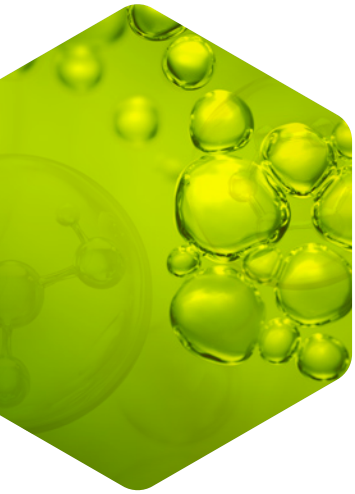

Accelerating Innovation in Life Sciences

A Primer on Technology Transfer in the Field of Biotechnology

WIPO

Accelerating
Innovation in
Life Sciences

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WORLD
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Contents

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Summary

A Primer on Technology Transfer in the Field of Biotechnology aims to help biotechnology innovation stakeholders understand the environment needed for sustainability, legal certainty, and effective technology transfer in this sector. In addition, it considers challenging issues such as the role of intellectual property (IP) in the creation, protection, commercialization, and transfer of research outcomes from laboratories to public and private users.

Biotechnology innovation takes place in both the private and public sectors, and biotechnology innovation stakeholders may be involved in, for example, research and development (R&D), production, evaluation, protection and out-licensing, funding, marketing or commercializing of these innovations. Stakeholders may be working in universities to transfer research outcomes from laboratories to end-users and may also be found in other settings such as businesses, manufacturing, government agencies, independent research institutes, non-governmental or intergovernmental organizations, or public–private partnerships. Given the current scale and scope of university-based technology transfer, the main focus of this *Primer* is to provide guidance, with templates and suitable language, for technology transfer professionals who are tasked with managing the out-licensing of university-generated innovations in the field of biotechnology. The term "technology transfer" as used herein will most often refer to the process of licensing or otherwise facilitating the transfer of biotechnology innovations resulting from university research to the commercial sector for further development, with the goal of commercialization and at the same time benefiting society. Nevertheless, because the *Primer* discusses the issues that arise at many steps in the technology transfer process, and the perspectives both sides may bring to a strategic decision, biotechnology innovation stakeholders working in other settings will find useful guidance here.

The *Primer* provides an overview of the unique nature and specificities of biotechnology R&D, the resulting life sciences innovation ecosystems and their benefit to society. It also provides real-world examples of successful transfers of health-related biotechnology innovations from academia to industry to illustrate some of these unique aspects. Examples of important inventions that have arisen because of publicly funded research in collaboration with commercial stakeholders are included. Finally, the *Primer* provides a detailed description of the various types of agreements that are often utilized when university-derived biotechnology innovations are transferred to and commercialized by industry partners.

The *Primer* has been developed with the help of prominent experts with the goal of providing information that is accurate, practical and up to date. However, it is not intended to provide an exhaustive overview of biotechnology technology transfer as there are additional types of agreements that may be used in the development, manufacture, marketing and commercialization of biotechnology products. Instead, the *Primer* highlights various issues and factors for technology transfer professionals around the world to consider, all with a specific focus on biotechnology innovations.

1 What is biotechnology?

Biotechnology is the applied science that uses living organisms, biological processes, and products to develop goods and services for human use. Though definitions vary, they all emphasize applying science and technology to biological systems to create products and services. This chapter presents a brief history and overview of the biotechnology field.

Biotechnology is an applied science that involves the deliberate utilization of living organisms, biological processes and biological products to develop products and processes for human use. While there is no internationally agreed definition of "biotechnology" in existing international IP agreements, regional and plurilateral definitions have been adopted. The Organisation for Economic Co-operation and Development (OECD), for example, defines biotechnology as "the application of science and technology to living organisms as well as parts, products and models thereof, to alter living or nonliving materials for the production of knowledge, goods and services".[1] In the European Union (EU), the European Medicines Agency (EMA) defines biotechnology in the pharmaceutical context as "the use of living organisms to create or modify products, including medicines".[2] The World Intellectual Property Organization (WIPO) glossary refers to Article 2 of the Convention on Biological Diversity (1992) which defines the term as "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use".[3] In summary, biotechnology is inherently innovative because it involves taking organisms, processes, structures or products out of their so-called "natural" context and then utilizing them under conditions such that they function like tools to achieve a desired result.

Brief history of biotechnology

The first biotechnological applications were developed thousands of years ago. Archeological evidence suggests that humans have been practicing a form of biotechnology for over 6,000 years, beginning with the use of yeasts for brewing and bread making, and the use of microorganisms and enzymes for processing milk into various foods, such as yogurt and cheese. Humans have devised hundreds if not thousands of ways to utilize entire organisms such as bacteria or yeasts, or portions, tissues or extracts of animals, plants or fungi, to provide useful products and processes such as foods, fibers, dyes, compost, silage and medicines. As scientific advances allowed researchers to study normal biological processes at the cellular, molecular and genetic level, they used this knowledge to develop more sophisticated biotechnological tools. Since the 19thcentury, modern biotechnology has increasingly drawn on microbiological and, since the middle of the 20thcentury, also on molecular biological, genetic or genetic engineering findings and methods. This has made possible the development of manufacturing processes for chemical compounds to use as active ingredients for pharmaceuticals or as basic chemicals for the chemical industry, diagnostic methods, biosensors, new plant varieties and more.

1 OECD, Glossary of Statistical Terms, https://stats.oecd.org/.
2 European Medicines Agency (EMA), Biotechnology, https://www.ema.europa.eu/en/glossary/biotechnology.
3 WIPO, Glossary, https://www.wipo.int/tk/en/resources/glossary.html#8.

The mid-20th century

By the mid-20th century, researchers had started using a natural process of gene exchange by means of plasmids (small pieces of deoxyribonucleic acid (DNA), usually circular, that can be transferred from one organism to another and confer new properties) to create novel organisms with desired properties. Subsequently, it was understood that DNA encoded information, that expression of a gene (expression of the encoded information) resulted in a product such as a protein, that ribonucleic acid (RNA) molecules mediated translation and regulation of gene expression, and that DNA molecules could be deliberately manipulated to change the encoded information. This is called the central dogma of molecular biotechnology and the utilization of its various natural subprocesses in technological applications has led to an exponential increase of biotechnological innovations. Concretely, this led to the development of a rapidly expanding toolkit for recombinant DNA technology (also known as "genetic engineering") whereby coding and regulatory sequences can be assembled by precisely cutting preexisting DNA at defined sequences (often using enzymes derived from bacterial defense systems), and splicing the cut ends (often using enzymes that are normally involved in cellular damage repair) to build a construct that allows expression of a gene in an environment where it does not naturally occur; for example, the expression of a human gene from a construct inserted into a bacterium (often called transgenic expression or heterologous gene expression).

The 1970s

One of the first commercial products of recombinant DNA technology in the 1970s was recombinant insulin made by splicing DNA encoding chains of human insulin into the genetic material of a bacterium and using the cellular machinery of the bacterium to produce insulin chains. Recombinant DNA techniques were soon used successfully to produce other therapeutic proteins including antibody-based therapies for cancers and immune disorders. These techniques were also used to create modified plants and animals with desired traits. Recombinant DNA techniques have thus revolutionized not only therapeutic options through the development of new innovative drugs, such as biopharmaceuticals, and therapeutics, but also diagnostics by providing methods and products for detecting specific genetic signatures or biomarkers associated with specific diseases.

The 1980s and onwards

The groundwork for the development of new products, processes and technologies to address global challenges in healthcare, the environment and food supply was laid by further technical innovations made in the 1980s and continues to develop dynamically. Polymerase chain reaction (PCR) technology enabled great advances in genetic analysis, precision synthesis of DNA and diagnostics. Genome editing techniques allowed researchers to make direct changes to the DNA of a living organism by inserting, deleting or changing sequences at a precise location. It is important to note that genome editing using technologies such as zinc-finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs), or the more recently developed (2010s) clustered regularly interspaced short palindromic repeats (CRISPR)-Cas systems, differs from previous recombinant DNA techniques because it makes precise changes to the existing DNA of a living organism to achieve the desired effect, and does not require building and inserting recombinant DNA constructs into a cell. This new technological practice of precise, site-specific editing of genomes of organisms without the use of, often patented, recombinant DNA constructs has also led to new legal practices in the prosecution, acquisition and exercise of IP rights for the resulting inventions, such as new licensing and technology transfer practices.

Alongside the new genome editing techniques, genomic sequencing has been another transformative technology that is reshaping the field of biotechnology. Sequencing parts or all of an organism's genome is putting vast and ever-increasing amounts of genomic sequence data at the disposal of biotechnological innovation. Just like genome editing, the rise of high-throughput genomic sequencing has led to significant changes in IP practice in many fields of biotechnology and has therefore reshaped technology transfer practices.

Furthermore, these advances in feasible biotechnological applications, such as genome-edited plants rather than genetically modified plants, have created new questions at the interfaces between IP and related regulatory frameworks, which may affect technology transfer for biotechnological inventions. According to current understanding, interventions in the genetic material of organisms are irreversible, and potentially undesirable consequences may only occur phenotypically in the next generation or the generation after that. Thus, a distinction must be made between biotechnological processes that interfere with the genetic material of an organism and those that do not.

