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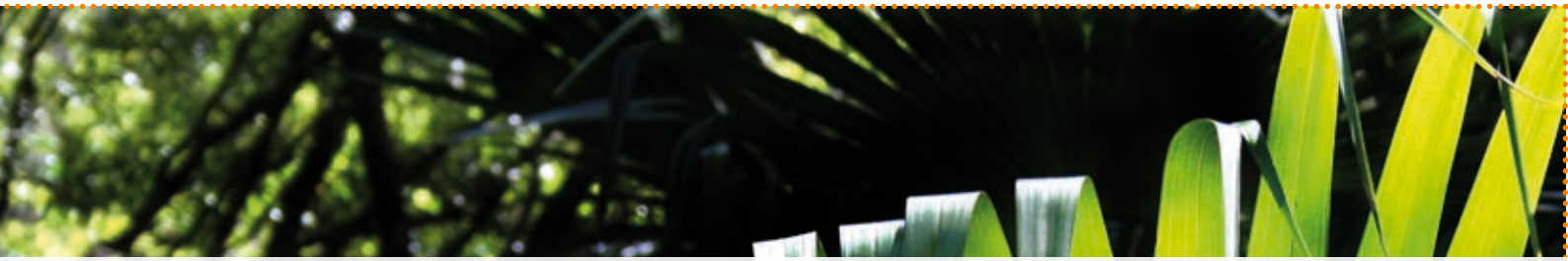
European Federation of Pharmaceutical Industries and Associations

GOOD BUSINESS & PRACTICE CASE STUDIES ON BIODIVERSITY

EFPIA Submission in response to CBD COP 8 DECISION VIII / 17



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This document was drafted by Brendan Barnes and Lorraine Gallagher, EFPIA

CREDITS

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LIST OF ABBREVIATIONS

ABS ..... Access and Benefit Sharing

CBD ..... Convention on Biodiversity

CNA ..... Competent National Authority

COP ..... Conference of the Parties

GR ..... Genetic Resource

GMP ..... Good Manufacturing Practices

HTS ..... High Throughput Screening

ICC ..... International Chamber of Commerce

IP ..... Intellectual Property

IR ..... International Regime

IUCN ..... International Union for the Conservation of Nature & Nat. Resources

MAT ..... Mutually Agreed Terms

NP ..... Natural Product

PIC ..... Prior Informed Consent

TRIPS ..... Trade Related and Intellectual Property Rights

1 > INTRODUCTION

In February 2004, the Seventh Conference of the Parties to the Convention on Biological Diversity (in (COP) (Decision VII/19D)) mandated the Ad Hoc Open Ended Working Group on Access and Benefit Sharing

> *"…to elaborate and negotiate an international regime on access to genetic resources and benefit sharing with the aim of adopting an instrument/instruments to effectively implement [key provisions of the CBD]."*

The German Government (and indeed other European governments), which hosts the Ninth Conference in 2008, is keen to see significant progress towards such a regime. As a critical stakeholder in the debate surrounding access and benefit sharing (hereafter ABS), the research-based pharmaceutical industry is pleased to respond to the call by the secretariat of the CBD to develop and promote the business case for biodiversity.

1.1 | AIMS

This submission aims to advance the debate regarding how best to achieve the objectives of the CBD. Previous debate on the issue of access and benefit sharing (hereafter ABS) has at times been marked by a polarisation of standpoints and a lack of understanding of the practical complexities, subtleties and implications of the issue. It is important that policy makers and stakeholders involved in the debate are fully aware of what is actually at stake for various stakeholders and indeed for society in general.

EFPIA considers that the contribution that pharmaceutical research could make in advancing the goals of the Convention will be put at risk if the International Regime is over-prescriptive or inflexible in the way it deals with business. This paper, therefore, aims to increase awareness of the issues at stake from a commercial point of view and present case studies of good business practice built on partnership in order to move the discussion forward.

1.2 | STRUCTURE

This document will provide an overview of the issues surrounding the use of genetic resources by the research-based pharmaceutical industry and will be divided into three main sections:

(i) Understanding the business case for biodiversity
(ii) Case studies: successful and responsible business practice
(iii) Moving the debate forward - recommendations and conclusions

1.3 | KEY POINTS

It is through a greater understanding of the relevant issues, which includes an appreciation of the practical implications for the research-based pharmaceutical industry, that a solution satisfying all involved stakeholders is most likely to be found. It is critical that pragmatism and practicality remain central to the debate.

Any ABS framework or policy tool proposed must be evaluated in terms of its usefulness to safeguard CBD objectives and its ability to facilitate access to genetic resources. EFPIA would like to emphasise the following regarding the position of the industry:

- **The research-based pharmaceutical industry fully supports the aims and objectives of the Convention of Biological Diversity** and is committed to the sustainable use of biological diversity and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources."[1]
- **Industry should be, and wants to be, involved** in all stages of the development of the regime
- **Without research investment, there will be no benefits** or commercial rewards to share with countries of origin nor technology to transfer to those countries
- **Companies and others who invest in research must have legal certainty** as to what is needed to ensure the security of their investment.

[1] *CBD, Article 1*

2 › UNDERSTANDING THE CURRENT RESEARCH ENVIRONMENT

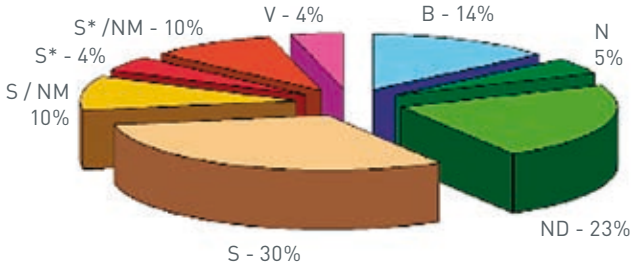
2.1 | THE CURRENT CONTEXT AND CHALLENGES FACED BY INDUSTRY

Research using natural products

Natural products have a strong track record as pharmaceuticals. In times when scientific capabilities were more restricted, they were the main source of new pharmaceutical concepts. One study suggests that over 42% of the 1184 new chemical entities that reached the market over the last 25 years have their origins in nature (Newman et al, J. Nat. Prod, 2007). The full analysis in the paper classified the source of all New Chemical Entities as follows:

[Figure 1]

All new chemical entities, 01/1981-06/2006, by source (N) 1184).



B . . . . . Biological
N . . . . . Natural product
ND . . . . Derived from a natural product and is usually a semisysnthetic modification
S . . . . . Totally synthetic drug, often found by random screening, modification of an existing agent
S* . . . . . Made by total synthesis, but the pharmacophore is/ was from a natural product
V . . . . . Vaccine
NM . . . . Natural product mimic

One of the most valuable contributions of the above survey is that it highlights very clearly that, although a very limited number of natural products are actually approved as medicines, natural products make a much wider contribution to the research process as a whole.

This track record is even stronger in cancer, and well-known examples include Taxol (from the roots of the bush Taxus brevifolia) and Doxorubicin (produced by the bacterium Streotomyces peucetius). These examples, and many other examples of commercial medicines in other therapeutic areas, attest to the value of naturally derived molecules in medicine.

Anti-Cancer Agents	Origin
Paclitaxel (TAXOL)	Roots of the bush Taxus brevifolia
Vincristina (ONCOVIN)	Leafs of *Catharanthus roseus ocellatus*
Irinotecan o CPT-11 (CAMPTOSAR)	Leaf of the plant *Camptoteca acuminata*
Etoposido (VEPESID)	Roots of the plant *Podophyllum peltatum*
Doxorubicina (ADRIAMICINA)	Bacterium *Streptomyces peucetius*

Many believe that molecules isolated from natural sources often contain structural features that are outside the scope of combinatorial or synthetic medicinal chemistry, for example they are often larger, more rigid and more chirally complex (Feher M. and Schmidt J.M., J. Chem. Inf. Comput.Sci.43, 2003). Such novel chemical structures often result in new modes of action and open up the potential of new ways to treat cancer and other diseases.

Despite this, the attraction of using natural products for pharmaceutical research has diminished within the industry. Within modern drug discovery, natural product approaches have been deprioritised by the industry (Koehn and Carter, Nat. Rev. Drug Discov. 4, 206, 2005). Concerns include:

- Discovery timelines - typically slower than synthetic approaches
- Sourcing logistics - scientific or political hurdles make many species inaccessible
- Reproducibility - organisms change their chemistry with season, age, etc
- Identification - complex extracts containing many nuisance compounds
- Production - about 80 % of natural structures are intractable to synthesis, and large-scale production of most is impossible.

Important technological changes underlie the shift in research strategies and this has created competition between different research strategies. The overall

Reasons for the decline in pharmaceutical industry natural products research in the last decade[2]

1. Introduction of high-throughput screening against defined molecular targets (and the move from natural products extract libraries to 'screen-friendly' synthetic libraries);
2. Development of combinatorial chemistry, which appeared to offer more drug-like screening libraries of wide chemical diversity;
3. Advances in molecular biology, cellular biology, and genomics, which increased the number of molecular targets and prompted shorter drug discovery timelines;
4. Declining emphasis among major pharmaceutical companies on infectious disease therapy, a traditional strength of natural products;
5. Possible uncertainties with regard to collection of biomaterials as a result of the Convention on Biological Diversity.

effect has been to place the understanding of disease at the centre of research to a greater degree than before.

Advocates of natural products research will point to the historical track record and the low current productivity of the pharmaceutical R&D and argue that these changes have not brought positive results. Others will argue the contrary. Where there is consensus is that pharmaceutical R&D is a socially vital but difficult and complex process, which largely depends on the legal and regulatory environment for its viability.

Unfortunately, the post-CBD regulatory environment has not been a positive influence and it is easy to conclude that the overall effect has been to deter exactly the type of research that the CBD should promote. 15 years after the signing of the CBD, which originally aimed to create simple, workable legal and regulatory frameworks for ABS, providers and users of genetic resources are 'increasingly estranged, and the environment in which bio-prospecting takes place is often characterized by misunderstanding, mistrust, and regulatory confusion'.[3]

This section will highlight some of main challenges faced by industry regarding the use of genetic resources and their efforts to ensure ABS compliance, namely the following:

(a) Incomplete frameworks at national level

(b) Legal uncertainty and inconsistency

2.1.1 Incomplete frameworks at national level

The regulatory framework for industry working with genetic resources and ABS is far from comprehensive. Following the entry into force of the Convention of Biodiversity in 1993, the adoption of the Bonn Guidelines in 2002 was designed to accelerate the implementation of ABS provisions. However, out of the 188 Contracting Parties to the CBD, only 26 have adopted ABS laws and procedures and these existing ABS measures are often 'sectoral and patchy'.[4]

Where laws exist, they may not be adequate. A 2005 report on the commercial use of biodiversity commissioned by the secretariat of the Convention for the Ad Hoc Open-ended Working group on ABS[5], concluded that there remain many gaps in national legislation despite the explicit aims of the 2002 Bonn Guidelines. These gaps pose significant challenges

[2] *Koehn, FE and GT Carter (2005), The Evolving Role of Natural Products in Drug Discovery, Nature Reviews, Drug Discovery, vol 4, March 2005. www.nature.com/reviews/drugdiscovery.*

[3] *Laird, S & Wynberg, R (2005): The Commercial Use of Biodiversity: an update on current trends in demand for access to genetic resources and benefit-sharing, and industry perspectives on ABS Policy and implementation - UNEP/CBD/WG-ABS/4/INF/5, page 5. Report commissioned by the CBD for the fourth meeting of the Ad Hoc Open-ended Working Group on ABS - available here*

[4] *Ibid., p.36,* [5] *Ibid.*

for industry wishing to negotiate ABS with a provider country and must be addressed in any discussion regarding a potential ABS framework. Likewise, a gap analysis is vital to establish what is needed in order to fill the gaps at national level highlighted in the following points:

- The 2002 Bonn Guidelines recommend that each country designate a **competent national authority (CNAs)** or national focal point for ABS. Most countries have yet to designate or clearly define the tasks of CNAs, and industry regularly experiences difficulties locating government officials that can clearly explain and authorise access to genetic resources (GR) for collections and research.
- Many **governments remain ill-informed** about the scientific and commercial realities of bio-prospecting and industry often faces undue bureaucracy and delays before receiving permits;
- Without implemented regulatory regimes, it is **effectively impossible to prove compliance** in many cases.
- There is often a **lack of "political will"** within governments to improve this situation and industry may often face unrealistic expectations and **excessive transaction costs.**[6]

2.1.2 The need for legal certainty

Given that allocation of significant resources is needed for any R&D investment, ensuring a secure investment is paramount for industry. In the field of natural product research, the legal framework at national level is often inadequate and, as underlined above, the tendency has been to explore other forms of research, which involve natural products to a lesser extent. Those who do use natural products for research are faced with many challenges in understanding the nature of any national legal obligations, e.g. the inconsistent and variable use of core concepts, which may render it impossible for a potential developer or user of genetic resources to know if the ABS requirements in force in any particular country have been met.

