Biodiversity and biopiracy

Biodiversity

Challenge

"Biodiversity," or biological diversity, refers to the variety of life on earth. It encompasses three categories: genetic, species and ecosystem diversity. Biodiversity is vital to maintaining the balance of life on our planet.

- Genetic diversity refers to the variation of genes within species.
- Species diversity refers to the variety of species within a region.
- Ecosystem diversity refers to the different communities or habitats found in a given location.

The world's natural ecosystems are deteriorating at a rate unprecedented in human history. Preserving biodiversity and ensuring the sustainable and fair use of natural resources stand out as key issues worldwide. Today they are an essential part of any corporate social responsibility policy, and are considered critical topics for Sanofi.

The pharmaceutical industry places a great deal of importance on biodiversity because natural resources are critical for the discovery and development of new drugs. Natural resources have valuable potential as sources for new chemical substances and active ingredients. Today, biologists consider that natural resources are the treasure troves of pharmacopoeia in the 21st century, given the remarkable diversity of their substances and active ingredients.

The Nagoya Protocol

In October 2010, the Conference of the Parties to the Convention on Biological Diversity (CBD) held their tenth meeting in Nagoya, Japan, drawing up what is referred to as the Nagoya Protocol. It was designed to contribute to the conservation and sustainable use of biodiversity.

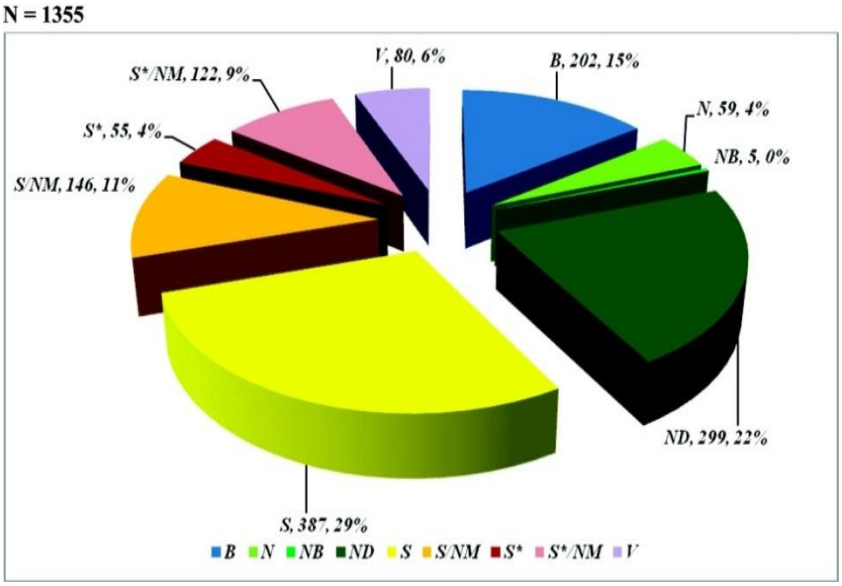
This international agreement provides a legal framework to ensure the fair and equitable sharing of benefits arising from the utilization of genetic resources, directly addressing one of the three objectives of the CBD.

The Nagoya Protocol has been at the center of debate in the business world and society at large, and Sanofi takes an active part in these discussions. Questions remain to be answered concerning how the protocol will be implemented, and how companies can prepare themselves to satisfy the new requirements set out in the protocol.

The Nagoya Protocol was open for signature by Parties to the CBD from February 2011 until February 2012 at the UN Headquarters in New York. The protocol will enter into force on the 90th day after the day of deposit of the 50th instrument of ratification. At the end of February 2013, 14 countries had ratified the protocol.

Biodiversity and the pharmaceutical industry: origin of compounds

Over the past 30 years, 46% of the 1,355 new chemical entities that have been marketed worldwide have come from substances found in nature.



These 1,355 new compounds may be broken down as follows:

N = Natural product

NB = Natural product botanical (in general these have been recently approved)

ND = Derived from a natural product and is usually a semisynthetic modification

S = Totally synthetic drug

NM = Natural product mimic

S* = Made by total synthesis, but the pharmacophore is/was from a natural product

V = Vaccine

References: Source: David J. Newman and Gordon M. Cragg, "Natural Products as Sources of New Drugs over the Last 30 Years from 1981 to 2010"," *Journal of Natural Products*, 2012, Vol.75(3), p 311-335.

For more information about natural products as sources of new drugs, see: http://pubs.acs.org/doi/full/10.1021/np200906s#

Strategic approach for the Group

Sanofi concentrates on three key issues relating to biodiversity:

- the controlled use of natural plant and wild animal species for research projects to discover new drugs;
- determining the fair distribution of benefits resulting from putting this type of resource on the market; and
- ensuring the preservation of biodiversity surrounding the Group's sites and beyond, particularly in fragile or protected zones.