While the ever-evolving toolkit for biotechnological innovation continually adds new techniques, it also retains tools such as fermentation and selective breeding that have been used for thousands of years. This is particularly the case in plant breeding, where conventional selective breeding techniques are still used despite the increasing use of new plant breeding techniques. The widespread uptake of biotechnology products and processes has led to attempts to define "categories" of biotechnology based on their field of use and the issues of regulation and perception that are triggered by use in each field.

Main categories

The major categories are:

- **medical biotechnology** ("red biotechnology") for the development of drugs and therapeutics, vaccines, diagnostics and detection methods; this encompasses a wide range of biotechnological applications from biochips for medical diagnostics and personalized medicine to drug production and gene therapy, often involving the use of genetically modified organisms;
- **agricultural biotechnology** ("green biotechnology") for the improvement of crops and livestock in agriculture and food production, such as drought-resistant or pest-resistant crops, or biocontrol agents;
- **industrial biotechnology** ("white biotechnology") for the industrial production of organic chemicals as well as active substances with the help of optimized enzymes, cells or micro-organisms, using living cells or isolated enzymes that have been designed for purposes such as cleaning, degreasing, bioremediation, degradation of biological waste, production of products such as biofuels or biopolymers (bioplastics), or reducing energy needs by acting as biocatalysts.

The expanding use of biotechnology products and processes into new fields to address new problems has generated a rainbow of additional classifications. Descriptions of these classifications vary between life science sectors and thus several classifications and color codes are used. However, one available summary describes them as follows:[4] blue biotechnology – the application of biotechnology methods to living organisms from the sea or to aquatic organisms more generally; yellow biotechnology – applied to improve nutrition; gray biotechnology – applied to environmental preservation and contaminant removal; and brown biotechnology – applied to desert and arid lands. There are also associated fields such as bioinformatics (gold), biotechnology law, regulation and IP (violet) and bioterrorism (dark biotechnology).

This classification scheme is merely a way of trying to organize complex information. There is some overlap between classification systems, as most use the same technical and analytical tools. Similarly, some emerging fields, such as synthetic biology, are difficult to classify because they cannot be clearly assigned to any of the classifications mentioned. Synthetic biology is focused on engineering biomolecular systems with novel capabilities, where the systems may be contained in a cell or organism that produces a novel product or has a novel metabolic pathway, or may be acellular, such as an array of enzymes on a scaffold that form a novel pathway. Products of synthetic biology can be found in most categories of biotechnology. Because every field of biotechnology is based on the same (or similar) underlying biological and technical principles, research in every category will use tools such as PCR, library screening, genome editing, random mutation or phage display as may be needed for a specific project,

4 Kafarski, P. (2012) Rainbow code of biotechnology. *Chemik* 66, 814–816.

although certain techniques may be adapted to a specific organism or use. The entire field is supported by platform technologies such as high-throughput screening, large-scale arrays, automation (of assays, sequencing, genetic manipulation) and analytic platforms that utilize existing scientific data such as information from genetic analysis or combinatorial chemistry or that solve problems computationally, such as protein folding, predictive structure–function models or deep genome projects.

2 How is biotechnology in the life sciences used today?

This chapter looks at how biotechnology is used in daily life, from health technology applications, environmentally friendly products such as enzyme-based detergents and biodegradable plastics, to agricultural applications that enhance crop resistance and nutrition, to developing climate-resilient plant varieties crucial for global food security amid climate change.

Products and processes of biotechnology are ubiquitous in today's world and are improving the everyday lives of end-users globally. The results of innovation in biotechnology are being applied to develop medicines to treat diseases that were previously incurable or difficult to treat, and vaccines to prevent communicable diseases; to synthesize new forms of fuels to replace petrochemicals; to achieve high-yielding, environmentally adapted crops and livestock; and to provide environmentally friendly products.

In health, biotechnology is used to reduce rates of infectious disease through messenger RNA (mRNA) and DNA technologies and new target discoveries. It is also used to provide treatments for chronic diseases through the development of biological therapeutics, somatic cell and gene therapies, [1] and powerful new technologies such as CRISPR-Cas genome editing. In the context of personalized medicine, biotechnology can make a decisive contribution to tailoring treatments to individuals in a way that minimizes health risks and side effects. These technologies are also valuable in that they are more precise tools for disease detection. In short, biotechnology products are a new generation of products being used to combat serious illnesses or rare diseases and public health threats confronting the world.

Biotechnology has been used to develop many products that are now used daily. Through fermentation processes biotechnology harnesses biocatalysts such as enzymes, yeasts and other microbes to become microscopic manufacturing plants. Products like cleaning detergents are made using biotechnology. Enzymes and microbes are used to produce alcohol as well as biofuels. Chymosin, a naturally occurring enzyme, is used to improve the efficiency of cheese production.

Certain types of microbes found in soil or seawater store energy as a polymer polyhydroxyalkanoate (PHA). The same microbes can break down PHA-based items and recycle them into food, eliminating plastic pollution even in landfills. Biobased plastics made from renewable resources such as sugarcane, soybean oil and corn are now available and cost-competitive, and many are biodegradable. Polyester, a synthetic polymer fiber historically made from fossil fuels and used to make clothing, blankets, carpets and other fabrics, can now be made by an engineered bacterium that ferments corn sugar into lactic acid which, when heated, creates a renewable polyester with improved ecofriendliness.

1 With regard to genome editing in humans, it should be noted that there is a ban on germline intervention in humans in many countries, and scientists worldwide have spoken out in favor of such a ban. For example, a UNESCO panel of scientists, philosophers, lawyers and government ministers has called for a temporary ban on genetic "editing" of the human germline and for a wide public debate on genetic modification of human DNA (https://www.unesco.org/en/articles/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits). A distinction should therefore be made between genome editing for germline intervention and somatic gene therapy which is widely accepted.

With a view to food production and global food security, biotechnology is being used to improve crop insect resistance, enhance crop herbicide tolerance and facilitate the use of more environmentally sustainable farming practices. Some of the food products of biotechnology include crops with enhanced nutrition profiles that solve vitamin and nutrient deficiencies, and foods free of allergens and toxins with improved oil content to improve cardiovascular health. In light of the pressures exerted on agricultural production by global climate change, agricultural biotechnologies also allow the development of climate-smart plant varieties and animal breeds with climate-resilient traits that can sustain global food security even during the anticipated increased impact of climate stresses on agriculture. Such climate-smart traits include increased drought tolerance, salinity tolerance, water efficiency, flooding tolerance and also resistance to climate-induced pests and diseases.

For the purposes of this *Primer*, however, red, or medical biotechnology will be the primary focus and will be used to illustrate the unique aspects of life science innovation in the technology transfer and commercialization process.

3 The life sciences innovation ecosystem: from bench to market

The journey of biotechnology products from laboratory discovery to market availability is complex. This chapter highlights the capital-intensive, lengthy process of biotech development, subject to strict and varying regulatory requirements across jurisdictions, including patent application and prosecution, licensing strategies, jurisdictional differences in technology transfer laws, , non-patent approaches for extending exclusive rights, and extensive clinical trials.

Early-stage development

The development and commercialization of the products of biotechnology innovation require complicated, elaborate and therefore lengthy and costly R&D efforts as well as complex manufacturing capabilities.

Manufacturing facilities for the production of biotechnology-derived medicines, as well as the drugs themselves, are subject to strict licensing requirements by regulatory authorities around the world. Complex regulatory approval processes apply in particular to biosimilars, the successor products of biopharmaceutical drugs, which – unlike generics as successor products of chemical-synthetic drugs – cannot be reproduced identically.

A similar complexity is also evident in other areas of biotechnological innovation. When products such as genetically modified crops or livestock or biocontrol agents, as well as some foods or industrial enzymes, made through biotechnological processes are released into the environment, they are subject to strict environmental regulations. Similarly, in most jurisdictions, biotechnologically modified plant varieties that might be used in plant breeding need to comply with phytosanitary measures and other market approval and registration requirements, as set out in seed laws for all seeds entering the market. Finally, foods based on genetically modified crops have to meet strict requirements set out by environmental and food laws.

Such regulatory requirements differ significantly among jurisdictions and, in practice, may interact with the exercise of IP rights by the innovators at the technology transfer and commercialization stages of those biotechnological innovations in those jurisdictions. While they are not addressed in this *Primer*, it should be noted that, in the life sciences field, market approval requirements additionally make the technology transfer and commercialization of biotechnological products and processes time and resource intensive. In short, research in biotechnology is very capital intensive, takes longer to mature than other fields of technology, and the manufacture of innovative products is often more expensive when compared with other domains.

To facilitate understanding of what it takes to bring a biotechnology product to market, this section of the *Primer* traces a biotech medicine from the start of R&D activities to the moment an active ingredient is discovered, through to testing and application for market approval by the competent authorities, and on to market approval and use in the patient who needs

it, and finally to post-marketing surveillance obligations once the product is on the market. Oftentimes it is the discovery of a gene or a gene product (usually a protein) with a unique property that ultimately leads to a commercial product. This discovery can take place in a public sector institution such as an academic research laboratory, or in a private-sector laboratory. The example presented here considers a discovery in an academic research laboratory that is likely to be the recipient of public funding.

