strain lineages, such techniques are currently only available in a very few laboratories, all in developed nations. Suitable safeguards will have to be developed, but current practice may have to rely on trust."[28]

DEMAND FOR ACCESS: MICROORGANISMS

Over last 15-20 years, scientific and technological advances have transformed our ability to research and use microorganisms, and there has been a dramatic shift in industry interest towards marine and terrestrial microorganisms, and away from plants. Researchers can now study many of the 99% of microorganisms that were invisible to them under previous laboratory conditions[29], and can look more deeply within each organism's genome to detect biosynthetic pathways that produce a wider range and number of



"We get microorganisms by picking up some of these old collections that no one wants anymore, and now have one of the largest collections in the world. But with modern techniques, we can also scratch a little dirt off the sidewalk, and can scan out the microbial genome universe. DNA pervades the environment around us, and the code is a citizen of the world. We don't need whole organisms, just a snippet of DNA, we don't need to sequence whole genomes. As a result, overseas collections aren't really necessary. "

– Alexis Borisy, CEO, Warp Drive Bio.

interesting compounds. Chemical and biological diversity has therefore become available from sources researchers thought already examined and exhausted. The genomes of microorganisms can also be more easily sequenced than those of plants or insects, and microorganisms can be grown in culture, which makes it easier for companies to deal with supply issues as research progresses.

DEMAND FOR COLLECTIONS

Demand for access to 'new' biological diversity from field collections around the world is less than in previous years. New research tools mean that diversity found in companies' backyards and existing collections, particularly that found in the previously inaccessible genomes of microorganisms, can keep researchers busy. Overseas collections are significantly reduced in scale from the 1990s. Plants – which share less genetic material than microorganisms and so produce more novel compounds across the globe – were the focus of many bioprospecting collections, but are not of interest to most companies now. Microorganism and marine organism collection programs still continue in some academic institutions and commercial companies, many funded by governments. But with the shift in focus to genes and looking deeper within organisms, and most researchers having easy access to large internal and external compound libraries that can now be examined in new ways, the value of mass scale collections in high biodiversity regions has been reduced.

However, novelty and diversity from nature will always be of interest. As Frank Koehn, head of the Natural Products Unit at Pfizer said: "We will always be interested in new organisms and compounds. One way to get this is to go to some bizarre place in the world (inside a live volcano or the bottom of the ocean) to find new bugs, but another way is to focus on the vast majority of bugs that are not culturable. In your backyard you can dig up a teaspoon of soil which will contain 10,000 organisms or more, but we can only culture 1% of these organisms, and can't get others to grow in colonies or a fermentation vial, so we can find new organisms by finding new ways to culture them. In the wild these organisms are very dilute and they live with thousands of other organisms. In the lab we grow them at high cell density, in uniform populations. Another way is to not worry about the organisms, only the DNA – metagenomics – and just take the DNA out of the soil and put those genes into an organism you can cultivate. This is still in its early stages, but it allows us to find a deep well of biodiversity."

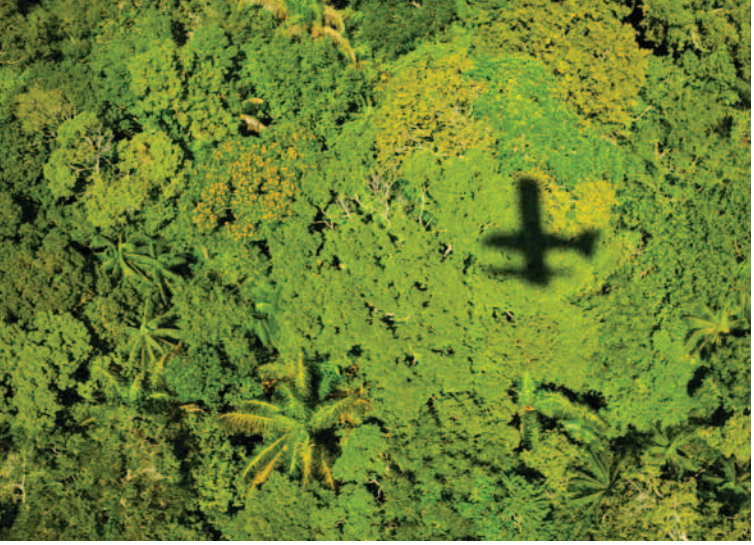
DEMAND FOR TRADITIONAL KNOWLEDGE

The role of traditional knowledge (TK) in pharmaceutical discovery has been relatively small in recent decades and with advances in science and technology orienting R&D ever more towards genes, and away from organisms, it is likely to grow smaller. Increased interest in microorganisms and marine organisms as the source of genetic diversity and leads, and a decline of interest in plants, further reduces the potential role of TK in R&D. Industry is also focused on therapeutic categories that do not feature prominently in traditional medicine. In sum, pharmaceutical R&D today does not easily integrate TK, although some companies consult TK literature and databases if a species shows promise.

IMPLICATIONS FOR ABS AND THE NAGOYA PROTOCOL

Scientific and technological advances since the CBD entered into force have changed the way companies use and value genetic resources. Significant developments include reduced demand for access to genetic resources in high biodiversity regions, as companies look deeper within organisms found in their own backyards and existing collections. New understanding of the extent to which microorganisms share genes around the world mean that an interesting compound produced by an organism collected in one country can often be found in many other countries, including the researchers' own. The quantity of material required to discover new molecules is also a fraction of that needed even ten years ago, with only a few micrograms sufficient in many cases. Return to provider countries to obtain raw material for expanded research or manufacture has long been an important component of monitoring in bioprospecting agreements, but this may no longer be a critical step in the R&D process. Additionally, genetic information is now published and made available in the public domain, creating further complications for monitoring in the absence of effective ABS measures.