Since 2012, the biodiversity policy is under the responsibility of the Sanofi group Bioethics Committee. The objectives for 2013 are to establish a roadmap to assess the access and supply of natural substances though all Sanofi affiliates.

Adhering to the Convention on Biological Diversity

The Sanofi Group adheres to the Convention on Biological Diversity outlining the principles for obtaining and using natural resources and stipulating that suppliers must comply with the CBD. These contracts set conditions for sharing the benefits arising from the use of these resources.

For more information: Convention on Biological Diversity www.cbd.int

Complying with the Group's own guidelines

Sanofi's biodiversity policy is summarized in the Group's position paper. This paper presents an overview of all the principles that our Natural Product Science (NPS) Center in Frankfurt, Germany, has implemented over many years to preserve biodiversity. It also demonstrates that biodiversity and the fight against biopiracy are key issues for Sanofi, and establishes a clear position on fighting all forms of biopiracy.

For more information:
Please refer to the Group's Position Paper on Biodiversity and Biopiracy in the Download Center.

These guidelines are consistent with the Group's human rights principles, specifically in regards to the fair and equitable sharing of the benefits arising from the use of genetic resources.

For more information:
Please refer to the Group's human rights principles in the 2012 CSR Report and Download Center.

Taking action to preserve biodiversity

In order to translate our policy into action, in 2011 and 2012 the Group has committed to:

- verify, prior to placing an order, that relevant plant species are not on the lists established by:
  - CITES: The Convention on International Trade in Endangered Species of Wild Fauna and Flora. See www.cites.org; and
  - IUCN: The International Union for Conservation of Nature Red List of Threatened Species. See www.iucn.org;
- ensure that all new relevant contracts are in line with the Convention on Biological Diversity and take into account the IUCN Red List criteria;
- ensure that suppliers produce, if necessary, the official authorizations that allow them to collect the plants that have been ordered; and
- continue to reduce the weight of powdered plant samples used in research.

Sanofi ensures compliance with local regulations. Regarding the preservation of protected natural areas surrounding the sites concerned, the Group carries out relevant environmental impact assessments.

The pharmaceutical industry will need to address a number of questions arising from the application of the Nagoya Protocol. Once the Protocol goes into effect, Sanofi is committed to updating the Group's positions on key issues, such as the use of influenza strains coming from various locations across the globe, which are essential for the production of Sanofi Pasteur's annual flu vaccine.

Actions

Natural substances used in R&D

The actions implemented to adhere to the Convention on Biological Diversity, and to comply with the Group's position on biodiversity, focus on the use of natural substances to develop new drugs. They entail:

- limiting the quantities of genetic resources used for research;
- identifying protected natural substances (IUCN Red List) and finding alternative solutions;
- establishing contracts with suppliers stipulating that they must comply with international conventions and national legislation on preserving biodiversity; and
- adhering to the principle of sharing benefits generated by the Group with countries that give access to their natural resources as well as with local populations having specialized know-how, whenever products made from natural substances are commercialized (see Biopiracy section, below).

For several decades, Sanofi's NPS Center has specialized in natural substances research. It brings together numerous experts and focuses primarily on investigating natural substances that may provide a source to develop new drugs. The center also shares knowledge with all the Group's R&D operating units that study natural substances for Sanofi's various therapeutic areas. During 2012, strategic considerations were initiated by the R&D management on new innovative models for global natural products activities.

For example, in 2011 this center had a collection of some 9,000 plants/plant extracts. Between 2003 and 2010, the Group's experts studied 647 natural substances from 152 plants. In 2011, following the implementation of a new extract screening method no plant-derived compounds were studied.

In an effort to preserve the species being used, Sanofi continuously seeks to streamline our R&D programs involving natural substances. Screening operations by the Group involve much smaller quantities than in the past for the 5,500 plant extracts screened recently. In 2000, a few hundred grams were required to study a plant's components, whereas today it only takes a few dozen grams.

With an eye to respecting protected species, since 2010 Sanofi has regularly evaluated all the species held by the Group. These evaluations focus on assessing these substances based on the IUCN Red List of Threatened Species criteria. The list is updated annually. Therefore, natural species used by Sanofi that were not protected when preliminary research was carried out may have been added to the list after this research was initiated. It is also important to note that the IUCN Red List is a recent initiative. Sanofi has been compiling our natural substances database for several decades – before the IUCN list was developed and at a time when the scientific community could not predict the extinction of certain plants.

Results from the most recent evaluation show that only 1.3% of plants held by Sanofi appear on the 2011 IUCN Red List of Threatened Species.