Jurisdictional divergences

In many countries, research arising from public funding is governed by specific regulations designed to protect the public interest. These regulations set out specific requirements that must be met by the recipient of such funding. The subject matter, the conditions for patentability and the ownership of an innovation may differ from jurisdiction to jurisdiction.

The United States of America

In the United States of America (US), the transfer of technology developed from publicly funded research (research funded by federal grants to an academic research laboratory or nonprofit research institution, for example) to private entities for commercialization is governed by the Bayh-Dole legislation.[1] This act has been one of the most successful national statutory frameworks for facilitating technology transfer from academic research institutions to the private sector and a similar approach has been followed in many jurisdictions. Nevertheless, technology transfer legislation differs widely among jurisdictions worldwide and technology transfer policies and by-laws within each jurisdiction further differ widely among relevant universities and academic research institutions. This diversity of laws and by-laws cannot be addressed in this Primer, but more specific information on technology transfer laws and policies is available on the WIPO website at the WIPO Technology Transfer Section webpage.

European Union

For example, in the European Union there is no legislation at an EU level. Regulation therefore differs between EU member states. With regard to technology transfer agreements, the EU Technology Transfer Block Exemption Regulation (TTBER)[2] may apply and protects certain technology transfer agreements from being classified as anticompetitive.[3] However, the TTBER deals exclusively with the antitrust implications of technology transfer agreements, but not with the question of financing of R&D, and in particular not with the question of private or public financing.

The United Kingdom

In the United Kingdom (UK), although there is no specific legislation as such, the 1977 Patents Act, which harmonized UK law with the European Patent Convention, makes clear that inventions belong to inventors unless made in the normal course of their duties to their employers, in which case the invention belongs to their employer.[4] Japan's commercialization efforts are driven by Technology Licensing Offices and licensing is regulated by Japanese

1 The Bayh-Dole Act is a US federal law enacted in 1980 that enables academic institutions, nonprofit research institutions and small businesses to own, patent and commercialize inventions developed under government-funded research programs within their organizations. Key provisions include: 1) The university is entitled to retain ownership of any inventions created using federal government funding, unless the funding agency informs the university up front that it will retain title to inventions derived from the funded projects because of specifically identified "exceptional circumstances'" or other specified conditions. 2) The university must disclose the creation of an invention derived from federal government-funded research to the appropriate government agency in a specified period. The university also must patent all inventions it elects to own and commercialize. 3) The university must attempt to develop and commercialize the invention. If an attempt is not made, the federal government retains the right to take control of the invention. The government also may take control of the invention for other reasons, such as a need to alleviate health or safety concerns. This provision is referred to in the law as the government's "march-in" rights. 4) The university must provide the US government with a nontransferable, irrevocable, paid-up, nonexclusive license ("confirmatory license") to use the invention. 5) In granting a license to use the invention, the university also generally must give priority to small businesses, while maintaining the fair-market value of the invention. 6) When granting an exclusive license, the university must ensure that the invention will be "manufactured substantially" in the United States. 7) Excess revenue must support research and education. 8) The university must share a portion of the royalties with the inventor(s).

2 Commission Regulation (EU) No 316/2014 of 21 March 2014 on the application of Article 101(3) of the Treaty on the Functioning of the European Union ("TFEU") to categories of technology transfer agreements Text with EEA relevance ("TTBER"), OJ L 93, 28 March 2014, p. 17–23.

3 On May 1, 2014, the revised TTBER entered into force and the EU Commission issued related guidelines. The new regime is more restrictive in certain areas; e.g., passive sales restrictions, grant-back clauses and no-challenge clauses. From the guidelines, settlement agreements and technology pools can be identified as key aspects.

4 https://www.ipo.gov.uk/patentsact1977.pdf

patent law.[5] In Brazil, while there is no specific technology transfer legislation, license agreements must be recorded by the Brazilian patent office, INPI (Instituto Nacional da Propriedade Industrial). In the process of recording, INPI may make specific requirements or question specific payment methods, etc.[6]

Germany

In Germany, an employee invention is a patentable or utility model invention made by an employee in the course of his or her official duties. Under the German Employee Inventions Act, the employer is generally entitled to the rights to the service invention, whereas the employee only has a compensatory claim to remuneration. Even after the abolition of the so-called university lecturer privilege, special provisions apply to inventions made by employees at a university. The law also regulates the treatment of creative achievements by employees that cannot be protected by a patent or utility model or other means, but which improve the performance of a company ("technical improvement proposals").

Nevertheless, in an ideal setting, after many years of R&D, a researcher develops an invention[7] and, if it is deemed to have market value (in an academic institution this assessment is typically made by its Technology Transfer Office (TTO)), a patent application[8] is filed before the invention is made public to preserve the patentability of the innovation. The moment to file a patent application is, in practice, generally immediately after the conception of the invention and its commercial evaluation, before studies for the marketing authorization application are started. Due to the long regulatory pathway often required to move a biotech invention from a laboratory to the commercial marketplace, and the desire to have adequate patent life remaining to protect the invention once it reaches the market, patent rights are often (and ideally) licensed before a patent is granted.

Marketing authorization

In the marketing authorization procedure for a pharmaceutical product, the quality, efficacy and safety of the product must be tested before it can be administered to patients. In the context of efficacy, the medicinal product is assessed to ensure it has the described effect for the indication in question, while with regard to safety, any side effects associated with the product are evaluated. To enable the regulatory authorities to verify quality, safety and efficacy, the applicant must submit the results of preclinical and clinical studies with the application for marketing authorization.

5 The "Science and Technology Basic Law" (1995) states the government's responsibility for formulating and implementing policies for the promotion of science and technology and emphasizes the interaction between national R&D laboratories, academic institutions and business – a balance between basic and applied research and the improvement of research training. The Law to Strengthen Industrial Technology Capability (2000) relaxed the strict rules that prohibited researchers at public research organizations, as civil servants, from working for private companies. This law allowed university professors to consult for private enterprises and take managerial positions with companies in which their research was used. This also made it possible for the researchers to gain economic benefits for such activities. The enactment of the Industrial Vitalization Law (1999) transferred the ownership of inventions from government-commissioned research. This law, also called the Japanese Bayh-Dole Act, established the public research institution, commissioned by the state, as the owner of the IP emerging from the research. However, any invention or IP resulting from research done through the basic funding provided to each university professor was excluded, and the invention belonged to the professor.

6 Brazilian patent law determines that any improvement made on a licensed patent shall belong to the person who made the improvement. This is different from other licensing practices. The National Innovation Policy (NIP) of 2020 aims to "promote innovation in the productive sector" and "establish cooperation mechanisms between States, the Federal District and Municipalities," among other things. The NIP identifies six "axes" for implementation, including "alignment between … programs and actions to foster innovation promoted by the organs and public entities of the Union, the States, the Federal District and the Municipalities and the encouragement of private investments …." Id., Art. 5, §□□□□□□□□ I, II.

7 With regard to terminology, it should be noted that US patent law uses the word "discovery", while other jurisdictions use the word "invention". Concerning the terminology, see WIPO, *Learn from the Past, Create the Future: Inventions and Patents* (https://www.wipo.int/edocs/pubdocs/en/patents/925/wipo_pub_925.pdf), p. 5: "Generally speaking, an invention is a new product or process that solves a technical problem. This is different from a discovery, which is something that already existed but had not been found." The term "invention" will be used in the text but the terms "invention" and "discovery" as defined by national, EU or international patent law shall, however, not be affected by this Primer.

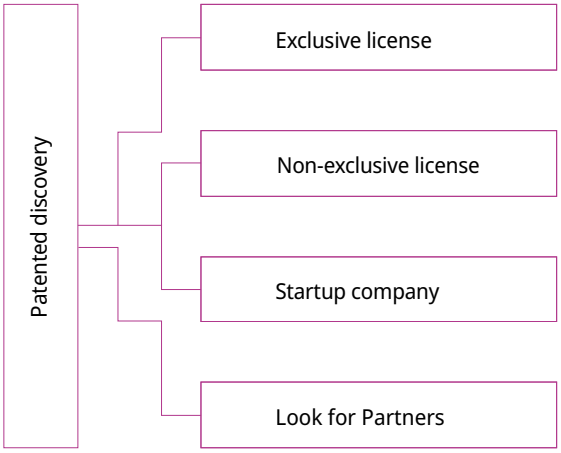
8 While detailing the different types of patent applications which may be filed on a biotech invention is outside the scope of this Primer, note that many academic institutions will file a Patent Cooperation Treaty (PCT) application early in the patenting process, as it has many advantages over filing directly in each country of interest. An institution can usually file a first application in its national or regional patent office and thereby gain up to a year to decide whether to file applications in other countries via a PCT application and/or direct filing. In most countries, the first application is a national application. Many US academic institutions will initially file a "provisional" patent application as allowed by the United States Patent and Trademark Office (USPTO), as it enables the applicant to have an additional year to generate data before a full nonprovisional utility patent application is filed in the USPTO and/or under the PCT and/or directly in other countries. For more information regarding PCT applications, see WIPO's PCT Applicant's Guide at https://www.wipo.int/pct/en/guide/index.html and the USPTO's summary of provisional and utility applications at https://www.uspto.gov/patents/basics/types-patent-applications/provisional-application-patent.