Researchers are left to guess whether obligations they are subject to are satisfied in each country because requirements are often opaque and imprecise. Many applicants face increasing delays, fines, or even loss of the right to patent his invention if an incorrect determination is made. These barriers are more than sufficient to make a scientifically valid research strategy commercially unsustainable.

There are three areas in particular, where legal certainty is lacking:

(i) The nature of the material subject to regulation
(ii) Requirements regarding in-situ and ex-situ materials
(iii) The nature and regulatory treatment of "derivatives"

Each of the issues highlighted below, and several others, need to be carefully addressed in devising national access and benefit laws and the international regime, which the Ad Hoc Open Ended Working Group is mandated to elaborate.

(i) Nature of the material subject to regulation

The meaning of terms such as 'genetic resources' and 'biological resources' is not clearly or adequately addressed in national legislation and in proposals for a disclosure requirement. In addition there is a need to distinguish between human and non-human material.

Some other unanswered questions regarding genetic resources:

- Would an international regime include only GRs or a broader class of "biological resources"?
- Will human GRs be excluded?
- Will non-human GRs found in humans be excluded? e,g. concerning HIV, H5N1 virus, malaria parasite
- What is "associated traditional knowledge"?

Each of these issues, and several others, will need to be addressed as part of the process of building an International Regime.

(ii) Requirements regarding in-situ and ex-situ materials

Regarding the definition of 'origin' there appears to be various interpretations, including both in-situ and ex-situ sources.

Many genetic resources, some of which may be valuable for pharmaceutical research, have long since been removed from their original natural environment

[6] *Mathur, E, C Constanza, L Christoffersen, C Erickson, M Sullivan, M Bene, and JM Short (2004), 'An Overview of Bioprospecting and the Diversa Model', IP Strategy Today. No 11 - 2004, 1 -21.*

(examples include vectors, plasmids, cell lines and other genetic resources that have been used for decades). Many have become commodities or staple commercial products in the trading system.

National laws, and any international ABS regime, must address how such materials are to be dealt with.

(iii) The nature and regulatory treatment of "derivatives"

The CBD seeks to promote the "fair and equitable sharing of the benefits arising out of the utilisation of genetic resources".

Products "arising out of the utilisation of genetic resources" are commonly referred to in the debates as "derivatives".

National laws and any international regime need to address whether and how to define, and whether and how to regulate use of and trade in, "derivatives" and, in doing so, the practical effect of decisions on such issues must be appreciated.

It must be acknowledged that, taken literally, derivatives could include such things as loaves of bread and bottles of wine as each "arise(s) out of the utilization of genetic resources". Is it really intended that national laws and any international regime should regulate the sharing of benefits made by those who manufacture and sell wine or bread. If not, what should and should not be regulated?

It is vital to consider carefully the nexus or connection that is needed between the final product which generates commercial value and a genetic resource that might have been used in the development process that must exist to trigger any obligation under national law or an international regime.

At one end of the spectrum of possible uses of genetic resources is the use that the CBD was intended to capture. Such a situation arises when a genetic resource - for example, a leaf - is obtained from a CBD member, a compound is isolated from that leaf and the compound - without modification - becomes the active ingredient in a drug.

At the opposite end is the situation in which a company uses purely synthetic mechanisms to develop novel small molecule compounds, but tests the utility of those compounds with commonly available or staple genetic resources, such as cell lines. Under such a scenario, a genetic resource is used as a tool in the development process but the final product does not incorporate a genetic resource.

National laws and any international regime must clearly define the nexus between the end product and the genetic resource, which triggers legal obligations in order to ensure legal certainty for any user of genetic resources. In addition, in order to comply with the CBD, this should be done in such a way as to facilitate access for environmentally sound reasons. Potential scenarios, which highlight the need for such clarity, are presented in the Annex 6.3.

And to the extent that any legal obligations will have an impact on trade in genetic resources and "derivatives" (however defined), the number of transactions that might be affected must be considered. The number of transactions involving materials that incorporate GRs - including legal transactions (trading) and functional transactions (use) - runs into many millions per day, every day. If derivatives (however defined) are included, the numbers of legal and functional transactions are multiplied. Indeed, every time a loaf of bread or bottle of wine is purchased, a legal transaction occurs using a derivative of a GR.

In the face of these multiple uncertainties, EFPIA believes that an understanding of the pharmaceutical R&D process is crucial in order to increase comprehension of what is at stake and to counteract unrealistic expectations and misguided claims that a particular genetic resource has directly led to a final product with commercial value. The reality of pharmaceutical R&D is much more complex than is commonly appreciated. The next section of this paper deals with the R&D process. Readers are encouraged to recognise both the role that natural products can play in R&D, but also the role of other inputs.

3 › THE R&D PROCESS AND ITS USE OF GENETIC RESOURCES

3.1 | UNDERSTANDING THE USE OF GENETIC RESOURCES AND THE R&D PROCESS

Among providers and users, one notes that there exist radically different understandings of the value of genetic resources to commercial product discovery and development[7] and indeed one of the greatest challenges regarding ABS is to match expectations of value with commercial realities. In this regard, it is vital that the following key points are understood about the nature and complexity of the R&D process:

- **Not all "uses" of a genetic resource (GR) are driven by a commercial motivation.** Many researchers never intend to use accessed genetic resources to develop commercial products. In such situations, uses of genetic resources could occur that would yield "benefits" - including scientific knowledge - that could theoretically be shared with the country of origin. Yet, the uses will not be linked in any way to a commercial exploitation. **Some uses of GR with a commercial purpose and value will be kept secret** and will not be published. This might be the case with a particular mixture of herbal medicines. In other cases, many years may pass between the initial work on developing a product and any commercialisation.
- **Very few uses of genetic resources will ever directly result in a commercial product.** Typically, many thousands or even hundreds of thousands of samples must be screened to identify potential leads for investigation. Once identified, those leads rarely yield compounds that merit serious investigation, fewer still yield compounds that possess attributes that could merit the filing of a patent application and even fewer lead to a commercial product.
- **Uses of GR and derivatives by the pharmaceutical industry**

The following list highlights the main possible uses of GR in the R&D process, which is subsequently explained:

- Use of GRs/derivatives as a starting point in developing active compound(s)
- Use of GRs/derivatives as elements of vaccines
- Use of GRs/derivatives as inactive parts of final product
- Use of GRs/derivatives as a tool in the research process
- Use of GRs/derivatives as a tool in the production process

As the rest of this section will highlight, the value-creation chain from GR to final product generally involves a number of diverse steps and players and, indeed, there may be numerous transactions from GR to consumer.

[7] *Laird, S & Wynberg, R (2005), op cit. note 6*

3.2 | THE PROCESS OF PRODUCT DEVELOPMENT

Step 1: Target Identification

Target Identification is the first formal stage in the Drug Discovery and Development process. To understand what is involved, imagine a disease as a series of physical events that ultimately lead to the disease showing its outward symptoms. Each step is a molecular event with its own specific characteristics.

Drug Discovery and Development

1. Target Identification

What we need to achieve in this phase:

- ✓ Identify a link to disease in animals
- ✓ Link a biological mechanism (target) to a key biological process
  Enzyme, receptor, ion channel, ion pump
- ✓ Identify a link to disease in animals
- ✓ Identify a link to disease in man
- ✓ Select a target balancing effect vs. risk

Hit Ident → Lead Ident → Lead optimisation → Concept Testing → Devt for Launch → Launch → Product Maintenance and Life Cycle Support

Each step produces some biochemical change in the human body. There are many such processes going on in the body at any point - repairing damaged tissues, maintaining functioning, etc. The disease-creating steps may only differ in quantitative terms, for example when the body is producing too much or too little of an essential enzyme. Alternatively, the change may lead to wholly detrimental changes, as would be the case with the steps leading to the proliferation of tumour cells.

A target is a point of intervention in the sequence of molecular events that lead to disease. Imagine a chain of fifty people of varying types, who are asked to pass a piece of paper from one to the other and each add one word to the paper while remaining grammatical. The input of one of the fifty people might be considered as a target for intervention with the aim of modifying what is written on the paper when it reaches the end of the chain. Not only is the contribution of the target changed, but so is everything downstream.

Target Identification is based on the company scientist's knowledge and intuition about the pathways of individual diseases. Advances in the number of research tools available to scientists mean that it is increasingly possible to understand these pathways at a molecular level. This can be contrasted with a more traditional approach where product development relied on observation of the effects of substances on the symptoms of disease. In this approach, natural products and traditional remedies were significant because they provided evidence of treatment and effect. The modern approach is inherently more direct, since it addresses itself directly to the nature of the disease though that too presents its own challenges.

The sort of issues in the scientist's mind are to find a point of intervention that will be specific to the disease, but will not affect other metabolic processes that might be affected by the same chemical pathway. Natural products and traditional knowledge can play a role here. Research based pharmaceutical companies have to choose strategies to reduce the overwhelming number of potential avenues of research. Opinions vary within the industry, but for some companies, the use of particular plants and traditional remedies is still a useful way of discovering original compounds and of directing the search for effective medicines.

The output from this stage is an idea about how a diseases process might be modified. Typically, this will lead to the isolation of a molecule or part of a molecule existing in the body, which is implicated in the hypothesis. Many molecules in the body are extremely large. The target may be a very small part of the molecule that is thought to be key to the molecule's role in disease. The action of the target may be modified through pharmaceutical intervention. The search then turns to whether other molecules can be found which will interact with the target, since any drug must interact with the target if it is to be effective. Chemicals, which interact with the target are known as "hits".

Step 2: Hit Identification

A modern pharmaceutical company will attempt wherever possible to preserve and develop its

Drug Discovery and Development

2. Hit Identification

What we need to achieve in this phase:

- ✓ Identify chemicals that interact with target
- ✓ Develop test systems to measure effect
- ✓ Screen millions of compounds for potency and selectivity-compound libraries,natural products (peptides, products from fungi, bacteria, animals, humans, plants), natural product fragments

Target Ident → Lead Ident → Lead optimisation → Concept Testing → Devt for Launch → Launch → Product Maintenance and Life Cycle Support

knowledge base concerning biochemical interactions. Knowledge of what doesn't work can be as important to a scientist as what does work. It has become popular to think of the interaction between a drug and the target as a lock and key. The analogy is a good one for explaining the end of a successful development process. At the beginning of any process, the companies have their collection of keys - usually over a million of them. Some look like they should work given ideas about certain locks, others have worked in the past, others are known not to work reliably, but can provide useful information on what would work.

As well as physical "libraries" of these compounds, companies have accumulated knowledge of their chemical behaviour, which is carried both in the heads of its researchers and in the companies' records of past discovery efforts. Every researcher carries his/her own library of hypotheses and knowledge, which may of course include knowledge of traditional remedies. In addition to their own resources, companies may source external libraries of compounds that they consider potentially relevant to the hypothesis about the target. These libraries may contain genetic resources or compounds, which have been produced using genetic resources in some way.