For more information: IUCN Red List of Threatened Species, www.iucnredlist.org/about

Contracts between Sanofi's NPS Division and natural species suppliers (currently based primarily in China and Madagascar) include clauses about preserving biodiversity. Suppliers are required to comply with the CBD and obtain local authorization, where necessary, to collect specimens.

Some contracts go above and beyond respecting these obligations. For example, collaboration between Sanofi and the Chinese firm Chengdu Diao, specializing in extraction, was set out in a contract that includes:

- a clause for sharing potential benefits if the natural substances studied are used for new drugs;
- a clause for transferring technology related to extracting, purifying and splitting compounds derived from these substances; and
- a commitment to train Chinese employees at the Frankfurt site on extraction and purification techniques.

Similarly, the contract between Sanofi and IMRA – the Malagasy Institute of Applied Research – includes a clause for sharing benefits if drug compounds are extracted from the supplied plants.

Collaborative partnership with Warp Drive Bio
In 2012, Sanofi R&D started to implement a new collaborative model for the use of natural products. Sanofi co-invested in Warp Drive Bio, which is an innovative biotechnology company focusing on proprietary genomic technology to discover drugs of natural origin. In this collaboration, the Warp Drive Bio team will assemble an array of technologies to create a platform for identifying potential drug candidates using microbiology, next generation sequencing, cutting-edge bioinformatics and chemo-informatics. Warp Drive Bio's integrated process pairs a 'genomic search engine' and customized search queries that enable natural products that are hidden within micro-organisms to be identified on the basis of their distinctive genomic signature. Sanofi will give Warp Drive Bio access to its strains library and natural product expertise.

Natural substances used in manufacturing processes

Production of Artemisinin
Artemisinin is a key ingredient of treatment of uncomplicated malaria and it is extracted from Artemisia Annua, sweet wormwood produced by local farmers mostly in Asia and Africa. In order to have an alternative source to the plant derivative Artemisia Annua, Sanofi has started an innovative project aiming to develop a new synthetic biology pharmaceutical manufacturing process to produce Artemisinin.

Farming alone cannot produce enough of the compound to meet the global demand. Nevertheless, sweet wormwood growers will continue to provide plants for a share of the Artemisinin market, but it will not be the only source of supply.

The Artemisinin project is led by a non-profit drug development organization OneWorld Health (OWH-drug development affiliate of PATH) and is funded by the Bill & Melinda Gates Foundation. The project began in 2004, and partners include a start-up - Amyris, Inc., Sanofi, and Professor Jay Keasling from the University of CA Berkeley. The novel use of synthetic biology technology is based

on pioneering inventions from UC Berkeley, Amyris, the National Research Council Plant Biotechnology Institute (NRC-PBI) of Canada, and Genoclipp Biotechnology BV.

Sanofi is the commercial partner and the Artemisinin project entered the industrial production phase in 2011. Several tons of materials were produced in 2012 and are available for testing to qualified buyers. Sanofi plans to produce approximately 30 tons of semi-synthetic Artemisinin in 2013, and scale up to 50-60 tons per year in 2014 and beyond.

Preserving biodiversity around Sanofi sites and beyond

Sanofi understands the importance of biodiversity for the pharmaceutical industry. As a global healthcare partner, we are committed to safeguarding the environment. The Group pursues many initiatives designed to preserve biodiversity at our sites and in the surrounding areas, and beyond. Notably, three of the Group's industrial sites (Swiftwater (US), Vertolaye (France), Csanyikvolgy (Hungary)) are located in environmentally protected zones where environmental regulations are more stringent. These sites are under particular scrutiny.

We endeavor to build on the momentum of the International Year of Biodiversity in 2010, a year-long celebration of the value of biological diversity for the planet. Through our actions, Sanofi shows support for the new Strategic Plan for Biodiversity, which aims to reduce biodiversity loss. We also plan to play a role in the UN Decade on Biodiversity, 2011-2020.

In addition to complying with the Convention on Biological Diversity, the Group defined its own biodiversity policy in 2010. We want to take tangible steps that make a difference, such as limiting the environmental impact of our activities around our sites worldwide.

For more information:

- Please refer to the Group's Position Paper on Biodiversity and Biopiracy in the Download Center.
- Convention on Biological Diversity: www.cbd.int

Sanofi sites are implementing a wide range of programs to preserve biodiversity in the areas surrounding their facilities. Here are a few examples.

- France: Sanofi's Toulouse site
- Ireland: Genzyme Waterford

France: Sanofi's Toulouse site

In 2011, our R&D site at Toulouse, France, initiated an environmental impact assessment, which we have entrusted to a specialized consulting firm (Gaiadomo).