Patent application licensing

When patent rights are licensed before a patent is granted, the license agreement will often address unique issues that may arise during the term of the agreement, including which party has the right to lead and make decisions regarding prosecution of the patent applications, what happens if the parties disagree whether to pursue or maintain a patent application filing, who is responsible for the patenting costs, and whether the licensee is required to pay earned royalties on pending claims of a patent application. If a patent application is not licensed within a few years of filing, the patent holder may decide to abandon the patent application because of its weakened ability to attract investment over time considering the ever-shortening patent life. Ongoing acceleration of innovation and shortening of product life cycles in multiple biotechnology sectors may further contribute to such abandonment decisions. As well as the time required, the high costs of building global patent portfolios may be a challenge for patent applicants.

Besides these practical considerations, the combination of increasingly data-driven incremental innovation in the delivery of biological services, such as genome sequencing or editing, together with raised eligibility requirements in multiple jurisdictions for certain biotechnology patents, particularly "gene" patents claiming complementary DNA (cDNA) sequences, for example, for diagnostic tools, further contribute to changing trends in the frequency and extent of gene patenting in various biotechnology sectors. As the role of patents therefore changes within IP and technology transfer practices in the life sciences, biotech innovators are seeking to develop new tools and arrangements to facilitate efficient technology transfer within evolving life science ecosystems. Box 3.1 presents an overview of the early stages of moving biotechnological inventions from bench to market.

Box 3.1. Bench to market – early stages



- Study of multiple active ingredients in laboratory (screening)
- Discovery in laboratory (public or private)
- Extensive research for conception of a patentable invention
- Patented within one year of discovery
  - Technology Transfer Office in university

Supplementary protection certificates (SPCs)

Supplementary protection certificates (SPCs) are an IP right that serve to extend patent rights, particularly protection of the reward for the investments made to obtain the invention. They apply to specific pharmaceutical and plant protection products that have been authorized by regulatory authorities and aim to offset the loss of patent protection for such products

that occurs because of the compulsory lengthy testing and clinical trials they require before obtaining regulatory marketing approval.[9]

The European Union, for example, wishes to provide sufficient protection for these products in the interest of public health and to encourage innovation in these areas to generate smart growth and jobs. An SPC can extend a patent right for a maximum of five years. A six-month additional extension is available in accordance with Regulation (EC) No 1901/2006[10] if the SPC relates to a medicinal product for children for which data have been submitted according to a "pediatric investigation plan" (PIP). PIPs are required to support the authorization of medicines for children and ensure that enough data are collected on the effects of the medicine in children. The extension compensates for the additional clinical trials and testing involved in PIPs.

Exclusive licenses

Additionally, biotech patents are often licensed on an exclusive basis to provide the licensee with adequate financial incentive to invest in further developing the market potential of the technology. An exclusive license agreement is one of the most commonly used agreements to facilitate the transfer of an innovation to the marketplace. It both supports the licensee's ability to seek outside investment (or to justify to its shareholders the expenditure of internal resources to develop the technology) and have adequate autonomy over commercial development, while at the same time providing the patent owner with some degree of control over its IP assets to ensure it will have the right to participate in the licensee's prospective financial success.

Nonexclusive licenses

However, in the case of some platform technologies (such as technologies that could be exploited in multiple fields of use) the licensing strategy may be instead to pursue as many nonexclusive licenses as possible (assuming such a strategy is palatable to prospective licensees), or to require the exclusive licensee to grant sublicenses in fields of use that it is not developing and/or that do not interfere with its development plans (in cases where nonexclusive licensing is not a viable strategy given low industry interest). This is particularly appropriate where a licensee cannot cover the whole market on its own. As a rule, technologies requiring large investments of money and time (such as biotech medicines) will be licensed exclusively. Other technology (a research tool that requires little further development, for example) can be licensed widely and nonexclusively.

Research exemption

Sometimes an inventor becomes involved as a key scientific member of the team that further develops the ideas in the patent. For many inventors, however, particularly those in an academic setting, their involvement ends with filing the patent. Occasionally, an inventor will pursue development of their invention in a small start-up company that has licensed it from the academic institution. Alternatively, an inventor may simply continue to do follow-on research that is related to the original invention but not focused on its commercialization. In such cases, it is important for academic technology transfer professionals to consider how the researcher will be enabled to continue to conduct such research. For example, it is common for academic institutions in the United States to reserve the right for the continued use of a discovery for academic and nonprofit research purposes in any exclusive license to the patents pursued on that discovery.

9 See EU Commission, Supplementary protection certificates for pharmaceutical and plant protection products, https://single-market-economy.ec.europa.eu/industry/strategy/intellectual-property/patent-protection-eu/supplementary-protection-certificates-pharmaceutical-and-plant-protection-products_en.

10 Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152, 16 June 2009, p. 1–10, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009R0469.

In the European Union, the patent holder has the right to exclude others from using the patented invention. The owner of a product patent has the right to prohibit third parties from making, offering, putting on the market, using, possessing or importing the product. In the case of process patents, the patent protection extends not only to the application and offering of the protected process but also to such objects that are direct products of the protected process. The patent proprietor may transfer their proprietary rights in whole or in part to others by means of a license. An exclusive license means that no person or company other than the named licensee can exploit the relevant IP rights; the licensor is also excluded from exploiting the IP rights. If the licensor wishes to continue to conduct any activity covered by the IP (for example, a university licensor may wish to continue its research), or if the licensor has previously granted any rights in relation to the IP, the exclusive license will need to expressly state that it is exclusive subject to those carve-outs.

Under the European Patent Convention (EPC),[11] the precise scope of rights conferred by a granted patent is governed by national patent law. Pursuant to German patent law, for example, a research privilege applies to acts for experimental purposes relating to the subject matter of the patented invention. In general, the patent owner obtains protection for the inventive achievement through the patent, which in principle covers all acts of use of the invention. However, the scope of patent protection is not unlimited; experiments on the invention, for example, to investigate its functioning or new uses, are permitted (Section 11, No. 2, German Patent Act).[12] The intention is to balance the interests of the patent proprietor, by providing the broadest possible protection under the patent, and the interests of the general public by preventing the patent proprietor from hindering or excluding research experiments that are necessary for the further development of the technology and are closely related to the patented invention.

Under Swiss patent law, as another example, a similar exemption is granted. Pursuant to Article 9, paragraph 1, of the Swiss Federal Act on Patents for Inventions (Patent Act),[13] the effects of the patent do not extend to "acts undertaken for research or experimental purposes in order to obtain knowledge about the subject-matter of the invention including its uses; in particular, any scientific research concerning the subject-matter of the invention is permitted".

Reasons for patenting early research results

In private laboratories, research leading to a potentially commercially viable product is patented not only to protect the resulting product or technology, but also to attract investors and potential partners/collaborators. Whichever path is taken, this is the beginning of the journey for this unique discovery. Regardless of whether the invention is made in a public or private laboratory, because nearly all biotechnology products may affect either the health of humans or animals or the environment, commercialization is generally not possible without prior regulatory approval. Approval procedures can take many years. For example, it takes an average of 12–15 years to move a drug from the laboratory to the clinic or market. Only five in 5,000 compounds that enter pre-clinical testing make it to human testing. One of these five tested in people is approved. Figure 3.1 outlines this process in its entirety from discovery and preclinical trials through the three phases of clinical trials for drug approval and on to further obligations, such as additional post-marketing testing required by the US Food and Drug Administration (USFDA) after the drug has been approved and is already on the market.

The processes shown in Figure 3.1 and Figure 3.2 apply to the authorization of all medicinal products and not just to biotechnological drugs.

11 European Patent Office (EPO), https://www.epo.org/law-practice/legal-texts/epc.html.
12 German Patent Act, https://www.gesetze-im-internet.de/englisch_patg/index.html.
13 Swiss Federal Act on Patents for Inventions (Patent Act), https://www.fedlex.admin.ch/eli/cc/1955/871_893_899/en.