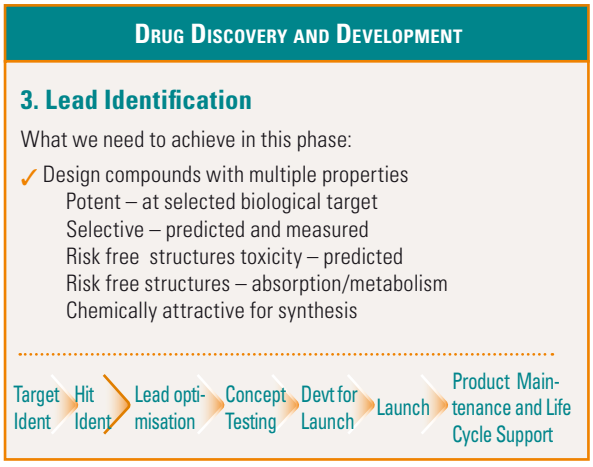
The composition of the libraries used differs between companies. Complete randomness is avoided. The construction of the library is a knowledge-building process aligned with the companies overall research strategy. One company may include a significant number of biological molecules and genetic resources in its libraries. Another may consider that, in light of the well-established challenges in turning such molecules into medicines, they prefer to limit the library to synthetic derivatives of key fragments of such molecules, which have been modified to align them more closely with the size and structures familiar to existing medicines. These choices are the essence of competition in a knowledge-based industry. For companies that are more heavily engaged in research involving GRs and their derivatives, it is likely that the starting point will have been an insight regarding the properties of a plant, organism or traditional remedy. For these companies, it is necessary to take the starting material, which will usually contain hundreds of different chemicals, and identify those active in relation to the disease in question. However, even for these companies, it is highly likely that the molecules identified would become the basis for a specific synthetically-designed sub-library for screening, rather than being tested alone. As in many other instances, the interaction between material covered by CBD and human intervention is complex.

Modern technology has enabled companies to present these libraries for screening in a highly efficient way. Companies also need to prepare appropriate test systems to ensure that the results of the screening exercise can be used to take clear decisions. Assuming that the screening process produces some hits, these will then provide the raw material for the next stage, but it is often the case that the "hits" are sufficiently diverse in their structure and in the degree of affinity that they show for the target, that the researchers do not have an ideal therapeutic molecule so much as a series of clues about what such a molecule might look like. Not all screening exercises deliver the expected results. This stage of the process may trigger re-evaluation of the underlying hypothesis - an iterative aspect of drug research that continues through later stages.

Step 3: Lead Identification

The Lead Identification process narrows the field. The molecules that have shown affinity for the target can now be more closely examined. Nevertheless, it is important to address a common misconception that the screening process identifies a preferred lead molecule, which then goes into development. It is rather the case that researchers start with a brief to identify molecules, which could lead to successful medicines. The Lead Identification process provides vital input, specific to the hypothesis at hand. Hence, close attention will be paid to better understanding the nature of the interaction between lead and target. This may be particularly important if, for example, the target molecule is relatively large.

However, there is another input to Lead Identification through which the researchers bring a range of design



Drug Discovery and Development

3. Lead Identification

We carry out chemical design to produce leads based on millions of fragments of information, hit screening, drug properties, competitor patents, physical sciences, safety sciences. This is our core skill and one of our key IP steps.

parameters to bear on their challenge. Many of these parameters are predictive in the sense that they are based on accumulated knowledge of the characteristics of successful medicines. The parameters are a mixture of generally accepted principles (e.g. that structure X is toxic) and company-specific guidelines.

Regarding the role of materials relevant to the Convention on Biological Diversity, it is possible that the molecules of interest identified in the previous stage are derived from genetic resources. This is highly likely if the company has a commercial niche, which depends entirely on identifying biologically-active and naturally-occurring molecules.

However, the need to design a drug is paramount. As a result, for many companies, regardless of how the hits were sourced, this is the point in the research process at which interest in such "natural" materials is replaced by a focus on molecules, which offer greater certainty regarding safety and ease of manufacture.

Drug Discovery and Development

4. Lead Optimisation

What we need to achieve in this phase:

✓ Design a compound with required profile
- Potent at selected target
- Selective for target mechanism
- Absorbed
- Safe in short term animal tests

Step 4: Lead Optimisation…and beyond

Lead optimisation introduces a greater level of specificity regarding the required characteristic of a medicine. It is also the first time that the lead compound is used in animal studies. Prior to this, the only evidence that the company can have of effectiveness has been gained in artificial circumstances. The behaviour of a large organic molecule in isolation may be different from its behaviour in a functioning organism. These early animal tests are the only way that the researchers can assess the specificity of action of the compound (does it affect only the target or the target and several other related molecules, which may have different and important functions in the body?). They also provide an opportunity to examine how the lead compound is absorbed, metabolised and excreted in an organism. By this stage, the company has made the fundamental choices about the chemical structures, which it is to pursue. It is unlikely that the lead compounds include naturally-derived products, but it is possible that such products will be used as tools in the process of identification and optimisation.

It also important to emphasise what the company does not know. It does not know if the preferred compound will be effective or safe in human subjects, nor what dose will be required to produce a therapeutic effect. As this shows, the knowledge-development process is far from over when the process of chemical manipulation is finished. From this point on, the use of natural products (if any) is likely to be limited to their use in bulk production of precursors of the medicinal compound.

Patenting will normally have taken place by the time that lead compounds have entered lead optimisation. Though multiple uncertainties regarding commercial return still surround the lead compounds, unless the company has secured the rights, it will have no commercial basis to take the molecule(s) into further development.

Quite aside from the progress of the specific research projects, the knowledge development process will continue in parallel. Some of the results of the research will be disclosed through publication in scientific journals, while internally within the company, knowledge acquired through the process will feedback into other relevant projects.

3.3 | PROBABILITY THAT USE OF GENETIC RESOURCES LEAD TO A DRUG COMPOUND

While the previous section has traced the steps of R&D, it is also vital to understand the truly minute probability that a natural product will contribute to drug discovery and to underline the enormous failure rate involved in drug research and development. In the following diagrams, a hypothetical, but typical scenario is presented. Starting first with the company's collection of compounds that are normally screened (High Throughput Screening - HTS) for activity with the target, we can see that approximately only 2000 of a total library of 700,000 are of natural origin. The rest of the slide describes how hypothetical results of the initial screening are further refined resulting in two lead series.

From HTS To Lead Series

700'000 compounds
(incl. 2000 natural products)

Typical result of **high throughput screening** (HTS):
- ✓ 500 compounds identified as actives ("hits"),
- ✓ Grouped in 20 clusters

Typical result of **filtering of HTS hits**[1]:
- ✓ Only 1-5 clusters selected to explore
- ✓ Synthesis of 50-200 analogues (= "lead generation")

Typical result of **lead generation**:
- ✓ Only 1-2 hit cluster full fill lead series criteria[2]

[1] filtering criteria: chemical tractability, selectivity, PK, pys. chem. prop.
[2] lead criteria: similar to filtering criteria, but more stringent.

The next steps of this hypothetical scenario are illustrated in the slide From Lead Series to Market. In this example, two clusters of molecules are selected as the basis of lead optimisation. The chemical characteristics of these clusters are analysed and a set, a so-called 'library' of 10,000 analogues[8] is created. All of these molecules are new creations. They have never been described before, and with an extremely high probability, they never existed on our planet before.

To illustrate the optimisation process, imagine this as creating a library of words. It may be that lead Identification produced the word "procrastinate", which showed affinity for the target but is considered too large to be a feasible compound to take into development. The company can make certain other assumptions about 'pro-cras-tin-ate', For example, let us say that the company has past experience which leads it to be concerned about the toxicity of "tin". It is believed that the active element of the lead is "ate", which is unfortunately chemically unstable. The lead optimisation strategy is to identify a range of candidates, all of which must be between 5 and 9 letters in length, not include "tin" and all of which must contain a structure very similar to "ate" somewhere. As indicated above, in all likelihood, the optimum development candidate will be completely different from any of the hits identified in the screening process. The major difference between compounds and words is that there is no finite dictionary of compounds. The only limit is human ingenuity.

From Lead Series to Market

2 lead series

Typical result of **lead optimization:**
- ✓ Synthesis of 10'000 analogues
- ✓ Max. 1 lead series fulfill criteria
- ✓ Max. 1-2 compound(s) fulfill criteria for development
- ✓ Finally selected compound incorporates various structural elements that were not present in HTS hits

Typical result of **Clinical Development:**
- ✓ Only 1 out of >10 compounds that enter development reaches the market.
- ✓ Not all compounds that are launched are profitable

To summarise:

- Probability that a compound in the library is the starting point for a lead series is in the range of 1/350'000 - 1/700'000 (cf. 2 lead series from a HTS.)
- Probability that such a compound is a natural product: considerably lower due to usually very low chemical tractability; i.e. less than 1/1 Mio.
- Probability that no lead optimization is required for a natural product: best guess 1/1000.
- Probability that a development compound originating directly from a natural compound reaches the market: even lower due to the general attrition rate during clinical development, i.e. less than ~1/10,000 Mio.
- Taking the number of natural compounds (~2000) in the library into account: the probability that a development compound, originating directly from the collection of natural compounds, reaches the market: in the range of 1/10 Mio.

[8] Analogue: a chemical compound that is structurally similar to another but differs slightly in composition

3.4 | R&D INVESTMENT AND THE NEED FOR LEGAL CERTAINTY

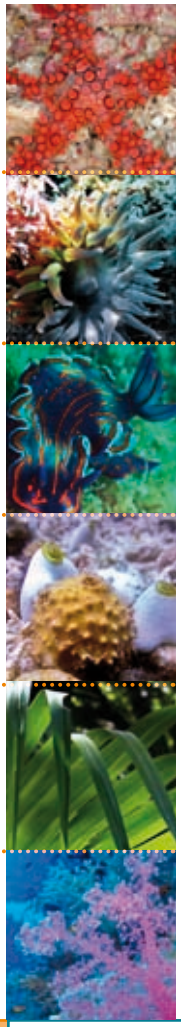
The business case for biodiversity can only be understood if the R&D process (as described earlier) is understood as a commercial venture, where choices are made regarding the allocation of resources and the likely returns on investment. Risk calculation is a fundamental factor influencing decisions regarding the investment of resources and companies who invest in research must have maximum certainty in order to ensure the legal security of any investment. Likewise, legal risk should be minimal and legal certainty must be assured.

There are many common misunderstandings regarding the actual value of genetic resources for R&D. There is no straightforward means by which the association can be made. The industry argues that that the diversity of possible contributions, coupled with the overarching objective to promote responsible research, renders a detailed taxonomy of "nexus" both impractical and unnecessary. Higher expenditure and greater risk associated with drug development compared to drug discovery, coupled with the low probability that any one GR sample will lead to a commercial product[9], are two such issues that are poorly understood. In addition, the internal competition between genetic resources research programs and other research programs within companies is often poorly appreciated[10].

