

Opinion

Commercial product exploitation from marine microbial biodiversity: some legal and IP issues

Camille Tichet, Hong Khanh Nguyen,
Sefia El Yaakoubi and Jean-François Bloch*
*Protéus SA, 70 allée Graham Bell, Parc Georges
Besse, 30035 Nîmes CEDEX 1, France*

Summary

The biodiversity found in the marine environment is remarkable and yet largely unknown compared with the terrestrial one. The associated genetic resource, also wide and unrevealed, has raised a strong interest from the scientific and industrial community. However, despite this growing interest, the discovery of new compounds extracted from marine organisms, more precisely from microorganisms, is ruled by a complex legislation. The access and transfer of genetic resource are ruled by the Convention on Biological Diversity. One of the three core objectives of this convention is to ensure the fair and equitable sharing of benefits generated by the use of genetic resources and to split these benefits between the different stakeholders. From the discovery of a microorganism to the commercialization of a product, three main stakeholders are involved: providers of microorganisms, e.g. academic institutes, the scientists who will perform R&D on biodiversity, and the industrial companies which will commercialize the final product arising from the R&D results. This article describes how difficult and complex it might be to ensure a fair distribution of benefits of this research between the parties.

Introduction

Microorganisms coming from different environments provide many economically valuable products and processes, such as the enzymatic synthesis of fine chemicals or the production of ingredients for cosmetic creams by simple cell extraction. They can be useful as sources of

enzymes, metabolites, peptides or proteins, antimicrobial substances (Quévrain *et al.*, 2009) and other bioactive compounds. Extreme environments represent a vast untapped reservoir of genetic and metabolic microbial diversity. More than 70% of the earth's surface is immersed and consequently, sustains a large proportion of the planet's biodiversity. Nevertheless, nearly 99% of this marine biodiversity is still unexplored.

As a result, many campaigns have been set up to sample and discover marine microorganisms around the world. These expeditions were key events for the scientific knowledge, aiming at characterizing this marine microbial diversity and discovering of new genes. An example of these expeditions was the EU-funded BIODEEP (BIOTECHNOLOGIES FROM THE DEEP) project, which aimed at exploring the deep hypersaline anoxic basins discovered in the Mediterranean Sea at a depth of 3000 m. These deep-sea environments contain novel biodiversity that led to the discovery of a new division of *Archaea* (Van der Wielen *et al.*, 2005).

A well-known example of commercial use of marine biodiversity is the discovery of the *Pfu* polymerase found in the hyperthermophilic archaeon *Pyrococcus furiosus*, which has proofreading ability allowing high-fidelity PCR amplification (Lundberg *et al.*, 1991).

However, the commercial exploitation of biodiversity raises a number of questions. There is a very complex relationship between the different stakeholders, including (i) the microorganism owner, (ii) the scientists carrying out the research, and (iii) the industrial companies exploiting the collected biodiversity and the results obtained by the scientists. In this article, these relationships will be analysed with respect to the Convention on Biological Diversity (CBD), a binding international treaty that governs exchanges between these actors, based on the principle of fair sharing of the commercial benefits arising from the access and use of genetic resources (UN, 1992).

The lack of definition of key terms such as 'provider', 'user' and 'stakeholder' can be a source of uncertainty when interpreting the CBD. For the purpose of this article, the provider is an entity wishing to transfer genetic resources. It can be the providing country directly, suppliers of resources such as private or academic institutes,

Received 19 July, 2010; accepted 27 July, 2010. *For correspondence. E-mail jfbloch@proteus.fr; Tel. (+33) 4 66 70 64 64; Fax (+33) 4 66 70 64 60.

universities or landowners. The user is considered as the entity wishing to access genetic resources. It can represent, respectively, various actors, e.g. the bioprospectors, research institutes, universities, *ex situ* collections, R&D or industrial companies.

The origin of biodiversity has become an important issue; however, the present study regarding the microorganisms is limited to their collection in territorial waters. Therefore, this article will not study the various issues arising from international seabed and arctic areas, which are not covered by national law.

Stage 1: Collecting and bioprospecting

The right to collect microbial biodiversity is ruled by the CBD. This Convention is an international treaty, approved by more than 168 countries in 2010, that promotes a balance between conservation, sustainable use of biological diversity, and fair and equitable sharing of benefits arising from the use of genetic resources (Article 1 of the CBD). It is a framework tool for the implementation of appropriate regulations at national level providing key objectives and general principles.

The CBD defines in Article 2 'biodiversity' as:

the variability among living organisms from all sources including, *inter alia*, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part; this includes diversity within species, between species and of ecosystems.