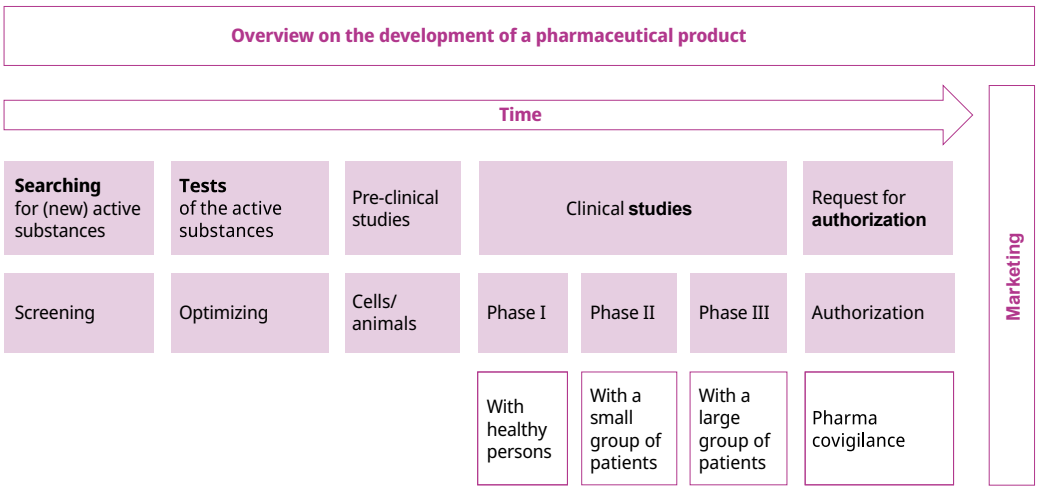
Figure 3.1. The drug discovery, development and approval process

Category	Years	Test population	Purpose	Success rate
Discovery/ Preclinical Testing Years	6.5	Laboratory and animal studies	Assess safety, biological activity and formulations	5,000 compounds evaluated
	File IND at FDA			
Phase I	1.5	20 to 100 healthy volunteers	Determine safety and dosage	5 enter trials
Phase II	2	100 to 500 patient volunteers	Evaluate effectivenes look for side effects	
Phase III	3.5	1,000 to 5,000 patient volunteers	Confirm effectiveness, monitor adverse reactions from long-term use	
	File NDA at FDA			
FDA	1.5	Review and approval process		1 approved
Total	15 Total			
Phase IV	Additional post-marketing testing required by FDA			

Source: FDA Review

In the European Union, similar development and approval processes apply. These are shown in Figure 3.2.

Figure 3.2. Simplified overview of the development of a pharmaceutical product in the European Union



Source: Claudia Seitz, Gesundheitsrecht, Orell Füssli, Zurich 2023

Typically, once a patented invention has been licensed to a company (regardless of whether it is licensed from a public institution to a private company, or from a private laboratory to a private company), the company sets about refining the research and begins the development process. Through trial and error, the company gains the know-how necessary to produce a consistent product on a large scale. Each of these steps along the discovery spectrum requires funding, much of which is obtained through investment by the private sector.

Attracting financing

It is the early stages of development (proof of concept research) that are most vulnerable to perturbations in the capital markets. While it is relatively easy for entrepreneurs to obtain seed financing (generally from angel investors, governments and nonprofit foundations/ organizations), it is the follow-on financing, such as the second and third rounds of venture investment required to fund companies beyond proof of concept and through clinical trials and approvals, that is often the most difficult to obtain. At this stage, for privately developed biotechnology products, what the capital markets require is the assurance that their investment in the discovery will bear a return on that investment. It is here that patents play a significant role (see "Academic institutions and the biotechnology industry" for detailed discussion of IP in financing). The patent portfolio associated with a particular product or technology can make or break investor confidence; therefore, throughout the development process, the company will seek additional IP to defend against competitors and to further buttress its portfolio. For example, a licensee will try to protect a key synthetic process; derivatives and variations of a chemical or biological structure; use of an important vaccine adjuvant; or a unique companion diagnostic.

Regulatory considerations for products of medical biotechnology

The United States of America

A crucial step in bringing a drug from bench to market is the regulatory review and approval process. Due to the significant US market, an application for drug approval is almost always filed with the USFDA.[14] Most countries have a regulatory agency equivalent to the USFDA: China has the National Medical Products Administration; Hong Kong has the Drug Office – Department of Health; Japan has the Pharmaceuticals and Medical Devices Agency (PMDA); South Korea, the Ministry of Food and Drug Safety; Taiwan, the Food and Drug Administration; India, the Central Drugs Standard Control Organization; Singapore, the Health Sciences Authority; Israel, the Ministry of Health – Pharmaceutical Division; Russia, the Federal Service for Surveillance in Healthcare; and Australia, the Therapeutic Goods Administration (TGA). These regulatory authorities have specific requirements for approving medicines and medical devices, many of which either overlap or have similar elements to the USFDA requirements.

The European Union

Regulatory review and approval processes in the European Union are generally within the competences of individual member states. According to Article 168 of the Treaty on the Functioning of the European Union there are a few exceptions. In these cases, the EMA, as an agency of the EU Commission, has the authority for regulatory review and market approvals. In the European Union there are several procedures available for the marketing authorization of medicinal products. The type of marketing authorization procedure depends on the medicine itself and whether the pharmaceutical company intends to market the medicinal product only in one EU Member State; in several EU member states; or in the European Economic Area (EEA). Medicinal products can be authorized by a national procedure, a mutual recognition procedure, a decentralized procedure or a centralized procedure. For the authorization of certain drugs, in particular medicines with new active substances for severe diseases, the centralized EU authorization procedure must be used. Innovative medicinal products and/or those where it is in the public health interest to do so, should be marketed throughout Europe.[15] The centralized authorization procedure can also be chosen optionally.

Approval is granted by the EU Commission, which has devolved this task to the EMA, giving it responsibility for the scientific evaluation of applications for centralized marketing authorizations in the European Union. This authorization procedure allows pharmaceutical companies to submit a single marketing authorization application to the EMA and to market

14 The USFDA is commonly referred to as "the FDA" but the term "USFDA" is used to unambiguously identify the agency in official documents such as agreements, and therefore will be used here.
15 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136 of 30 April 2004, p. 1–33, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=DE.

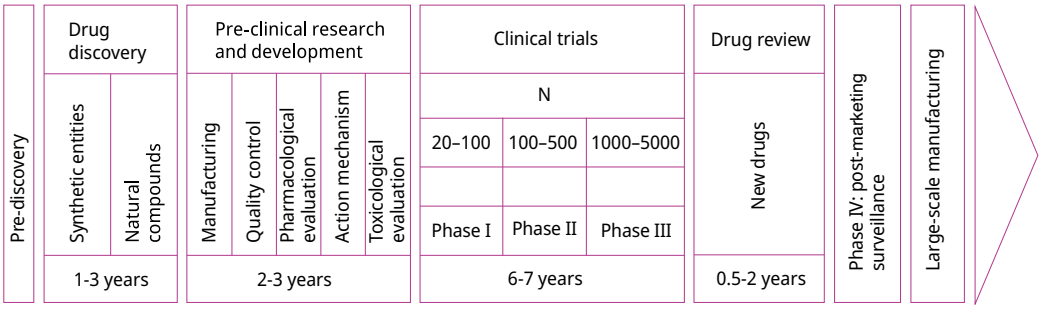
the medicine and make it available to patients and healthcare professionals throughout the EEA on the basis of that one marketing authorization.

Financing to complete regulatory review

One of the primary goals of fundraising in the biotechnology drug development process is to raise enough money to take the commercial invention through the regulatory review process. To obtain approval for biotech medicines, sponsors[16] must not only submit significant safety and efficacy data (generally assembled through clinical trials), but also data that assure the regulatory authority that the large-scale manufacturing of said product meets strict regulatory requirements (good manufacturing practices, or GMP)[17] throughout the life cycle of the product and following approval. Similar regulations are mandated by the EMA[18] as well as other regulatory authorities. In fact, 54 regulatory authorities from Europe, Africa, the Americas, Asia and Australasia are members of the Pharmaceutical Inspection Co-operation Scheme[19] which is a nonbinding, informal cooperative arrangement between regulatory authorities in the field of GMP of medicinal products for human or veterinary use. These regulatory authorities follow specific, agreed guidance and practices in GMP.

For the purpose of illustration, this Primer will follow the path of drug discovery and approval through the USFDA. Figure 3.3 shows this pathway, which is discussed in more detail below.

Figure 3.3. Schematic illustration of the drug discovery and development pathway



Drug discovery/screening

R&D for new pharmaceutical products usually starts with a time-consuming and expensive screening process to pick out promising compounds or molecules from the vast number of natural and synthetic compounds available. Testing large numbers of compounds to see if they produce an appropriate biochemical or cellular effect is one of the first steps in the drug-discovery pathway for both chemical and biological drugs, including biotechnological pharmaceutical products.

Preclinical trials

Once it has been determined that a compound or molecule has therapeutic promise, the drug must be shown to have promise for use in humans. This phase, which bridges the gap between discovery and clinical trials, is generally considered the preclinical phase of drug development. It is at this point that the sponsor begins the process of gathering clinical data. In the United States, for example, sponsors are required to first file an investigational new drug (IND) application, which is a request from a clinical study sponsor for authorization from the USFDA to administer an investigational drug or biological product to humans.

16 The term "sponsor" in drug development is a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution (whether the academic institution from which the invention arose can serve as the "sponsor" of a clinical trial involving the invention depends on the institution's policies as there may be potential conflict of interest concerns – Stanford University, for example, includes an obligation in its license agreements that the licensee must notify Stanford's TTO before commencing any clinical trials at Stanford), private organization or other organization.
17 https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations
18 https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice#ema-role-section
19 https://picscheme.org/en/members

The IND requires animal pharmacology and toxicology studies, manufacturing information and clinical protocols and researcher information [20] to be submitted to the USFDA. Several other drug regulatory authorities around the world, including the EMA, PMDA, Health Canada and TGA, have similar requirements. In the European Union, pharmaceutical legislation known as the Clinical Trials Regulation came into force on January 31, 2022. [21] It aims to ensure the EU offers an attractive and favorable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants. [22] Clinical trials not only require preclinical studies but also an approval from the competent ethics committee of an EU Member State.