[9] *Laird, S., Wynberg, Rl, op.cit., note 6. It is estimated that one in 10,000 samples makes it into a commercial pharmaceutical product, and Cragg et al (in press) estimate that less than 4% of patented pharmaceutical drug candidates become commercial drugs.*

[10] *Kaiser, R, 2004, Ibid. As one researcher said of bioprospecting for fragrances: "...if it becomes too difficult to do this research from a legislative perspective then it will stop, which would be a terrible shame."*

4 › GOOD BUSINESS PRACTICE & SUCCESSFUL PARTNERSHIP: CASE STUDIES



Successful progression towards an effective and fair system of ABS, while facilitating innovation will depend on the understanding of various issues. As a critical stakeholder and user of genetic resources, the research-based pharmaceutical industry can contribute its knowledge, experience and skills and hopes that this submission will further the discussion in with a view to ensuring both access and benefit sharing of genetic resources. The research-based pharmaceutical industry is committed to working in partnership with all stakeholders in order to find a solution that is accepted by all and which will promote the CBD objectives, enabling a sustainable and beneficial use of global biodiversity. This section

- Introduces industry regulatory approaches
- Identifies the benefits that have been derived from existing partnerships and,
- Describes some important real-life examples

4.1 | INDUSTRY CODES OF CONDUCT AND COMMITMENT TO CBD OBJECTIVES

Following CBD negotiations, the pharmaceutical industry has shown itself to be committed to the objectives of the Convention and has worked to encourage best practise. Evidence of the industry explicitly aligning policy and practice with the three objectives of the CBD is found in two relevant code of conducts, which aim to encourage best practice and ensure equitable sharing of benefits among industry.

1. **Guidelines for IFPMA Members on Access to Genetic Resources and Equitable Sharing of Benefits Arising out of their Utilisation**[11]

2. **Guidelines for BIO Members engaging in Bioprospecting as defined by the biotechnology industry**[12]

INDUSTRY COMMITMENT TO RESPONSIBLE ACCESS & BENEFIT SHARING (ABS)[13]

1. To obtain prior informed consent (PIC) to the acquisition and use of genetic resources controlled by a country / indigenous people and provided to the company in accordance with local law.
2. In obtaining PIC, to disclose the intended nature and field of use of the GR
3. To gain necessary approval to remove materials found in situ, and to enter into formal contractual benefit-sharing agreements reflecting the MAT on the use of the GR obtained through that removal. These agreements may contain conditions on permissible uses of the genetic resources, transfer of the genetic resources to third parties, and appropriate technical assistance and technology transfers.
4. To respect existing use(s) of the genetic resources in the manner it has been used in the source or any other country.
5. To agree that any disputes as to compliance with the clauses contained in formal contractual benefit-sharing agreements are dealt with through arbitration under international procedures or as otherwise agreeable between the parties.

[11] *IFPMA Guidelines are available at: http://www.ifpma.org/pdf/ABS_Guidelines_26Jan07.pdf*

[12] *In June 2005 BIO, the world's largest biotechnology industry association issued Guidelines for Bioprospecting for its members (www.bio.org/ip/international/200507guide.asp)*

[13] *Taken from Guidelines for IFPMA Members on Access to Genetic Resources and Equitable Sharing of Benefits Arising out of their Utilisation*

4.2 | PARTNERSHIPS AND BENEFIT SHARING

Pharmaceutical companies see benefit sharing as an integral part of business and as the following case studies will underline, partnership with provider countries and institutions is the most common model for genetic resource use by the pharmaceutical industry[14]. By developing partnerships with source country institutions mutual benefits are enjoyed by both the user and provider and ABS negotiations are generally much more fruitful.

Through partnership, numerous benefits for both parties are made possible. Depending on the case in question, benefits to the provider country or institution may be both monetary and non-monetary and could include the following examples:

MONETARY BENEFITS	NON-MONETARY BENEFITS
Fees per sample	Training
Milestone payments	Capacity-building
Royalties on net sales	Research exchanges
Licensing agreements	Supply of equipment
	Technology transfer
	Joint publications[15]

Importance of non-monetary benefits

As highlighted in the UNEP study, groups with the most experience in benefit sharing, stress 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 both the discovery and development phases.

As highlighted in section two of this document, the probability of any one partnership yielding a commercial product based on genetic resources is truly minute, and likewise the chance of GR-based products generating royalties is extremely small. The simplistic claim that genetic resources are widely used to develop blockbuster drugs is simply false and misleading. Most industries products rarely, if ever, achieve this status[16]. However, what is realistic is the enjoyment of potential benefits by both user and provider as the following list shows:

Benefits for companies

- Enables companies to access local expertise and resources in areas
- Greater insurance to companies that the resources they access are legally obtained
- Research capacity may be built more affordably in provider countries
- Assistance with local bureaucracies and national PIC requirements[17]

Benefits for provider country institutions

- Oversight of the collection and use of genetic resources
- Construction of scientific and technological capacity for research in provider country
- Technology and knowledge transfer through scientific collaboration
- Exchange opportunities to work and train in the user country
- Greater opportunity to monitor the ways samples are collected and used, i.e. companies often do not need to go back to providers to re-collect promising species
- Employment opportunities for scientists to work and learn in their home country and stem brain drain

[14] *Laird, S & Wynberg, R (2005), op.cit., note 6*

[15] *As part of their roughly 125 agreements since 1993, the ICBGS (International Co-operative Biodiversity Groups) 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 - In Laird & Wynberg (2005)).*

[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-In Laird & Wynberg (2005)).*

[17] *The US National Cancer Institute (NCI), for example, found that it is most effective for local partners to obtain all necessary permits and PIC from relevant government authorities as well as local communities (Cragg et al, in press - - In Laird & Wynberg (2005)).*

4.3 | CASE STUDY 1
ASTRAZENECA AND GRIFFITH UNIVERSITY, BRISBANE, QUEENSLAND, AUSTRALIA

AstraZeneca is one of the world's leading pharmaceutical companies with over 12,000 people working on the Research and Development of new medicines for treating human health. AstraZeneca scientists investigate new treatments for cancer, infection, pain and cardiovascular, respiratory, inflammation, gastro-intestinal and central nervous system diseases as well as others.

Griffith University, Brisbane and the Queensland State Government entered into an agreement with AstraZeneca in 1993. This set up a Natural Product Discovery laboratory in Brisbane; specifically located to take advantage of the intellectual strength in Brisbane and the proximity to the unique natural environment of Queensland - the rainforest and reef. Australia is one of the twelve mega-diverse countries and is a party to the Convention on Biodiversity.

The agreement was set up in compliance with the Biodiversity laws of the State of Queensland and the Australian Federal Government[18]. These laws encourage the Conservation of Biodiversity and the sustainable use of natural products, and they further encourage Access and Benefit Sharing. Some general principles include:

- Give effect to CBD & other international obligations
- Facilitate ecologically sustainable access and use
- Enable fair and equitable sharing of benefits
- Ensure use of traditional knowledge undertaken with cooperation and approval of holders of such knowledge
- Enhance biodiversity conservation and value
- Facilitate continued non-commercial research
- Integrated into biotechnological development policies and strategies

Under the agreement, Griffith University retains intellectual property rights with AstraZeneca having the first right to develop a product arising from the collaboration. Sale of any resultant product would lead to a royalty for the University. AstraZeneca has placed more than A$120 million funding into Griffith University since the collaboration started.

The Natural Product Discovery laboratory collects specimens from the Queensland rainforest and from the Great Barrier Reef. These specimens are then screened at the laboratory against a wide variety of medicinal targets using High Throughput Screening (HTS). If a specimen shows an interesting result, the chemists at the laboratory then isolate the active ingredient(s) and identify the chemical structure(s).

The active ingredient is usually not suitable to develop as a medicine but is a lead for creating different chemical structures for extensive pharmacological investigation.

Since the collaboration commenced, the Natural Product Discovery laboratory has tested over 35,000 specimens from plant and marine environments. These specimens have been collected via contracts with the Queensland Herbarium and with the Queensland Museum as well as from other sources.

Benefits for Griffith University, Queensland and Australia

The agreement and associated funding has established a world-leading research facility in the area of natural product discovery. This facility has lured several leading Australian researchers back to their homeland.

Natural Product Research Institute, Brisbane.

These researchers have maintained contact with global developments in pharmaceutical research, not only through their academic contacts but through very close interaction with research scientists of many different scientific disciplines throughout AstraZeneca. These interactions maintain Australian knowledge of cutting edge science.

Over 50 people work at the Natural Product Discovery laboratory and their general knowledge and skills feed into the Australian academic community. Technology transfer is enabled. The work of the Natural Product

[18] *Australian Federal and State Government Biodiversity policies, available at: http://www.environment.gov.au/biodiversity/science/access/index.html*

Discovery laboratory directly supports the collecting facility of the Queensland Herbarium and Queensland Museum, as well as supporting other suppliers.

Benefits for Biodiversity

The laboratory has over 35,000 specimens in its library. The vast majority of 7,500 marine specimens have been collected in Queensland and represent about 4,000 species, the majority of which are new.

Many of these specimens and organisms are totally new to science. The work of the laboratory has led to a massive expansion in knowledge, especially of marine fauna, such as

- Phylum Cnidaria - soft corals, gorgonians, jelly-fish, anemones
- Phylum Porifera - sponges
- Phylum Chordata - tunicates, ascidians
- Phylum Bryozoa - moss animals, lace corals

The laboratory has amassed a large biota library.

The work of the laboratory and the Museums has led to a much greater understanding of the biodiversity of Queensland, such as in distribution of plant species and, in particular, in the biodiversity of the Great Barrier Reef. This knowledge of marine biogeography and mapping of the 'hot spots' of biodiversity over the years is of great benefit for active management of the Reef for future generations.

Benefits for AstraZeneca and Medical Science

The Research and Development of a new medicine is a long process involving hundreds, if not thousands, of skilled scientists (chemists, biologists, pharmacists, doctors, etc). It can take 15 years from idea to market with the first few years spent investigating the idea and the last 8-12 years spent developing a specific molecule through the scientific, safety and clinical challenges. The challenges are great as over 90% of developments fail, even though compounds are carefully selected before they enter development.

The Pharmaceutical industry is always investigating new ideas and new leads for drug discovery, as there is considerable unmet medical need in society. The work of the Natural Product Discovery laboratory has added different and diverse approaches to AstraZeneca's drug discovery over the years of the collaboration.

The difficulty of drug discovery, selecting a promising molecule for development and then taking that molecule successfully through development has meant that to date, although the collaboration has been very successful, no new drugs arising from this collaboration have been developed to the market

Summary

This collaboration between AstraZeneca, Griffith University and the State of Queensland builds on Australia's strong intellectual and academic prowess, its unique natural environment and the Government's policy on implementing the Convention of Biodiversity. The collaboration has strengthened Australia's scientific base and has given AstraZeneca a wider scope in drug discovery efforts. Finally, the collaboration has stimulated and has enabled a greater understanding of the natural environment, including the discovery of many new marine species.

4.4 | CASE STUDY 2
PHARMAMAR - ADVANCING CANCER CARE WITH MARINE RESOURCES

Case study number two focuses on PharmaMar, a biopharmaceutical company whose mission is to advance cancer care through the discovery and development of innovative marine-derived medicines. The sea provides the starting point for research at PharmaMar.

More than 99% of marine biodiversity is as yet still un-explored and over millions of years marine life forms have evolved towards great biological and chemical diversity and the new chemical entities isolated from the marine organisms typically have entirely novel structures and often show great structural complexity.

These novel chemical structures often result in new modes of action against tumour cells that opens up the potential of new ways to treat cancer and it is hoped that this rich bio-diversity and chemical diversity provides qualitative advantages when discovering new drugs.