Although the CBD has a larger scope, this article will focus only on the case of microorganisms.

Individuals and entities, including researchers who seek for, collect and derive genetic materials from biodiversity for a commercial purpose, are called 'bioprospectors'. Exploration of marine environments, isolation and culture of microorganisms offer new opportunities for research and biotechnology companies to identify new molecules. However, the rights to collect a microorganisms collection to access biological materials and genetic resources from a specific environment, require a good knowledge of the national laws of the country where the bioprospecting takes place. Rights to collect microorganisms are regulated in each country by national legislations and may vary widely from country to country.

The CBD recognizes in Article 15 that:

...the sovereign rights of States over their natural resources, the authority to determine access to genetic resources rests with the national governments and is subject to national legislation.

The concept of Access and Benefit Sharing (ABS) is derived from this Article 15. It provides that each country shall take measures with the aim of sharing the benefits derived from the use of genetic resources in a fair way.

Nevertheless, bioprospecting has become very complex because the procedure for granting access to genetic resources differs much depending on the country, as some countries have no ABS law while others have a very procedural ABS regime.

Countries such as Brazil, India and Colombia have very strict ABS policies that lead to a restricted approach of bioprospecting. For instance, in Brazil, the authorization for bioprospecting is difficult to obtain. Every year, about 400 applications to access genetic resources are filed, while the processing rate per year is 25–50 applications (Thornström, 2007). Thus, the procedure to obtain access to biological materials can last up to 3 years (Laird and Wyndberg, 2007).

Collecting and commercializing resources without the prior consent of the countries of origin, and without enabling those countries to have a share of the rewards that result from these activities, is called 'biopiracy'. This can lead to fines and imprisonment. For instance, in Colombia the penalties consist in 'imprisonment of 2 to 5 years, and a fine of up to ten thousand times the current monthly minimum wage' [Article 328 of the Colombian Criminal Code (Law 599 of 2000) (Young, 2009)]. In some countries, biopiracy can delay the process for obtaining permits/authorizations, or even a denial of future applications in the collection area (Thornström, 2007). Regulations on access and use of biological resources has therefore become a very complex and exhausting process for potential bioprospectors, depending on the country and the ABS legislation thereof. This is mainly due to the different interpretations and the misuse of the Convention. Since countries have sovereign rights over their natural resources they can decide to implement an ABS system or not. Thus, bioprospectors should always first check if there is a compulsory prior consent procedure to sample biodiversity.

Given the lack of clear definition of the ABS' principle, and the lack of uniformity in its implementation in the laws of the Contracting Countries, the international community decided to adopt the Bonn Guidelines, a non-binding legal document (Secretariat of the Convention on Biological Diversity, 2002). The Guidelines address the question of ABS by providing assistance and a 'checklist' for providers and users of genetic resources. These Guidelines also suggest the creation of national monitoring and reporting bodies, means for verification of compliance, settlement of disputes, remedies by the designation of Competent National Authorities (CNAs) and National Focal Points. These two authorities are responsible in particular for granting access to genetic resources and for advising on the negotiation process, monitoring and evaluating of ABS agreements.

Under the Bonn Guidelines, the first step of the process of accessing biodiversity is the delivery of an administra-

tive authorization called: Prior Informed Consent (PIC) by the CNAs to applicants wishing to collect microorganisms. Then, applicants need to conclude Mutual Agreed Terms (MAT) with the providing country. MAT will specify for example the type and quantities of microorganisms, the possible use and the distribution of benefits (financial and non-financial). The purpose of these agreements is to ensure sharing of benefits arising from the commercial or any other use of these genetic resources. Nevertheless, only few countries among the Contracting Parties have adopted ABS laws, which are considered as sectoral and patchy, and most countries have not appointed CNAs yet.

To facilitate the implementation of the ABS policies, reinforce the Bonn Guidelines and ease the transfer of genetic resources, the international community has created a code of conduct named MOSAICC, which stands for the Micro-Organisms Sustainable use and Access regulation International Code of Conduct (BCCM, 2009). This initiative is supported by the European Commission and the World Federation for Culture Collections (WFCC). The MOSAICC provides conditions for facilitating access to microbial genetic resources, including the terms of agreement on ABS, the PIC and appropriate Material Transfer Agreement (MTA). Likewise, many other sources, such as the International Institute for Sustainable Development have also set up ABS Management Tool to provide guidance for compliance with the Bonn Guidelines (<http://www.iisd.org/abs/>).