Sanofi's Toulouse site is located in a rich natural setting that is adjacent to ecologically important areas including those listed on the Inventory of Natural Areas of Ecological, Faunistic and Floristic Interest (known as ZNIEFF in French). It is also near some Natura 2000 areas. Natura 2000 is a European network of areas for bird conservation and for protection of land and marine habitats that are home to rare and endangered wild species of flora and fauna.

Also in close proximity to our R&D site is the Garonne River, one of the principal waterways in France and an important part of the country's river network. Sanofi wishes to determine how our activities impact species and natural habitats along the river.

This pilot environmental impact assessment project consisted of a study both *in situ* and *ex situ* to meet the following goals:

- establish a baseline;
- identify risks and opportunities related to biodiversity;
- determine environmental challenges at and around the site;
- develop ways to limit the site's environmental impact and better plan its development;
- strengthen and enhance existing environmental approaches; and
- recommend specific actions that will make a clear contribution to developing biodiversity.

This initiative will help the Group improve its in-house expertise in regards to preserving biodiversity in relation to its facilities.

The findings of this pilot project were presented in February 2013 and recommendations at the level of the Toulouse site were proposed. Based on the findings of the study, a handbook of recommendations on '10 Best Practices to Enhance Biodiversity at Sanofi Sites' has also been developed and will be shared with site managers and HSE team members worldwide.

Ireland: Genzyme Waterford - Conserving Local Biodiversity

As in other Sanofi facilities, Genzyme Waterford is implementing an initiative to conserve its local wildlife and provide a green area for Genzyme's employees. This initiative grew from the discovery of the presence of the common frog, Rana temporaria, which lives and breeds in the wetland habitat found on site.

As the common frog is a protected species in Ireland, Genzyme Waterford is playing its part in conserving the local population. By enhancing the ecosystem to support the frog, hundreds more species will also benefit. Plans are in place to create a small walkway for Genzyme employees through this green area. Minimal development of a raised, recycled-plastic boardwalk will occur in the wetland habitat which the frogs inhabit. A wildlife corridor will be created to connect the wetland to a grassland meadow south of the site. In this existing meadow, a large wildlife pond will be established to support the breeding of frogs and some native fruiting trees and additional wild flowers will also be planted to support wildlife. With the construction of a wildlife pond, Genzyme Waterford is hoping to attract a second protected species to the site, the smooth newt, Triturus vulgaris.

In Waterford, we have a very high environmental standards, encompassed in our ISO 14001 standard. Our last ISO 14001 audit had zero non-conformances, and the protection of this area is identified on our environmental aspect register. This is Genzyme Waterford's chance to pilot an environmental project where we manage our land in the long term to benefit all. By investing in the environment we own and for which we are responsible, we are investing in the health and vitality of our entire workforce.

We officially opened our La Marche project to all team members at the beginning of February 2013, to coincide with International Wetland Day.

Biopiracy

Each time the Group investigates the use, for R&D purposes, of a new product isolated from natural sources, a contract is established, stipulating our adherence to the Convention on Biodiversity. This commitment aims to safeguard against biopiracy.

Biopiracy refers to the commercial utilization of endemic resources and local knowhow without sharing the profits with the communities or countries that are the source. The Convention on Biological Diversity (CBD) describes the principles governing such utilization, although local laws vary to a great extent.

Natural substances used in R&D

Sanofi's Natural Product Science Department, located in Frankfurt, Germany, is the Group's research department that performs most investigations of natural products. Each time NPS purchases new natural sources for its research, a contract that must comply with the recommendations of the Convention on Biological Diversity is established. Only after this contract has been drawn up does the research department receives the samples and may it proceed with its research project. In particular, the contract may cover pre-existing knowledge and industrial property, the conditions for the use of results, the modalities of the transfer of knowledge, and if it leads to development and market authorization, any consequential royalties and financial profits.

Each new natural source studied (for example, a plant) is registered in a database internal to NPS. Once the natural compounds have been isolated and identified (for example, from a plant), the structures of the pure natural compounds are registered in a Group chemical database. Moreover, when a biological activity is demonstrated for one of these compounds, it is also recorded in another Group database – the biological database. Links between the biological and chemical databases make it possible to determine, for each new chemical compound created, whether or not there is a connection with a naturally derived compound.

Depending on the original contract, it may be possible to file a patent when a new biological activity is demonstrated; compound development is then carried out in compliance with the terms of the original contract, and may lead to royalty payments if the compound is brought to market or key clinical steps are taken. Raw material supplied for production may be provided either by extraction from the original source, or by chemical synthesis (semi-synthesis or total synthesis), which is sometimes competitive from an economic standpoint. In the case of extraction, a feasibility discussion will be carried out with partners depending on the quantities required.

For more information: Convention on Biological Diversity, www.cbd.int