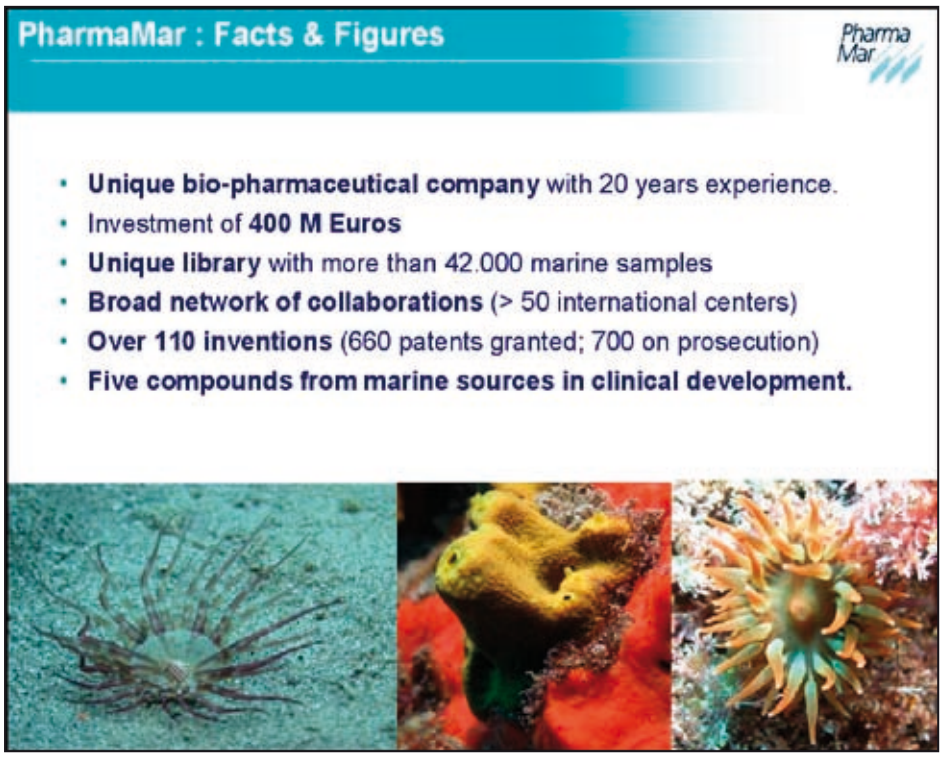
Over the last 20 years, PharmaMar has built up a unique collection of over 42,000 marine invertebrates and micro-organisms and approximately 7000 new chemical entities have been discovered and 30 new families of compounds identified. In additional, the company has a full pipeline of emerging products, including five compounds in clinical development and a portfolio of different molecules at different stages of pre-clinical development.

Only after 20 years of research and significant investment, has PharmaMar reached a position where it is able to plan commercial launch of its first marine-derived medicine. This attests to the length and complexity of the drug development process and the high up-front and sustained investment required to bring nature-inspired medicines to the market.

The following text attempts to highlight the role natural resources can play in yielding bioactive molecules and the complexity and uncertainties involved in converting these molecules into medicines.

1. Challenges & risks with Natural Product research

The use of biodiversity for drug discovery is just one of many different possible options. These include knowledge-based approaches (using literature and patent-derived molecular entities, endogenous ligands or biostructural information) and purely serendipity-based methods (such as combinatorial chemistry and high-throughput screening), as well as the amalgamation of both extremes.

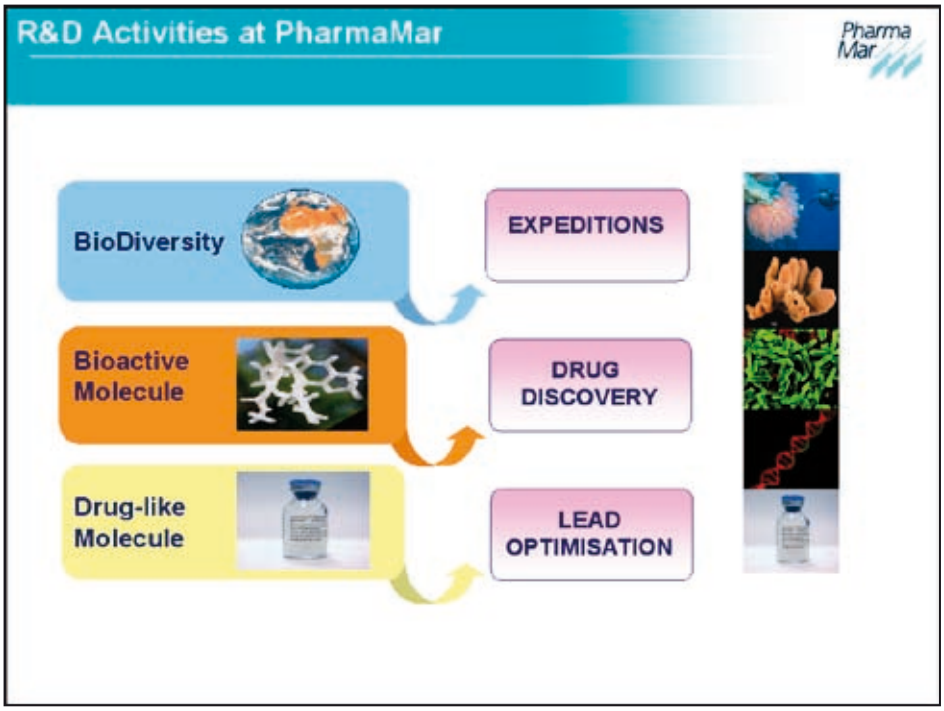


These combined hurdles represent an additional barrier to developing new medicines using biodiversity. The positive side is that despite the higher risk there may be greater opportunity to be innovative.

2. Complexity of R&D

PharmaMar's business model has many similarities with those of most pharmaceutical companies. In particular, the outline of the research process presented earlier is very much the same.

The business model differs from other bio -pharmaceutical companies in that all the new molecules developed by the company are derived from marine invertebrates or micro-organisms and the collection of these organisms is an essential part of the drug discovery process.



However, the creation of a natural product library is only the starting point. Without significant further work, it is impossible to know whether any individual natural product sample has any value for drug discovery.

To understand the role of biodiversity in the drug discovery process, it is important to understand the differences between a bioactive molecule, a drug-like molecule and a medicine.

2.1 Bioactive Molecules

The drug discovery process starts with the search for bio-active molecules.

Each natural sample is extracted and purified by chromatographic techniques in order to isolate a pure sample of the different molecules present. A few grams of natural sample is all that is required to provide sufficient quantity of the different molecules present to allow elucidation of their chemical structures and an initial assessment of the in vitro activity.

Even though most natural product samples contain a tremendous array of different molecules, the majority of the molecules present in such samples do not show in vitro activity. It has been estimated by the US National Cancer Institute (NCI) that just 1 % of samples from marine organisms tested in the laboratory reveal anti-tumour potential (which compares favourably with just 0.01% of samples of terrestrial origin).

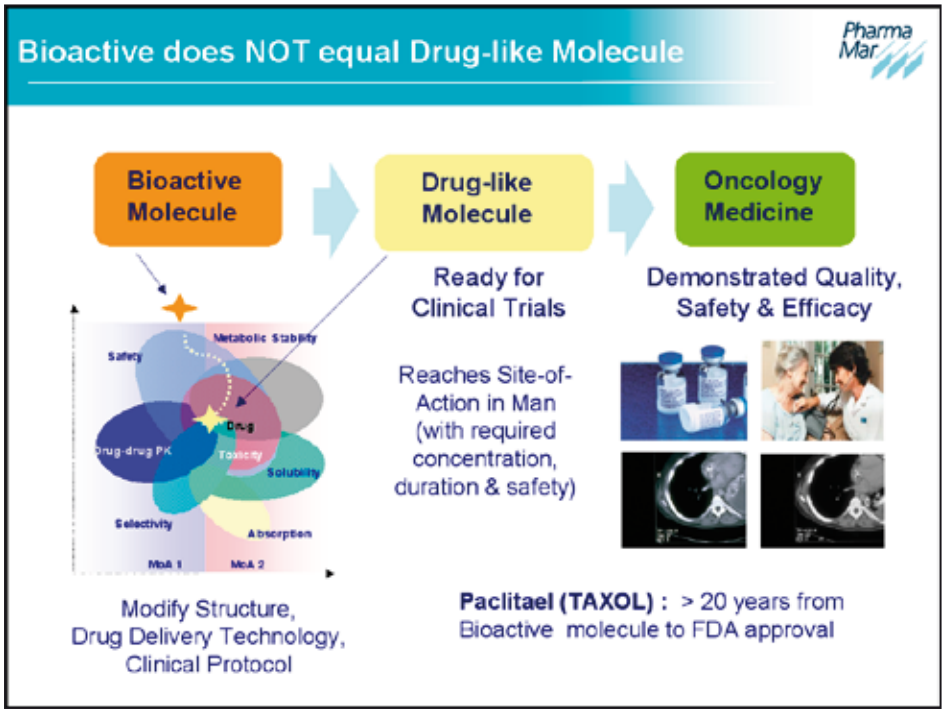
The isolation and characterisation of a new molecule with in vitro activity, a **bioactive molecule,** from the natural source is an important early milestone in the drug development process.

Once a new bio-active molecule has been identified, PharmaMar follows all the usual steps required for any new medicine including a full programme of pre-clinical testing (to design a drug-like molecule) and clinical development (to produce a medicine).

2.2 Drug-like Molecules

Even though a compound from the natural source may possess in vitro activity, it is highly unlikely that it will also possess all the other characteristics (physiochemical and biological) required to become a successful medicine.

All bio-active molecules require significant further effort in order to optimise their properties and produce a drug-like molecule for the start of clinical trials. This process of optimization is critical for the downstream success.



Structural modifications may be introduced (using chemical, enzymatic or biological methods) to enhance certain aspects of the molecules properties. The new molecules thus obtained have chemical structures based on the original naturally occurring compound but are not themselves naturally occurring. Medicines developed using such compounds are best described as inspired by nature rather than natural medicines.

For administration to patients, all molecules need to be formulated. The resulting presentation (freeze-dried vial, capsule, tablet, cream etc) contains not only the active molecule (whether as found in nature or after modification) but also different excipients and other components to ensure the suitability of the formulation. Many sophisticated drug delivery technologies are also available to further optimise drug performance.

2.3 Medicines

The conversion of a **bioactive molecule into a medicine** is a long and risky process. For example, following structural elucidation and identification of taxol as a new bioactive molecule, it took over 20 years to achieve FDA approval to market a medicine containing this molecule.

Furthermore, the chance of a bioactive molecule successfully negotiating all the hurdles and reaching the market are typically about 1 in 100.

2.4 Responsible Use of Natural Resources

The approach used permits the isolation of novel molecules from small samples of marine material. Once the anti-tumour activity of these chemical entities has been recognized and characterized, a synthetic process is established to produce further quantities for development and for commercial supply and to avoid dependence on the natural source and damage to the marine environment.

Invariably, the natural source would not be considered as an appropriate or viable source of larger quantities of the bioactive molecules, which are usually present in only minute amounts in the marine organisms.

3. Monetary and non-monetary benefits used

3.1 Partnership, collaboration and mutual benefits

Drug discovery at PharmaMar starts with the selective collection of small quantities of marine invertebrates and micro-organisms around the world. This work is carried out by experienced in-house marine biologists and in collaboration with worldwide local research institutions.

PharmaMar supports the protection, conservation and sustainable use of the precious resources from the sea and the fair and equitable sharing of the benefits.