The lack of harmonized system for ABS has led the CBD parties to consider the adoption of an International Regime on ABS which should be finalized in October 2010 in Nagoya. This Regime will enable to rule the global implementation of the ABS protocol. This harmonized system of ABS might be the solution for enabling a transparent access to genetic resources by preventing their misappropriation and misuse. This new regime should ensure compliance in user country with national law and requirements, in particular with PIC and MAT of the country of origin (CBD COP 9, decision IX/12, 2008).

However, 18 years after the signature of the CBD, despite all these efforts, the implementation of a simple regulatory regime for ABS, which was one of the main goals of the convention, is not yet fulfilled as the CBD remains a complex and confusing legal framework.

The status of genetic resources depending upon the origin of collections is also a complex issue to solve. For instance, a problem might appear when the same genetic resources are found in different places, for instance within the territory of neighbouring countries. These countries can possess different policies regarding the ABS regime, and therefore lead to complications linked to bioprospection. If a same microorganism, collected by a bioprospector in more than one country, appears to possess a valuable gene, which country

should this bioprospector share the benefits with? The International Regime is supposed to help solving this issue by encouraging those countries to implement a transboundary cooperation.

Besides, some countries have not assigned yet CNAs nor a National Focal Point, which implies some difficulties for bioprospectors to grant a permit for access to genetic resources. Indeed, those that intend to collect genetic resources from a specific environment needs to obtain a PIC from the appropriate authorities. The complexity of finding these stakeholders prevents bioprospectors to have access to genetic resources, and leads them to prefer countries where focal points are clearly established, even if the local biodiversity is less interesting.

The CBD allows countries to give access to their genetic resources, but instead of having a unique competent authority that provides PIC, potential bioprospectors have to obtain the approval from various parties, as for instance, communities or property-owner. This has led in practice some companies to partner directly with academic institutes which ensure compliance with these procedures (Laird and Wyndberg, 2007). The CBD has indirectly encouraged the consideration of a partnership as a way of accessing genetic resources.

In the case of technology invention subject to patents and other Intellectual Property Right (IPR), the access and transfer of microorganisms shall be provided on terms which recognize and are consistent with the adequate and effective protection of IPR. The CBD recognizes that patents and other IPR may have an influence on the implementation of the Convention. Thus, the CBD specifies that Contracting Parties shall cooperate in order to ensure that such rights are supportive of and do not run counter to its objectives (Article 16 of the CBD).

To force bioprospector to implement the CBD, and in particular its Article 15, some countries, such as Brazil and India, require the disclosure of the origin of genetic resources in patent applications. Some countries suggest to go even further by adding the PIC and the proof of an ABS agreement. This disclosure is currently debated. Numerous countries do not support this idea, and consider it inconvenient. According to them, patents require a disclosure of the invention in a manner sufficiently clear and complete for it to be carried out. Thus, the origin of the genetic resource, which relates to another system, would be considered as irrelevant.

The disclosure of the country of origin would be difficult to implement in practice. Which country should the applicant disclose in the case of multiple sources for the same microorganism? Should the applicant mention all the countries of origin where the microorganism can be found or only the country where the microorganism was collected? It may be difficult in some cases to provide evidence of a fair sharing of the benefits in countries which

have not yet assigned CNAs. Would the scope of the claim be limited only to the microorganism originated from the country where it was collected?

In summary, because of the complexity of the CBD and the various national regulations on access and use of biological resources, bioprospecting leads to a number of complex issues.

Stage 2: Industrial research and development

Biotechnology tools allow for an extraordinary advanced use of genetic resources, leading to discovery of novel proteins and other biochemical compounds for industrial application.

The objective of the user, such as a biotech company, is to perform Research and Development (R&D) from biodiversity to develop a product or process of industrial interest. Before starting any R&D programme, the user needs to obtain the rights to access and use biological resources in compliance with the provision of the CBD.

Microorganisms are collected and kept by various entities such as universities, private companies, national and international culture collections. Public or private research institutes and commercial companies often set up partnership in order to undertake bioprospecting of marine microorganisms. For example, a partnership between the biotechnology company Protéus and academic laboratories within the frame of the Biodeep project was established to collect marine microorganisms in the deep-sea hypersaline anoxic basins of the Eastern Mediterranean sea. To comply with the provisions of the CBD, numerous conditions have to be fulfilled before setting up a partnership, such as the negotiation of MTA, including benefit sharing for future exploitation, intellectual property, agreements/contracts, compliance and legal remedies in the event of a breach of contract.

The discovery of molecules of industrial interest from microorganisms requires a long-term commitment, expertise and significant financial and human resources. Generally, bioprospecting is only upstream R&D programmes which aim at developing a product, the ultimate goal for industrial companies being to establish a commercially viable product or process.