According to the Knowledge Network on Innovation and Access to Medicines (a project of the Global Health Centre at the Graduate Institute, Geneva, funded by a grant from the Open Society Foundations), [23] the preclinical phase of drug development costs anywhere from tens of millions to hundreds of millions of dollars in out-of-pocket expenses.

Clinical trials

In the United States, once the IND is approved by the USFDA, the sponsor sets out to gather data to file either a new drug application (NDA) under 505 (b)(1), [24] or a biologics license application (BLA) [2] under 351 (a). [25] In both instances, sponsors are required to conduct clinical trials and provide enough information to allow determination of "whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks; whether the drug's proposed labeling (package insert) is appropriate, and what it should contain; and whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity".

Clinical trials follow a rigorous protocol beginning with small-scale phase I studies, moving through slightly larger phase II trials to late-stage, large-scale phase III studies. Only if a treatment is successful in one phase, will it move on to the next. A successful clinical trial process continues until the sponsor files a marketing application (NDA or BLA) with the USFDA or a regulatory authority in another country for the medication to be approved for doctors to prescribe to patients.

The processes and the procedures of clinical trials in the European Union and EU member states are similar to those in the United States. All drug products, including biotechnological drugs, must go through preclinical and clinical trials before authorization. The phases and design of clinical trials may differ for certain diseases and specialized medicines, such as cancer drugs or gene therapies, but Box 3.2 provides a general overview of each phase of a clinical trial for most drugs.

20 https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
21 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance ("Clinical Trials Regulation"), OJ L 158, 27 May 2014, p. 1–76.
22 EMA, Clinical Trials Regulation, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation.
23 https://www.graduateinstitute.ch/research-centres/global-health-centre/completed-knowledge-network-innovation-and-access-medicines
24 The 505(b)(1) regulatory pathway is the traditional NDA. This pathway is used by sponsors to obtain the approval of a new drug whose active ingredients have not previously been approved.
25 Therapeutic biological products covered by BLA include monoclonal antibodies for in vivo use; cytokines, growth factors, enzymes, immunomodulators; thrombolytics; proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors); and other nonvaccine therapeutic immunotherapies.

Box 3.2. The phases of clinical trials

Phase I to evaluate the safety of the drug candidate.

- Between 20 and 80 healthy volunteers participate; the timeframe is variable but can take several months.

Phase II to assess effectiveness and further assess safety (e.g., side effects).

- Administered to several hundred patients (depending on the drug) who have the associated disease or disorder; can take several months to years.

Phase III to test drug in large populations of patients.

- Demonstrates whether a drug candidate offers a treatment benefit to a specific population and provides the basis for product labeling; this phase can last from one to four years.

Phase I

During phase I studies, researchers generally test a new drug candidate in between 20 and 80 healthy volunteers. The timeframe for this phase is variable but can take several months. The primary purpose of a phase I study is to evaluate the safety (for example, the side effects) of a new drug candidate before it proceeds to further clinical studies. In addition to safety, in a phase I trial researchers can answer questions related to how much of the drug is measured in the blood after administration, how the drug works in the body and the side effects associated with increased dosage.

Phase II

Around 70 percent of potential new drugs enter phase II. In phase II studies, researchers administer the drug to a larger group of patients (typically up to a few hundred) with the disease or condition for which it is being developed to initially assess its effectiveness and to further study its safety. A key focus of phase II studies is determining the optimal dose or doses of a drug candidate and how best to administer it to maximize possible benefits, while minimizing risks. The timeframe for this phase is also variable depending on the drug and can take several months to several years to complete.

Phase III

About 33 percent of drugs make it to phase III, which tests the potential treatment in the largest number of people. Phase III studies typically involve 300–3,000 participants from patient populations in which the medicine is eventually intended to be used. Phase III studies are often conducted as “double blind” studies: participants are assigned to receive the medication being evaluated or to a control group that receives either the current standard-of-care treatment or a placebo (a substance that has no therapeutic effect). Individual patients do not know to which group they have been allocated. In addition, the researchers do not know which patient group has received the drug. Phase III studies – among other things – demonstrate whether a drug candidate offers a treatment benefit to a specific population, provide more detailed safety data and serve as the basis for product labeling. Phase III trials last from one to four years.

When one or more phase III trials have been completed, the sponsor examines the results and decides whether the drug has demonstrated effectiveness and an acceptable safety profile in treating a disease. If so, the company can submit an NDA which contains all the data and information gathered at every stage of the process through to the results of the phase III clinical trial(s), as well as other information required by the applicable regulatory authority. The NDA is submitted to the USFDA (or analogous regulatory authorities outside the United States) for consideration for marketing approval.

According to the Knowledge Network on Innovation and Access to Health, this phase of the regulatory review process costs sponsors from hundreds of millions of dollars to more than USD 1 billion. A study published in the *Journal of the American Medical Association*[26] detailed the regulatory approval expenses incurred in relation to 63 new therapeutic drugs and biological agents approved by the USFDA between 2009 and 2018. The study found that it costs on average USD 985,000,000 to get a drug through the regulatory pathway (if failed clinical trials are also accounted for), with a range of USD 314 million to USD 2.8 billion.

Post-approval and follow-up/pharmacovigilance

The sponsor remains involved after the product has been approved and the drug enters the post-approval phase of regulation, which includes post-market surveillance and the approval of any modifications that are made when the product is manufactured after approval. This phase can take several years and often decades. For example, in the case of cell and gene therapy products, which are required to sustain long-term effects on the body, post-approval follow-up can take up to 15 years.[27] [28] This phase, which includes studies to test new indications, new formulations, new dosage strength and regimens, and to monitor safety and long-term side effects in patients as required by the USFDA as a condition of approval, costs approximately USD 312 million.[29] The estimates vary depending on the study, but regardless of the final cost, there is no question that the drug development/regulatory processes are extremely expensive and require significant capital investment.

Similar obligations also apply in the European Union and EU member states in the context of pharmacovigilance, which is defined by the EMA as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem". In line with this general definition, the underlying objectives of pharmacovigilance in accordance with the applicable EU legislation are: (1) preventing harm from adverse reactions in humans arising from the use of authorized medicinal products within or outside the terms of their marketing authorization or from occupational exposure; and (2) promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public. Pharmacovigilance is therefore an activity contributing to the protection of patients and public health.[30]

26 Wouters, O.J., M. McKee and J. Luyten (2020). Estimated research and development investment needed to bring a new medicine to market, 2009–2018. *Journal of the American Medical Association* 323(9), 844–853.
27 https://www.cellandgene.com/doc/an-overview-of-fda-s-new-guidance-on-long-term-follow-up-after-administration-of-gene-therapies-0001#:~:text=Since%20gene%20therapy%20(GT)%20products,as%20long%20as%2015%20years.
28 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products
29 DiMasi, J.A., H.G. Grabowski and R.W. Hansen (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health Economics* 47, 20–33.
30 EMA, Guideline on good pharmacovigilance practices (GVP), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf.

4 Market considerations for biotechnology products and the role of governments

Successful biotechnology development depends on, e.g., government support through R&D funding, strong IP protection, flexible technology transfer frameworks, data exclusivity, and science-based regulation. This chapter looks at how regulatory approval processes vary globally, creating challenges for product commercialization.

Countries with successful biotechnology sectors invest heavily in R&D of biotechnology products. This often includes:

- providing funding support for basic and translational research;
- creating a hospitable environment for risk taking in an already risky sector which includes strong IP protections;
- providing a flexible framework for technology transfer of any IP created;
- science-based regulation of the resulting products; and
- creating a market in which the product can be sold.

Regulatory approval

After an invention has been sufficiently developed, regulatory approval of a product is a critical step towards entering the marketplace. But since the marketplace is limited only to the jurisdiction where the approval is obtained, sponsors must file for approval in many countries around the world, each with their own laws and regulations. Some countries require new (sometimes redundant) testing at various stages of the development and manufacturing processes and still others require new, additional clinical trials, all of which add to the cost and time of development.

Governments can provide consistency in regulatory filings and improve the availability of biotechnology products by better streamlining their systems with globally recognized standards provided by institutions such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Nearly all countries require some form of dossier with regulatory data[1] to be submitted for approval, which may contain non-patented or confidential information. Through the ICH, common technical document guidance has been developed, which is being utilized by many regulatory authorities around the world, including Japan, the European Union, United States and many Association of Southeast Asian Nations countries.

Confidential information and data

Article 39 of the World Trade Organization's (WTO) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS Agreement) provides protection for this non-patented or

1 Regulatory data means regulatory information, data and results relating to the product which are necessary for product approvals, including in-vitro product testing data and study data, data queries, data tables, reports and case report forms generated during any preclinical or clinical study or registry study, for the product.

confidential information/data for a period of time generally determined by the WTO member states. During this time, ranging anywhere from five to 12 years depending on the country, the company that has developed the product can benefit from exclusivity in the marketplace. Pursuant to Article 39, paragraph 3 of the TRIPS Agreement, WTO member states, "when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use". In addition, WTO member states "shall protect such data against disclosure, except where necessary to protect the public or unless steps are taken to ensure that the data are protected against unfair commercial use". As a consequence, in the pharmaceutical field Article 39 paragraph 3 of the TRIPS Agreement deals with undisclosed test data that refers to "clinical trial data of a new drug which has to be mandatorily submitted before a regulatory agency in order to obtain marketing approval for the drug".