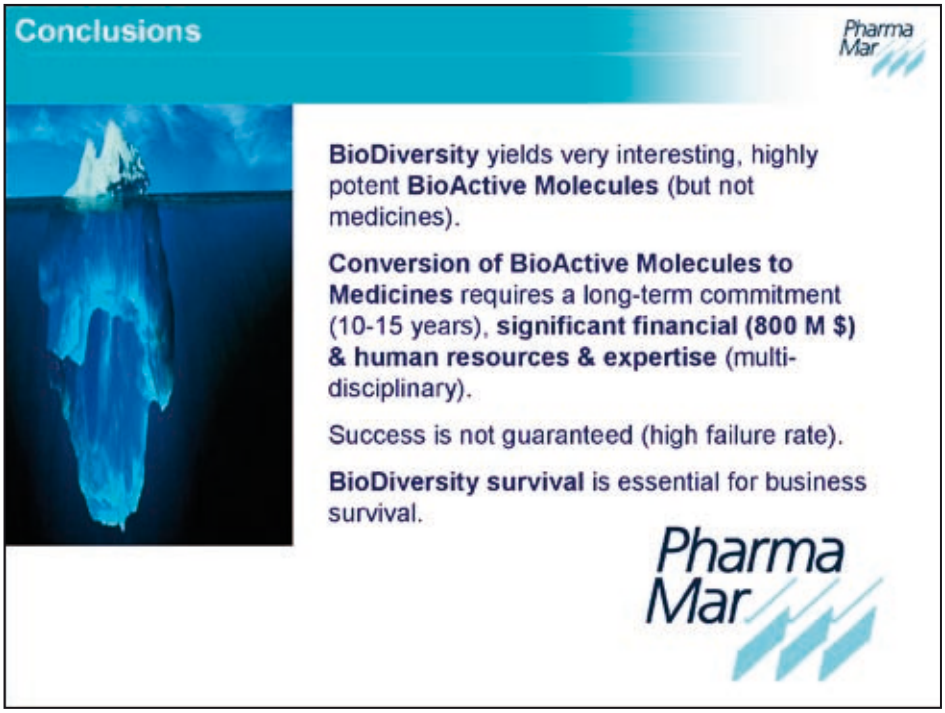
Ensuring the survival of existing biodiversity is essential for future business survival.

The PharmaMar approach to drug discovery not only contributes to the development of possible new treatments from just a few grams of marine sample, but also furthers knowledge and conservation of marine ecosystems. Such information is shared with local communities and teaching institutions and benefits both the local institutions and PharmaMar who uses the knowledge gained to optimise future exploration activities.

PharmaMar is supported by an extensive worldwide network of collaborators of all types who provide expertise and support throughout the drug discovery and development process from bio-prospecting and drug discovery through to clinical development, regulatory and marketing activities.

The opportunity to work with an international network of first class collaborators is essential in ensuring the success of the overall drug discovery process and is an important part of ensuring that the company remains at the forefront of all the new technologies and best-practice within the industry.

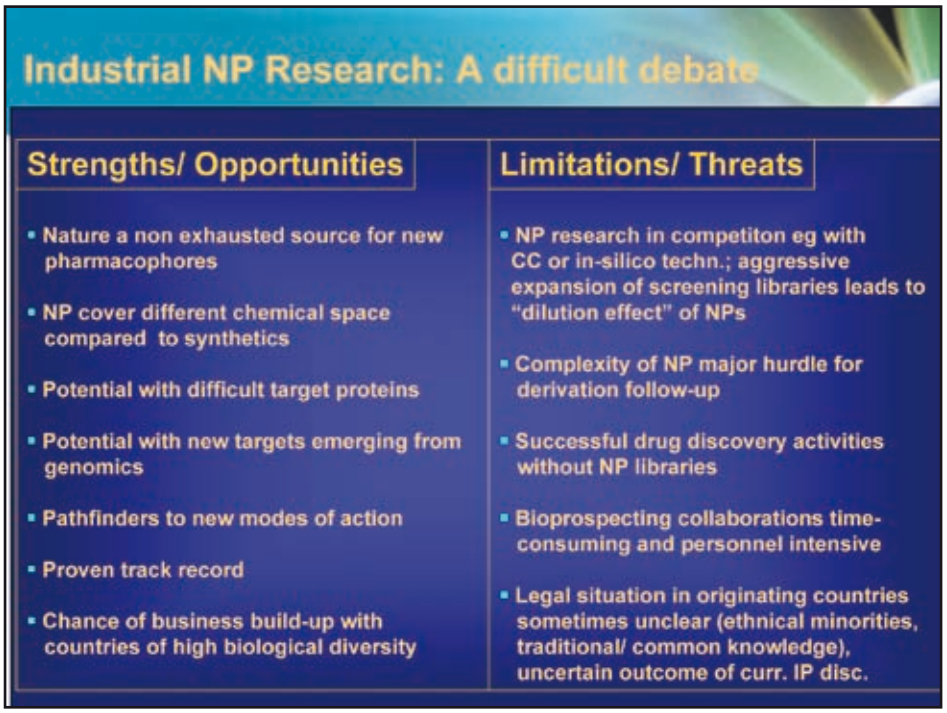
Each of the external collaborations is designed to complement in-house resources and such collaborations are only possible through the fair and equitable sharing of any benefits that may result.



4.5 | CASE STUDY 3
NOVARTIS - COLLABORATION AND COLLECTIVE GAIN

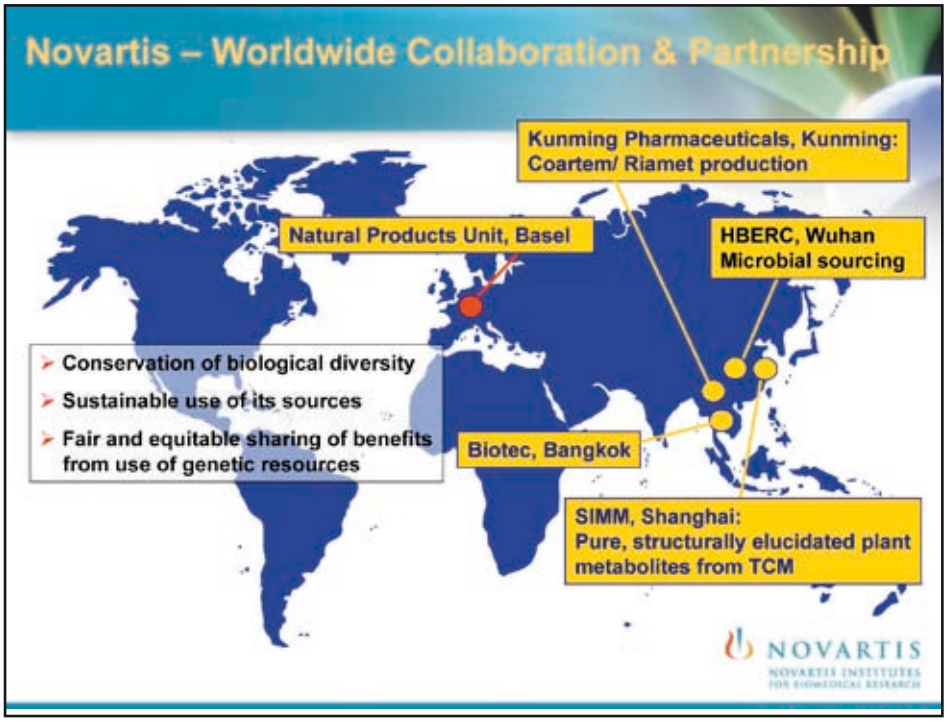
The importance or impact of technologies and research concepts are permanently balanced in industry. The same is true for the natural products programs in the pharmaceutical industry. There are many good reasons to leverage the unusual diversity of evolutionarily selected molecules in drug discovery efforts. On the other hand, the use of these molecules means facing intrinsic hurdles or challenges, which some companies may not be willing to take on.

Slide 1



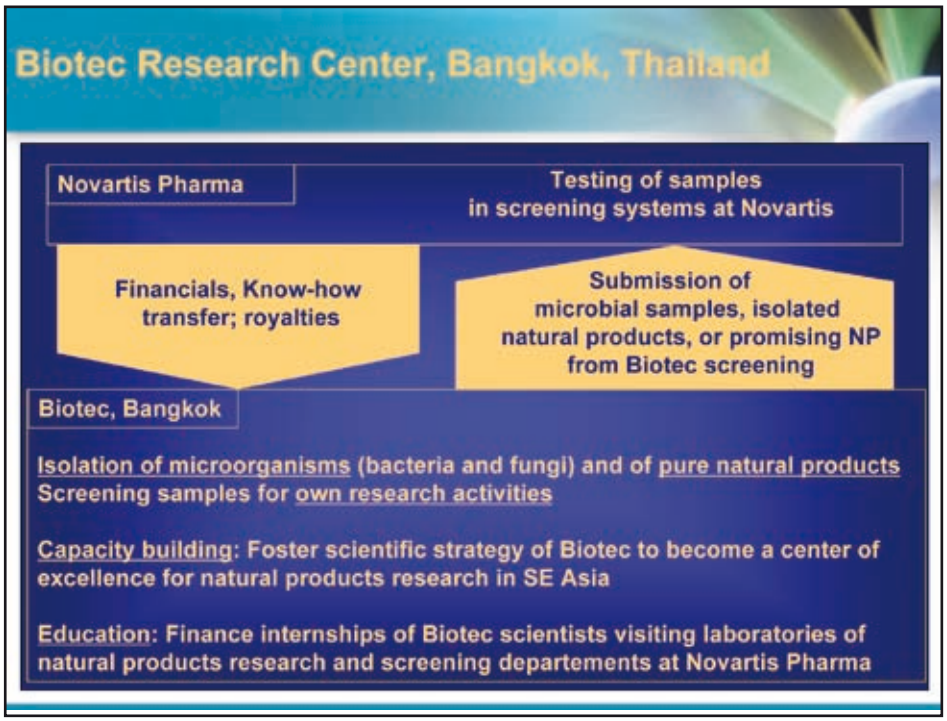
Novartis is strongly committed to natural products based research. A key aspect of this commitment is the creation of external partnerships with countries of high biological diversity. Currently Novartis focuses on collaborations with China and Thailand and in parallel is constantly evaluating other opportunities in order to diversify the access to biological sources.

Slide 2



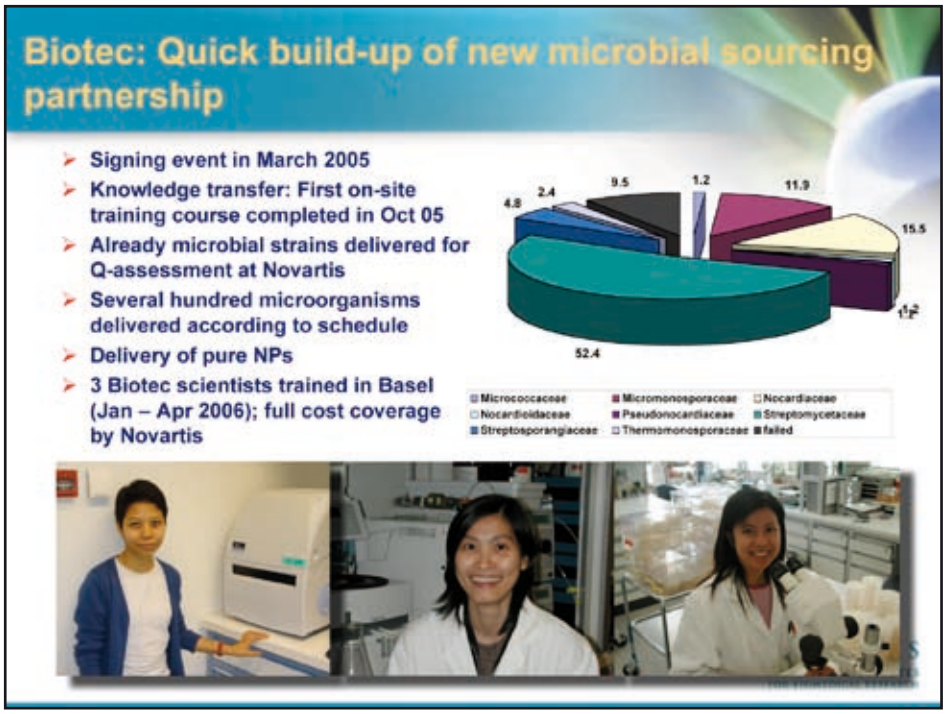
Partner institutes chosen by Novartis are internationally acknowledged specialists in the field of microbial and plant related natural products research. An integral part of current partnership agreements is the exchange of know-how by on-site training sessions, the education of scientists in the laboratories of the Novartis Institutes of Biomedical Research and the financing of technology related investments. In the cooperation contracts, success related milestones or royalty payments are also defined.