R&D programmes are divided into several tasks. Thus, the selection of biological resources is only a very early step within the research process. In fact, only few microorganisms from a collection would be selected as candidates to a commercial exploitation. For example, a novel enzyme screening project would include different steps, such as biodiversity screening, identification of candidate microorganisms expressing the targeted activity, cloning of the gene coding for the protein of interest. The protein should then be produced at small scale, and its activity be validated, before industrial expression and immobilization

of the enzyme can be carried out in order to obtain a biocatalyst in a form applicable to an industrial process.

All the parties engaged in this process need to negotiate and sign agreements in order to organize the rights and obligations of each party, that is to say the providers and the users, from the discovery of a microorganism and R&D projects, to commercialization of a specific product or process.

First, the bioprospector and the R&D user of a microorganism should enter for instance into a collaboration agreement for the development of industrial products from biodiversity. This agreement will provide essential clauses such as: identification of the collection transferred to the user and the product to be developed by the user (e.g. protein), the ownership of the collection, the rights granted to the user (to exploit the product, to grant licence on the product or process developed), financial or non-financial returns on the exploitation of products and the duration of this agreement. At this stage, users should verify that providers have obtained any required authorizations from the country of origin and comply with national legislation on ABS and therefore can transfer genetic resource to R&D users. This agreement should also organize the end of the collaboration by providing the duration of agreement, the notice required to terminate it, the ownership of the intellectual property rights created at the end of the agreement, dispute settlement provisions and the length of the confidentiality obligations.

Then, bioprospectors and users can enter under a second research and collaboration agreement for the discovery and development of products and processes. Under this second agreement, R&D users screen genetic resources provided by bioprospectors to extract and isolate information from a microorganism and select genetic resources of interest for an industrial partner. The results of the work performed by the R&D users under this agreement will then be developed further and incorporated into a product or a process.

When drafting this agreement the parties need to consider the specific clauses and issues such as description of the research programme, ownership of the results and IPR arising from the research programme (how to protect the results: keeping them secret as know-how or filing patents), the exploitation rights granted by the R&D user to the industrial and the applications/field in which the exploitation rights are granted and general clauses such as the term of the agreement, the provisions for early termination. Exploitation rights can also be covered by a separate agreement such as a licence agreement whereby the provider will grant to the user the right to manufacture a product or process in return for financial or non-financial compensation.

Finally, in order to protect the results of the R&D programme, the parties might agree on specific

confidentiality clauses and restricted publications and communications of the results. Confidentiality is important here because the disclosure of a product or its study may prevent a party from filing a patent application since one of its conditions is the novelty of an invention.

The new genes, proteins or processes resulting from the R&D programme can be protected by patents. A patent is a legal title granting its holder the right to prevent third parties from commercially exploiting an invention without authorization, for a limited period of time, within a territory where the patent is granted, in exchange for its disclosure to the public.

The extent of the protection conferred by a patent is determined by the claims. Nevertheless, the claims shall be interpreted in accordance with the description and drawings.

In Europe, Articles 52–57 of the European Patent Convention (EPC) provide criteria of patentability, and inventions that are patentable or not (European Patent Office, 2007). An invention can be protected by a patent if it has a technical nature. Therefore, things that do not belong to the field of technology such as 'discoveries, scientific theories and mathematical methods, aesthetic creations, schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers, presentations of information' are not patentable. However, it is to be noticed that rules for playing games, method of doing business, computer programs and presentation of informations can be patentable if they have a technical character, the technical character may be imparted by steps solving a technical problem or achieving a technical effect. Patent laws set conditions for granting of a patent for inventions related to process, machine, manufacture or composition provided that they are new, involve an inventive step, and are susceptible of industrial application, or utility, in the view of the prior art.

EPC sets out three criteria of patentability which are very specific.

First, the invention must be new. The novelty, governed by Article 54 EPC, stipulates that:

- (1) An invention shall be considered to be new if it does not form part of the state of the art.
- (2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application . . .

A new invention however is not necessarily patentable. The second patentability requirement, namely the inventive step, has to be met. It is provided by Article 56 EPC:

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.

Lastly, the invention must be capable of industrial application (Article 57 EPC):

An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture.

However, some inventions are not patentable, and specific exclusions are provided in Article 53b, such as:

plant or animal varieties or essentially biological processes for the production of plants or animals; this provision shall not apply to microbiological processes or the products thereof.