Data exclusivity

In certain jurisdictions, such data are given exclusive property rights if they pertain to a new drug, thereby preventing the authority from relying on such information while approving other similar drugs for which similar sets of data would have to be submitted in order to obtain approval once the protection of the patent and the SPC has expired. This approach is known as "data exclusivity". In other jurisdictions, the authority is allowed to rely on such data about a new drug for approval of generic drugs provided that the generic drug is proven to be "bioequivalent" to the new drug.

This procedure applies only to a limited extent for biosimilars as the succession products of biopharmaceutical products (which are, in general, biotechnologically produced drugs). The data exclusivity period, in addition to IP rights, allows the originator company that first brought the drug to the market to sell its product free from competition for a limited period to recoup investments in the drug's R&D and market authorization.

Access to medicines

In the health sector, there have been instances where restrictive drug regulation has affected the availability of medicines. This concern has typically been related to individuals with serious or life-threatening illnesses who might benefit from drugs that have been denied market approval or whose approval has been inordinately delayed because regulations are too strict. At times, governments have responded to these concerns by streamlining drug laws and regulations. Many countries, including the United States, Japan, Australia, Canada and Brazil, have developed country- and region-specific frameworks for regulating access to unapproved medicines. Examples of the types of drugs given expedited approval are cancer drugs, AIDS drugs and other drugs regulated under the auspices of compassionate use laws in the United States, EU member states, Switzerland and elsewhere.

Compassionate use laws generally regulate the use of an unapproved drug outside of clinical trials in people with serious or life-threatening conditions who do not meet the enrollment criteria for the clinical trial in progress. These serious or life-threatening conditions play an important role in the risk–benefit analysis regarding the use of unapproved drugs. In these instances, regulatory measures that allow for rapid approval of new drugs have sometimes led to the marketing of drugs with more toxicity than the public finds acceptable. The risk–benefit analysis in these instances is a fine line that generally falls within the jurisdiction of the role that governments play in the biotechnology sector.

Additional governmental incentives

Some drugs have benefited from additional government incentives. These incentives may include quicker approval time, as well as financial assistance and in some instances a guaranteed term of market exclusivity. Orphan drugs (that is, drugs designed to treat neglected or rare diseases) receive special consideration from various regulatory authorities, which encourages pharmaceutical companies to develop treatments for rare diseases.

In the European Union, for example, a rare disease is one that affects no more than one person in 2,000[2] and orphan drugs are granted an orphan drug designation which permits a 10-year market exclusivity period after market approval. The EMA is responsible for reviewing applications from sponsors for orphan designation pursuant to the EU Orphan Drug Regulation.[3]

In Switzerland, as another example, there is also an orphan drug designation. However, this designation does not lead to additional market exclusivity but to an extension of data exclusivity (15 years instead of 10 years after market authorization). Consequently, the development of orphan drugs normally grows at faster rates than the development of traditional pharmaceuticals. These facilitated regulatory pathways can be used to incentivize development of medicines for a variety of unmet medical needs including diseases of the developing world such as malaria, tuberculosis, Chagas' disease, dengue, trypanosomiasis, schistosomiasis and HIV.[4]

2 Between 6,000 and 8,000 different rare diseases affect an estimated 36 million people in the EU. See EU Commission, Rare Diseases, https://research-and-innovation.ec.europa.eu/research-area/health/rare-diseases_en.
3 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ 18 of 22 January 2000, p. 1–5, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN.
4 Khera, A. (2020). Expediting drug development regulatory pathways globally. *Clinical Researcher* 34(3). https://acrpnet.org/2020/03/expediting-drug-development-regulatory-pathways-globally/.

5 Role of intellectual property in biotechnology commercialization

This chapter outlines how the creation, protection, management, and licensing of intellectual property are critical aspects in biotechnology, given the length of time and high-cost R&D where only one in five drug candidates survives clinical testing. A robust IP portfolio is vital for biotech startups to attract financing, demonstrate market exclusivity potential, and to maintain strategic flexibility if primary products fail.

Because the R&D process in the biotechnology field can take more than a decade and cost more than one billion dollars to complete, patents and other IP protections, such as SPCs and trade secrets, are particularly important. Approximately one in five drug candidates survives clinical testing. As a result of the high risks of failure and the high costs, R&D must be funded by the few successful, on-market products. Table 5.1 shows the different phases of development and the cost associated with each, including the cost of failures. Again, it should be noted that the costs described apply to the authorization of all drug products and not specifically to biotechnological drugs.

Table 5.1 The costs of drug development by stage

Cost calculation one

	Average cost		
Phase	**w/o failures**	**w/ failures**	**% of total**
Discovery	8	196	14%
Pre-clinical	10	122	8%
Phase I	20	169	12%
Phase II	80	402	28%
Phase III	300	536	37%
NDA phase	10	11	1%
TOTAL	**428**	**1,436**	**100%**

Source: Verea Group LLC.

This type of venture is not amenable for the risk-averse investor. And those who are willing to take the risk will require a modicum of assurance. Strong and predictable patents are the main assets – besides SPCs and data exclusivity – utilized to assure investors of their return in risky biotechnology endeavors. These patents are also the assets utilized in knowledge transfer in the collaboration and sharing of technology between a university or a company and its partner(s). Accordingly, any perturbations that call IP rights into question are likely to create more unpredictability in an already risky commercialization endeavor.

Biotechnology patents

Most countries allow patents on biotechnology inventions directed to products, processes, methods and uses. In each country, the product or process must meet the requirements for patentability and not be directed to subject matter that is excluded from patentability in that country. Common patentable products of biotechnology innovation include proteins (polypeptides) described by their functional or structural properties, proteins (polypeptides) described by their amino acid sequences, plasmids, vectors, antibodies, antigens, epitopes, viruses, phages, bacteria, fungi, plant and animal cells, hybridomas, plants (as inventions, not varieties), animals, small molecule therapeutics, nucleic acids (polynucleotides) described by their nucleotide sequence, and the like. Plasmids and vectors can be identified in terms of their components, restriction map or their sequence. Microorganisms can be described by their properties; if these are not known or readily available, the description may have to refer to their deposit number in a qualified collection center under the Budapest Treaty administered by WIPO.

Patentable processes or methods may include methods for producing a particular substance, the process of developing new microorganisms, methods to create new probes, methods for treating a condition, methods for diagnosing a condition, methods for imaging, methods for the amplification of vectors, and so on. A patentable invention can involve the use of a known substance or product in any of a variety of ways that would make it patent-eligible, including but not limited to novel assays and the treatment or diagnosis of a particular disease.[1]

Intellectual property and financing biotech products

Often a biotech company's first (and constant) task is to attract and raise financial capital, typically through the sale of stock in the company to investors. In fact, a biotech company will often spend its first year or two of existence acting essentially as a virtual entity to determine whether it will be able to raise adequate funds to pursue further development and its only asset is its IP portfolio. To attract the level of financing required to survive the lengthy and expensive regulatory path to bring a therapeutic to market, biotech companies must possess from their inception a strong IP portfolio (in particular, patent rights) and a well-defined IP strategy. The startup will pitch its IP assets and strategy, along with its development plan, to investors (often angel and seed investors, but possibly also venture firms, established biotech companies, nonprofits, etc.).

Investors will expect to be reassured as to how their investment in the startup will be protected from an IP perspective. The startup should be able to explain the breadth of its current portfolio and how it will serve to exclude others from introducing alternative products in the marketplace. The startup will be asked whether it has conducted a freedom-to-operate (FTO) analysis to determine whether there are patents and/or pending patent applications that could potentially block its ability to develop or sell its products. Another common question asks what happens if the startup's lead product fails – does it have the ability (largely in view of its IP portfolio) to pivot, diversify and/or pursue secondary indications? Additionally, the startup should have an elaborate IP strategy that encompasses patent filings, FTO analyses, competitive IP landscape mapping and lifecycle management to ensure a robust defense against market competition and to facilitate potential pivoting opportunities.

Box 5.1 provides an overview of and further information about IP and financing.

Box 5.1. Intellectual property and financing

In biotechnology, it is generally accepted that the potential for a company to make money is closely linked to its IP portfolio. This is one of the reasons why biotech companies with little

1 It is important to note that in many countries, patenting methods of medical treatment is not allowed. This is in accordance with Article 27 paragraph 1 of the TRIPS Agreement which provides that WTO member states "may also exclude from patentability diagnostic, therapeutic and surgical methods for the treatment of humans or animals". In such situations it is in effect protected through the "purpose-limited product" claim, having the format "[substance or composition X] for use in [medical method Y]".

to no revenue can still be worth billions. In fact, most biotechnology companies do not have incoming revenue and actually lose money.