Slide 3



The project and investment goals are mutually defined in joint steering committee meetings, which are an important instrument to monitor project progress and, if necessary, to redirect collaborations. In the microbial sourcing collaborations, Novartis is responsible for the implementation of specific microbiology skills at the site of partner institutes, guaranteeing the high quality criteria of microbial strains as starting points for Novartis' internal project activities.

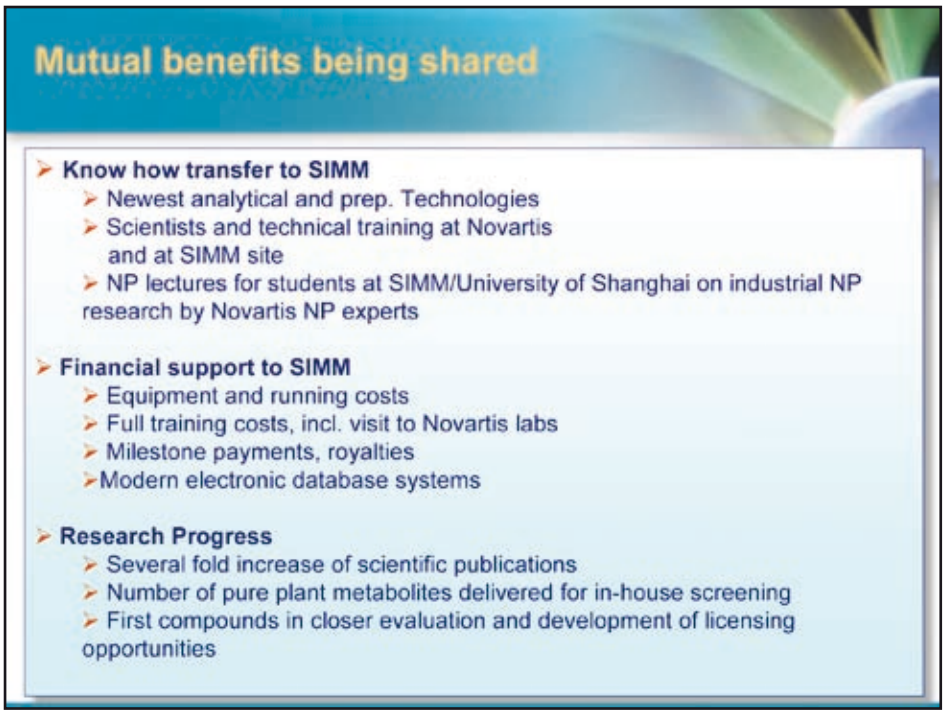
Slide 4



A particularly successful cooperation with the Shanghai Institute of Materia Medica should be mentioned here. Over a period of 6 years, Novartis received more than 1500 isolated molecules from plants used in Chinese traditional medicine from its Chinese partner. From its side, Novartis contributed significantly to the implementation of technological innovations at the Shanghai based institute. There are currently several compounds being considered for closer preclinical investigation at Novartis.

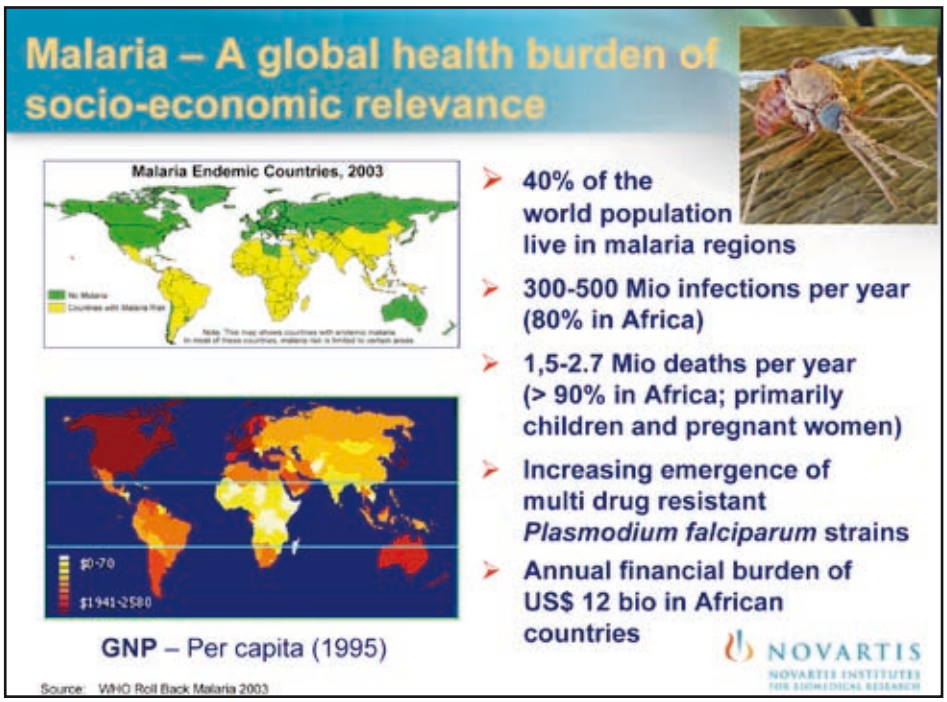
Slide 5

Slide 6



Although the Rio-Convention came into force more than 10 years ago, legal uncertainties regarding entitlement of institutes to start bioprospecting endeavours with industrial partners remain; undetermined responsibilities and authorities of national government and local administration, lack of official contact points within a country and the much discussed Access and Benefit Sharing framework. However, this issue is by no means an exclusive problem of biodiversity rich countries: the majority of the Western nations have also failed to implement suitable modus operandi. The most advanced Novartis project benefiting from traditional knowledge is related to a traditional Chinese medicine. Artemisia annua is a plant, which has been used in China to fight malaria for over 2000 years.

Slide 7



The active ingredient, artemisinin, was isolated in China in 1977 and demonstrated potent and highly selective activity against Plasmodia. The multi drug resistant Plasmodium falciparum can be effectively killed with the unusually structured natural product. In a joint development project with Chinese governmental institutes, an artemisinin derivative together with another plasmodicidal drug substance were combined in one tablet and were introduced successfully as Coartem(r)/Riamet(r) onto the pharmaceutical market in 1999. In 2001, the WHO added the anti-malaria drug to its essential medicines list.

Slide 8

In the following years, Novartis implemented full supply chain management. Significant investments were made in seed development; horticulture capacity was expanded in Africa and China and manufacturing infrastructure was put in place. Together with Chinese industry partners, the syntheses of the drug substances were developed to production scale and GMP (Good Manufacturing Practices) conform processes were established in China.

5 › MOVING FORWARD: WHAT SORT OF REGIME?

5.1 | IMPORTANT POINTS TO CONSIDER

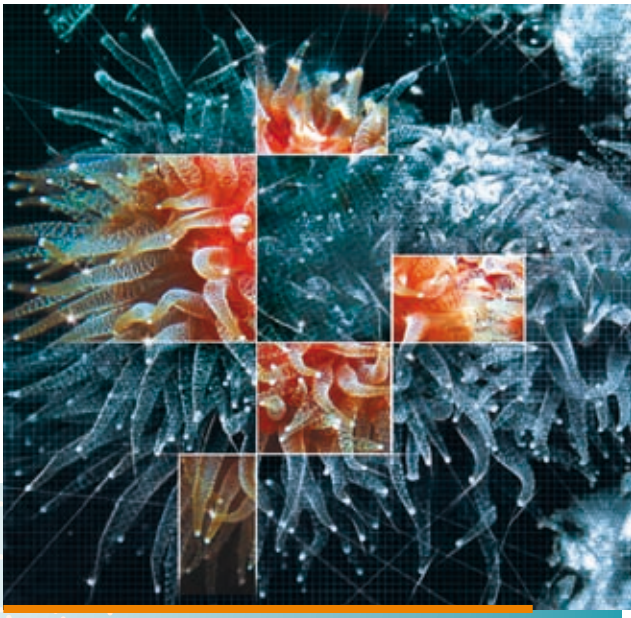
In considering any proposals for an ABS regime, the following points should be used to assess the value and effect of any potential element of an ABS framework:

1. What is the objective to be achieved or promoted by the requirement?
2. To what extent does the requirement achieve or promote that objective?
3. To what extent does such a requirement have undesirable consequences and do these outweigh the advantages of the requirement?
4. Will this requirement help achieve the CBD objectives and facilitate both access and benefit sharing?

It is necessary to address lack of clarity and to dispel myths in order to establish valid objectives. In section 2, examples of differences of opinion about fundamental concepts that underpin discussion of ABS were given. Underlying these differences is a lack of global consensus on almost every aspect of what might be termed the appropriate "regulatory philosophy." The preferred regulatory instruments depend in turn on one's perception of the problem. Those who believe, like some NGO's, that a generalised theft of genetic resources is taking place and who place the lack of ownership above the recognition of innovation will approach the question of regulation from a different point to those who believe that the core issue is to promote responsible use. An approach that is purely seeking to prohibit need deal only with the identification of certain actions, whereas as one that seeks to be facilitative must proceed from a deeper understanding of the processes involved.

The decisions made regarding ABS policies and laws, their clarity and workability will clearly affect the readiness of industry to invest in certain types of resource research and development. As legal certainty decreases and risks increase, the likelihood of investment in development of genetic resources will in parallel decrease. Any ABS framework must facilitate both access and benefit sharing and aim to ensure legal certainty. Without research investment, there will be neither commercial rewards to share with countries of origin nor technology to transfer to those countries.

The Regime must also confront the realities of the industrial processes which it is seeking to regulate. Pharmaceutical research is a "many-to-one" process, in which an enormous number of inputs contribute to a single new drug. Many of the inputs are attributable to sources outside the firm. Some are invisible, in that they are purely intellectual and exist in the minds of researchers. Some are substitutable; some are not. Some are expensive; some are commodities. From the research companies' point of view, there is a strong preference for knowing the cost of inputs in advance. For that reason, the industry favours solutions, which focus primarily on the point of acquisition of the genetic resource. The post-hoc attribution of value defers rewards to the source country for a long period of time and will inevitably be subject to debate.



5.2 | AVOIDING THE WRONG PATH

The example of "biopiracy" shows what happens when policy is developed from the wrong base. While some would claim that bio-piracy is a major problem, there is in fact little evidence that a significant practical problem exists and industry believes that this misconception is somewhat due to political rhetoric and misguided perceptions of biopiracy. It is important that debate on the issue is grounded in fact-based analysis.

EFPIA considers that the scale of biopiracy has been systematically and sometimes deliberately exaggerated. A 2005 IUCN report on bio-piracy pointed out a recurring observation made throughout interviews carried out for this report: "to some people, any ABS negotiation is 'biopiracy'"[19]. One of the perverse realities of the current situation is known as 'punishing the compliant' and this describes a situation where ABS claims are scrutinised and allegations of biopiracy are made regarding those who make the effort of meeting all government requirements.

Regarding the extent of misappropriation claims made, several persons have suggested that there are actually very few substantiated claims[20]. The above report suggests that the frequency of claims could very well diminish if a set of objectively determinable standards for ABS compliance (including clarification on when ABS compliance is required) were agreed at international and/or national levels[21]. Most claims reviewed in the 2005 IUCN report arose at least in part from uncertainty regarding ABS requirements and a lack of objective standards for determining whether a user is authorised to utilise genetic resources.

Yet another report for the 2005 Ad Hoc Open-ended Working Group on Access and Benefit-sharing, noted that the bioprospecting environment is often characterised by 'misunderstanding, mistrust and regulatory confusion.'[22] The same study reported widespread concern expressed by researchers in both academia and industry that traditions of trust and partnership among scientists has been undermined. However, as the case studies in section four show, there are numerous examples of good business practice, responsible use of NP and fair benefit sharing. To jeopardise such collaboration and partnership would be misguided and would benefit no-one.