An opinion that is widely repeated across academia and industry is that partnerships are the best way to achieve equity and benefit-sharing over time, and to build capacity within provider countries to undertake research on their own threatened biological diversity and genetic resources. As Gordon Cragg of the US National Cancer Institute (NCI) put it: "I've always maintained that natural product drug discovery and development is an international collaborative effort – no one country is dominant. That is why I think if source countries can develop viable and not too restrictive policies this can be a win-win situation for everyone. If policies are too restrictive, particularly with microbes as a source of new chemistry and potential new drugs, companies will just study the microbial resources they have in their libraries or their own backyards. The microbial area makes protecting countries' rights very tricky, since companies can find compounds discovered in microorganisms from one country in another – much more so than for plants. This is why NCI's policy has always been that the place where the original collection and discovery was made is the one that should benefit, and this is even more important today." [30]



THE NAGOYA PROTOCOL: RESPONDING TO SCIENTIFIC, TECHNOLOGICAL, POLICY AND MARKET CHANGE

There have been real and concrete gains under the CBD in the last 20 years. For example, large pharmaceutical companies support the need to sign agreements, reach mutually agreed terms, and share benefits. Benefit-sharing packages that include a wide range of monetary and non-monetary benefits over time have become standard practice. Collections by pharmaceutical company staff when they go on holidays, once widespread, have become a thing of the past. National sovereignty over genetic resources is widely accepted, as is the need to get permission for any collections. However, numerous unresolved issues and concerns remain.

The Nagoya Protocol is well-timed to respond to these concerns, clarify and streamline access procedures and requirements, build upon lessons learned in the last two decades, and integrate new scientific, technological and business realities into ABS measures. For example, implementation of the Nagoya Protocol can respond to the following specific concerns expressed in recent years:

Helping researchers and companies follow ABS laws – Many researchers and companies have expressed concern about a lack of capacity within governments, and an absence of guidance on how to navigate ABS measures in many countries. In addition to supporting information-sharing mechanisms and tools at the international level like the ABS Clearing-House (Article 14), the Nagoya

Protocol encourages governments to establish information dissemination and outreach programs, and to help researchers identify and follow what will be streamlined ABS procedures. Companies and academic researchers can also benefit from capacity built within user and provider country governments under the Protocol, including assistance with efforts to establish agreements with providers.

Legal certainty and clear, workable regulations – Difficult, time-consuming and bureaucratic regulations and permitting procedures, and an absence of legal certainty when acquiring genetic resources from some countries, are regarded by many companies as major stumbling blocks in natural products research. The Nagoya Protocol seeks to address these concerns and create an environment of legal certainty and mutual trust by requiring Parties to designate one or more competent national authorities to oversee ABS permitting. In addition, ABS national focal points will make information available on procedures for obtaining prior informed consent and reaching mutually agreed terms, including from indigenous and local communities and other relevant stakeholders (Article 13).

Building the capacity of governments – Article 22 of the Protocol also calls for building the capacity of governments to effectively implement the Protocol, including the development and implementation of ABS legislation, negotiation of mutually agreed terms, and improved capacity to undertake research on national genetic resources. Article 21 also promotes awareness-raising more broadly within both provider and user countries.

Defining the scope of ABS measures – Many in industry have expressed concern about the inclusion of biological and other resources within the scope of ABS measures. The Protocol, however, does not expand the scope of these measures to include the commodity trade of raw materials, local trade, or subsistence use. It specifically applies only to genetic resources and traditional knowledge as defined within the scope of Article 15 of the CBD (Article 3). In addition, as further clarified by the Protocol

(Article 2(c)), "'utilization of genetic resources'" means to conduct research and development on the genetic and/or biochemical composition of genetic resources…". Implementation of the Protocol within countries can further help to clarify and resolve the issue of scope.

Responding to scientific and technological advances – The Nagoya Protocol arrives at a time when science and technology have transformed the demand for access and the use of genetic resources. Many earlier approaches to monitoring, benefit-sharing triggers, and control of information must now be re-examined. The process through which the Protocol is implemented provides governments with an opportunity to update and modify previous strategies, and accommodate dramatic new scientific, technological and business realities.

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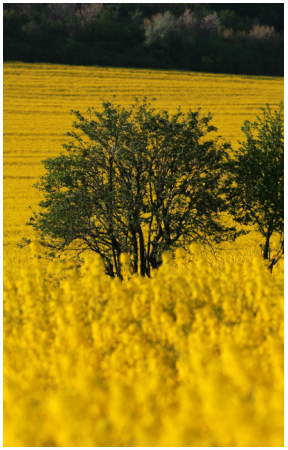

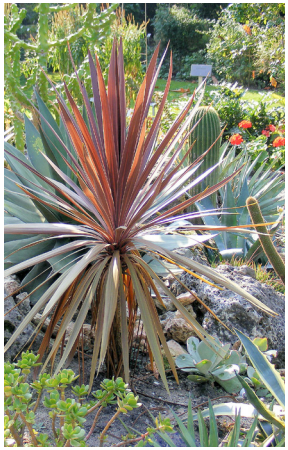

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