Although patentability of some biotechnological inventions is subject to controversy for ethical reasons, they can be protected provided they meet patentability requirements and specific provisions (Directive 98/44/EC, 1998). For instance, a DNA sequence with the indication of its function and its industrial application can be protected under a patent. An isolated microorganism with defined characteristics can be patentable for specific application(s) provided the biological material is deposited with a recognized depositary institution, if it is not available publicly and cannot be described in the application. Finally, the patent rights depend on the territory where the protection is given. A patent application must be filed, and a patent shall be granted, in each country in which the protection is sought. Patents can be filed within a national, regional (e.g. European and African regions) or international procedures. Each patent system has its own features. In general, the protection in a particular country is acquired by national filing. Then, the rights can be extended abroad by filing a regional application as an European patent application under the EPC, or an international application under the Patent Cooperation Treaty (PCT). In particular, PCT member states where protection is sought must be designated within the priority period (12 months from the first filing date of patent application). After expiration of a period of 30–31 months from the earliest priority application date, the international application must be converted into separate national and regional patent applications covering every country in which patent protection is sought. This procedure called National Phase Entry can be very costly since national fees must be paid in each country and the patent application have to be translated into the language of each country.

Patents enable the patent holder to protect and enforce their rights. In that sense, the patent rights convey the patent holder the right to prevent others from commercially exploiting its invention without its permission. Typically, whoever wishes to exploit a patented invention would have to take a license of this latter. Yet, a patent does not necessarily give the patent holder the right to exploit the patent. In fact, the patented invention itself may depend on other prior patents owned by others parties.

Stage 3: Industrial exploitation

Research programmes leading to the successful development and industrial production of the final product imply significant investments. Indeed, it is important for industrial companies to assess the risk before making any decision on the allocation of resources. Furthermore, before launching on the market and commercialization of the final product and/or process, several legal and economic criteria must be assessed including the Freedom To Operate (FTO), the regulatory aspects of said product or process, the distribution and market shares.

While the intellectual property experts ponder over product patentability, industrial companies question whether a product or process is free to operate or not. Indeed, FTO is a key element to be checked. FTO determines whether a particular action, such as making, selling, using, importing a product, can be done without infringing valid intellectual property rights of others. Therefore, in case of patents covering one or several elements of its product or process, industrial companies might need to buy a license for each patented elements.

Under the CBD, industrial companies exploiting genetic resources should share their commercial benefits with the provider, as discussed in stage 1. Typically, they shall conclude a contract to define any financial compensation or other returns. In this respect, the fair and equitable sharing of the benefits principle mentioned in the Article 15 of the CBD remains applicable to this relationship. When industrial companies collaborate with a user performing R&D programme based on biodiversity (as described in stage 2), the agreement shall provide compensation paid to the user in return for the exploitation rights granted. The user will then be responsible for distributing benefits to the provider in accordance with the provision of the agreement concluded with him. Monetary benefits may include, for instance, milestones payments, or licence fees (royalties) in case of product commercialization. The transfer can also be defined on a non-commercial basis, such as the sharing of R&D results, participation in product development, collaboration, cooperation and contribution in education and training or joint ownership of relevant intellectual property rights.

The total cost for developing a product or a process has to be weighted against a possible benefit made by selling the product. Decisions on this commercial venture depend on investment of resources and expected returns on investment.

Conclusion

Biotechnology has become increasingly important in everyday life in many areas such as healthcare, agriculture, food, environment and energy. It enables to develop environmentally friendly industrial processes and innova-

tive products. The process that leads from the discovery of a marine microorganism to the commercialization of a product requires substantial human and financial investments. In this respect, industrial companies have to assess many different parameters before launching a product.

Collecting microorganisms is a key step which can be discussed on a legal point of view due to the complexity of the terms and conditions surrounding bioprospecting. Then, industrial companies exploiting biodiversity must comply with the rules on ABS and should also take into account R&D, patent and license costs. Furthermore, FTO and evolution of the market should also be considered before launching a product. As a matter of fact, appraisal of the actual value of genetic resources for R&D programmes varies between users and providers. Although research can lead to the discovery of new microorganisms, these latter do not always have a successful industrial application. Among the few strain candidates selected within the frame of an R&D process only a very limited number of strains or elements derived from them would eventually be industrially exploited. In addition, the originality and the scientific value of a strain may not match its financial value. Therefore, providing countries should be aware that without R&D investments, production steps, marketing and sale there will be no products deriving from microorganisms on the market and therefore no benefit to share with the providers and no technology to transfer to those latter.

Companies are not reluctant to comply with ABS principles; however, they need security when developing commercial products from biodiversity. Providers, users and industrial companies need clear and straightforward procedures for the access to genetic resources and benefit sharing.

Since the ratification of the CBD, many efforts have been made to clarify the implementation of regulations regarding bioprospecting and ABS. However, additional guidelines such as the Bonn Guidelines and MOSAICC recommendations are still not sufficient to create a functional system.

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