The emphasis that has been placed on biopiracy shifts the attention of policy-makers away from the key points of reference in the search for equity. It has also delayed consensus regarding the key concepts, because in a situation of imagined threat there is a tendency towards blanket regulation, rather than the more considered approach that the issue needs.

Just as the issue of "biopiracy" has assumed an importance, which is not justified by rigorous, evidence-based analysis, so to has the patent system been misused as a scapegoat to be blamed for contributing to "biopiracy". A limited number of cases of invalid patents relating to use of genetic resources have been cited as evidence that biopiracy is widespread and facilitated by the patent system.

These cases have been used to build political support for a disclosure requirement which industry believes would create significant legal and commercial uncertainty and will provide no practical benefits. Indeed, there is no measure more likely to accelerate withdrawal from natural products research and deter investment in mega-diverse countries than a badly designed patent disclosure requirement. It is an "end-of-pipe" solution which discourages natural products research because of its unavoidable arbitrariness, whereas the interests of both acquirer and source country are much more closely aligned by a focus on the development of local research capabilities, around the point of sample acquisition.

The types of cases, which have been referred to in this debate, could generally have been dealt with by better search examination procedures. It is clear that a disclosure requirement would not help prevent the grant of patents in cases such as these because in several of the cases cited, the source of the genetic material was in fact disclosed and yet the patent was granted.

[19] *IUCN Canada (2005), "Analysis of Claims of Unauthorised Access and Misappropriation of Genetic Resources and Associated Traditional Knowledge." This paper was commissioned by the Secretariat of the Convention in response to decision VII/19E, paragraph 10 (c) of the Conference of the Parties and co-financed by Environment Canada. UNEP/CBD/WG-ABS/4/INF/6 - 22 December 2005*

[20] *This point is based on discussions of ABS issues in COP-7, including Working Group 1, and the ABS Contact Group meetings throughout that Conference. A review of recent literature will turn up numerous articles regarding the paucity of actual ABS-related claims.*

[21] *IUCN, op.cit., note 17, p.35*

[22] *Laird, S & Wynberg, R (2005), op.cit., p.38*

5.3 | CONCLUSIONS

Successful progression towards an effective and fair system of ABS, while facilitating innovation will depend on the understanding of many issues. As a stakeholder and user of genetic resources, the research-based pharmaceutical industry can contribute its knowledge, experience and skills and hopes that this submission will further the discussion in with a view to ensuring both access and benefit sharing of genetic resources. The research-based pharmaceutical industry is committed to working in partnership with all stakeholders in order to find a solution that is accepted by all and which will promote the CBD objectives, enabling a sustainable and beneficial use of global biodiversity.

The following are elements, which are seen as critical to any proposal or framework by the industry:

- **Flexible and Facilitative:** any international regime (IR) must be sufficiently flexible to enable countries to establish national regimes appropriate to their needs within the context of facilitating access - "provider flexibility"
- **User-friendly:** If it is to be binding, the IR must define rights and obligations which are sufficiently attractive and clear to encourage use of GRs - must avoid over-regulation/uncertainty - "user friendly"
- **Promoting all CBD Objectives:** care must be taken that obligations do not run counter to CBD objectives, i.e. facilitate both access and benefit sharing.
- **Added value:** detailed cost/benefit analysis of any certification scheme must be undertaken
- **Practicable and transparent:** any framework should be practicable, transparent, and efficient and avoid arbitrary treatment, consistent with the provisions of the convention

In summary, EFPIA suggests that the following points should guide the design of the International Regime:

- **National laws are key and that should be the focus of discussions.** In order to manage access to and use of genetic resources, national mechanisms must be created to regulate these activities and equitable benefit sharing should be achieved through contractual arrangements. Failure of countries to fulfil CBD obligations will automatically lead to non-fulfilment of ABS objectives.
- **An international regime will not remedy a legislative gap** given that many parties of the CBD have yet to implement adequate legislation. Therefore the promotion of national laws, which are appropriate for each country is vital, as is capacity building at national level.
- The international element of the Regime must be built around consensus standards of national implementation
- **It is critical to define the legal meaning of key concepts** that will underpin any proposed mechanisms. Questions raised in this document should be answered in order that the debate can move forward in certainty of the parameters being discussed.
- **Companies and others who invest in research must have legal certainty** as to what is needed to ensure the security of their investment.
- **Without research investment, there will be no benefits** or commercial rewards to share with countries of origin nor technology to transfer to those countries.
- **Provider flexibility and user friendliness are key** to any international ABS regime that can be effective
- **Industry should be, and wants to be, involved** in all stages of the development of the regime.
- **Nature is a valuable source of novelty and complexity** and so access should be promoted and facilitated so that the benefits of nature can be shared out in an equitable and faire manner.

FACILITATE - NOT RESTRICT - ACCESS

6 > ANNEX

6.1 | BIBLIOGRAPHY

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6.2 | GLOSSARY

6.2.1 Scientific Terms used

- Analogue: a chemical compound that is structurally similar to another but differs slightly in composition
- Genetic resource: means genetic material of actual or potential value[23]
- Lead: a chemical which has significant biological activity at a target and properties which make it attractive to design and synthesise analogues to optimise the desirable properties and remove any unwanted properties
- Target: a biological mechanism like an enzyme, a receptor or ion channel which is implicated in a disease process

6.2.2 Problematic or undefined Terms

- Bio-piracy: activities relating to access or use of genetic resources in contravention to national regimes based on the CBD. Accordingly, a legitimate claim of 'biopiracy' will involve unauthorized access to a controlled genetic resource and using that resource in a manner that contravenes the national regime. In practical terms, this means that (a) the activity in question occurred after the CBD came into force (December of 1993), and (b) the acts consist of a party gaining access without the consent of the source country, or in contravention to laws or regulations governing access to or use of genetic resources that the country has established[24].
  - Derivative
  - Origin
  - Traditional Knowledge

6.3 Potential scenarios involving GR and unanswered questions

As a result of discussions concerning the proposed patent disclosure obligation, the following illustrative scenarios were produced. They are all hypothesised but plausible examples of different levels of association or nexus between genetic resources and a final product. While the text explains the intellectual property issue, the questions raised by the scenarios can be applied to any situation where the production of a final product is used as a regulatory 'trigger point' for some sort of obligation on the producer.

Scenario 1

1. Company A is informed that rubbing a bruise with a leaf from the XYZ tree in Brazil alleviates bruising. It obtains the seeds (with appropriate consents) and grows sufficient quantities to enable it to extract and purifies the oils which it sells. It patents the purified oils, their use and the process of extraction and purification. Would the disclosure requirement apply?
2. Company A is informed that rubbing a bruise with a leaf from the XYZ tree in Brazil alleviates bruising. It obtains quantities of the leaves (with appropriate consents) and isolates and synthesises the active ingredient, which it develops and sells. It patents the active ingredient and its use. Would the disclosure requirement apply?
3. Company A obtains (with appropriate consents) leaves from 100 species of trees in Brazil. It knows nothing about their properties. Using various assay techniques, it discovers that one ingredient of one of the leaves is medically useful. It isolates and synthesises the active ingredient, which it develops and sells. It patents the active ingredient and its use. Would the disclosure requirement apply?
4. Under 3, does it make a difference to the applicability of any disclosure obligation if the medical use was known to a community in Brazil but not disclosed to Company A either at the time of collection or before application for the patent?
5. Company A does either 2 or 3 but finds that the ingredient it has isolated and synthesised has unacceptable toxicity. It finds a hitherto unknown analogue of it in the same class of compounds and patents and commercialises that analogue. Would the disclosure requirement apply?
6. Company A does 2, 3 or 5 but does not commercialise the product. On the basis of the patent disclosures of Company A, Company B develops, patents and commercialises a compound in a different class of compounds from those patented by Company A. Is there a need for Company B to disclose the origin of the leaf used by Company A? Does it make a difference if Company A had disclosed its origin?

Scenario 2

One of the thousands of compounds synthesised by Company A as part of its combinatorial chemistry program is Compound X. Its screening processes disclose that this novel compound has a medical use. It

[23] *CBD, Article 2*

[24] *This is merely one definition of biopiracy - that used by the International Chamber of Commerce, available at: http://www.iccwbo.org/collection4/folder165/id418/printpage.html?newsxsl=&articlexsl=*

patents the compound and its use. However, Company A cannot develop a cost-effective method of producing commercially viable quantities of the compound and does not commercialise it.

Company B is aware of the patent disclosure. It obtains access to a large number of micro-organisms from Brazil and discovers (it is not told) that one of them naturally produces Compound X , but not on a commercially efficient scale or with adequate purity.

Based on this discovery, it analyses a similar micro-organism which is native to Europe and finds that that micro-organism produces Compound X more efficiently than either the micro-organism from Brazil or the synthetic route disclosed in Company A's patent.

Company B genetically modifies the European micro-organism to improve production efficiency still further. It patents the micro-organism and compound X as produced by the micro-organism.

Company C genetically modifies the European micro-organism still further to improve purity of Compound X and obtains relevant patents.

Companies A,B and C cross-licence each other under the patents to enable sale of the commercial products.

Does Company A, B or C have to disclose the Brazilian micro-organism?

Scenario 3

1. Company D is informed that people wash clothes with a plant extract in Chile. It obtains the plant (with appropriate consent) and discovers a new lipase enzyme. It isolates the gene for the enzyme and patents the isolated enzyme, its DNA sequence, its use in laundry detergents and a process for its recombinant production. Would the disclosure requirement apply?
2. Company D is informed that people wash clothes with a plant extract in Chile. It obtains the plant (with appropriate consent) and discovers a new lipase enzyme, isolates its gene, and determines its DNA sequence. The company finds, however, it cannot withstand normal laundry temperatures, and publishes the work. Company E reads the publication and undergoes extensive R&D to mutate the gene to make the gene more heat stable. The new gene shares only 40% sequence identity with the original gene. Company E patents the mutated enzyme, its gene sequence, its use in laundry detergents and a process for its recombinant production. Would the disclosure requirement apply?
3. Under 2, does it make a difference to the applicability of any disclosure obligation if (i) Company D worked with Company E to generate the new enzyme and a joint patent application was filed? (ii) Company E later exclusively licenses Company D to make and sell the enzyme in washing powder? (iii) Company D did not publish, but gave Company E the information under a contractual obligation to pay royalties to Company D should a commercially viable enzyme be marketed.
4. Under 2 or 3, does it make a difference to the applicability of any disclosure obligation if Company D never discloses to Company E the source of the plant, and the plant is also found to be native to the country of Company D and Company E.

Scenario 4

1. Company F is informed that a plant virus is wiping out a cash crop native to Bolivia. The company obtains the plant (with appropriate consent) and discovers a receptor which the virus uses to infect the plant. The DNA sequence of the receptor is found and the receptor is cloned and used to screen compound libraries for chemical antagonists which would prevent viral infection. A patent application is filed on: the new receptor, its gene sequence, methods of finding antagonists, the chemical antagonists themselves, and their use. Would the disclosure requirement apply?
2. Under 1, does it make a difference to the applicability of any disclosure obligation if the receptor was found by the Bolivian Agricultural Department, and its sequence published, and i) Company F was given the vector comprising the gene for the receptor by the Bolivian Agricultural Department and the antagonists were found and patented? or ii) Company F synthesised the published gene sequence to discover and patent the antagonists?

Scenario 5

Consider all of the above cases and assume that, for whatever reason, relevant patents are held invalid. Producers of generic/unpatented products make large amounts of money selling the products. Are those producers obliged to share the benefits of their sales with the countries, which provided the materials?

Scenario 6

In order to make a wheat crop hardier, plant breeders crossed a conventional wheat variety with a variety obtained from Russia (with appropriate consent). Plant Breeders Rights were obtained (under UPOV) for the new variety. Would the disclosure requirement apply? What if several breeding steps were required to generate the new plant variety, and the Russian variety had been used 20 steps previously to the new variety being generated?

> NOTES

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