For example, Kite Pharma was acquired by Gilead in 2017 for nearly USD 12 billion, largely in view of Kite's robust chimeric antigen receptor (CAR)-T cell therapy IP portfolio – yet at the time of the deal, Kite Pharma had more than USD 600 million in accumulated debt (https://www.businessinsider.com/gilead-to-buy-kite-pharma-for-12-billion-a-cancer-immunotherapy-company-2017-8).

Investors and executives in the biotech sector are required to predict, often many years into the future, how valuable a company may be based on various factors and moving targets, including the company's IP portfolio and strategy, the chances that the company's products will receive regulatory approval and whether physicians will use those products, etc.

6 Academic institutions and the biotechnology industry

The synergistic relationship between academic institutions and biotech companies drives industry innovation. Universities contribute cutting-edge research, specialized facilities, and scientific discoveries, while companies provide commercialization expertise and investment capital. This chapter highlights how partnerships have yielded breakthroughs like COVID-19 vaccines and cancer treatments.

In the United States and other countries, the academic and private sectors have a long history of positive and productive interaction with the biotech industry. Key scientific developments from academia, pioneering companies and risk-taking investors have created an industry that is now one of the most important in the world. What drives this interaction? In a word, synergy.

A nonprofit academic institution trains students for future roles in biotechnology; performs leading-edge life sciences research; has specialized research facilities and equipment; and engages locally, regionally and globally in the economy. Using funding from government agencies, foundations, companies and other external sources, academic institutions add to the base of scientific knowledge in biotechnology and make discoveries with significant impact and commercial promise. However, an academic institution does not make and sell products or generate profits. It can take an innovation only so far, after which it needs a partner with the resources, expertise, market and knowledge application skills to go further. Two examples of successful collaboration between academic institutions and private companies, both of which resulted in regulatory approval for COVID-19 vaccines, are described in Box 6.1 and Box 6.2.

Box 6.1. The platform for mRNA COVID-19 vaccines created at Penn

The seminal work for the mRNA vaccine platform used by both the Pfizer/BioNTech and Moderna vaccines was performed in the laboratories of Dr Drew Weissman and Dr Katalin Kariko at the University of Pennsylvania (Penn).

Penn exclusively licensed the Weissman/Kariko mRNA platform patents to a small company, Cell Script, in 2016. Cell Script sublicensed the mRNA platform to Moderna in June 2017 and BioNTech in July 2017.

In October 2018, BioNTech signed a collaboration and exclusive license agreement with Penn which included a USD 5 million research budget and license terms that included USD 44.4 million in milestone payments, a low single digit royalty rate and a percentage of sublicensing income.

Also in 2018, Pfizer executed an exclusive license agreement with BioNTech for the mRNA platform patent rights that it either owned or controlled. The Pfizer/BioNTech agreement is reported to contain USD 185 million in upfront payments, USD 72 million in cash and USD 113 million in equity.

The Pfizer/BioNTech vaccine received emergency use authorization (EUA) on December 11, 2020 and full regulatory approval on August 23, 2021, making it the first USFDA-approved COVID-19 vaccine.

Moderna received its full regulatory approval in January 2022.

While academic institutions generally license platform technology on a nonexclusive basis so that the platform can be widely used, in this situation the exclusive licensee issued more than one sublicense, thereby allowing the platform technology to be more broadly used and provide greater public benefit. In the case of COVID-19, this resulted in vaccines being produced more quickly and on a larger scale.

Box 6.2. Oxford University/AstraZeneca rapid development of a COVID-19 vaccine

Prior experience and work with other coronaviruses such as SARS (severe acute respiratory syndrome) in 2002 and MERS (Middle East respiratory syndrome) in 2012 at the University of Oxford provided a foundation for the development of a COVID-19 vaccine. Long-term support from the UK Vaccines Network (a partnership between the UK Medical Research Council and Department of Health and Social Care) led to the development of the viral vector vaccine platform and optimized manufacturing methods which provided a substantial head start for the COVID-19 vaccine work.

In early 2020, Vaccitech, a spin-off of the Jenner Institute, and the University of Oxford co-invented a vaccine for COVID-19 using the ChAdOx platform. This platform is based on an adenovirus which can be modified to make one or more antigens – proteins specific to a pathogen (such as SARS-CoV2) or cancer. The ChAdOx vector particles are formulated into a vaccine or immunotherapy to deliver the genetic blueprint for the antigen into the cells of the body and induce an immune response.

The Jenner Institute and Oxford Vaccine Group of the University of Oxford granted AstraZeneca an exclusive license to ChAdOx1 nCoV-19 in April 2020 to develop and distribute the resulting vaccine worldwide. License terms for supplying downstream (post-pandemic) commercial markets were subject to a separate agreement.

Clinical trials began in April 2020 and regulatory approval was obtained in November 2020. The ability to store the vaccine in a normal refrigerator allowed it to be administered in a broad range of global health settings. AstraZeneca pledged to sell the vaccine at a not-for-profit rate for the entirety of the pandemic and entered into several licensing agreements with large manufacturers, including the Serum Institute of India.

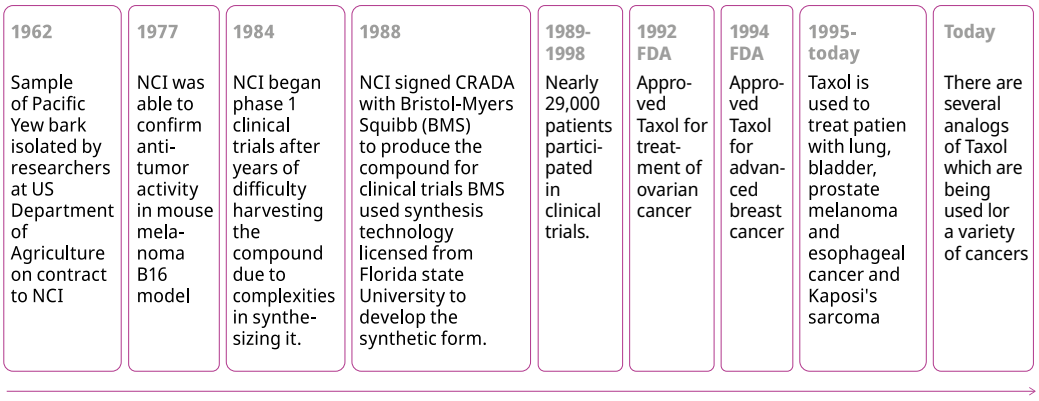
Through consistent funding from programs such as Europe's Horizon 2020 research funding program with its focus on international cooperation, China's Innovation Funding Program, which provides funding and financial incentives in China for European innovation stakeholders, and India's "Startup India Seed Fund Scheme" to name a few, public and private organizations have been able to develop foundational technologies that are ultimately used to develop life-saving therapeutics.

The characteristics and strengths of a biotech company complement what academia can offer. Often, a company can neither afford nor justify the immense cost and risk of basic biological research and the complex infrastructure that supports it. It can, however, track and assess discoveries and inventions coming out of laboratories. The company can option or license a promising invention and use its own or an investor's financial assets to further develop the idea. If the license is from an academic institution, ideally through an industry-supported research or consulting arrangement, the licensee can benefit from further studies by and continued interaction with the investigators who developed the invention and recruit key members of the scientific team when they complete their PhD studies. The company can

fund clinical trials at the originating institution or a network of medical centers and hospitals. These aspects are similar in many regards to licensing between private institutions, whether a research organization or another company, where agreements such as those between Pfizer and BioNTech[1] or between Novartis and BioNTech[2] can be used to delineate division of labor, finances or materials.

The marriage of academic and biotechnology industry resources and strengths had led to, and continues to lead to, far-reaching developments in the biotechnology sector that have improved the human condition. These collaborations include, for example, the development of the prostate-specific antigen diagnostic test, the discovery of the gene for cystic fibrosis, a synthetic process to produce Taxol and the development of Xtandi, a life-extending therapy for prostate cancer patients. Figure 6.1 illustrates the Taxol development timeline in more detail, while Box 6.3 outlines the development of Xtandi.

Figure 6.1. Timeline of the development of Taxol



Box 6.3. The development of Xtandi for the treatment of advanced prostate cancer

The patentable technology that became the blockbuster prostate cancer drug Xtandi was developed by University of California Los Angeles (UCLA) researchers Mike Jung and Charles Sawyers and their co-inventors. UCLA filed the first of a series of patents in 2004 and granted an exclusive license to Medivation in 2005. The timeline below shows the major events around Xtandi starting with the grant of this exclusive license. USFDA approval for the first approved indication for Xtandi was obtained in the third quarter of 2012 and was followed by regulatory approval in other major territories. In 2021, the first generic counterpart of Xtandi was approved.

August 2005 – Exclusive license

May 2012 – NDA filed

August 2012 – FDA approval

June 2013 – EC (European Commission) approval, first indication

March 2104 – Japanes Regulatory approval, first indication

November 2016 – Pressure on US Governmnet to exert "March in Rights"

November 2016 – India denies Xtandi patent

1 https://www.sec.gov/Archives/edgar/data/1776985/000119312519241112/d635330dex1018.htm
2 https://www.novartis.com/news/media-releases/novartis-signs-new-initial-agreement-biontech-support-fill-and-finish-mrna-pfizer-biontech-covid-19-vaccine

November 2019 – China National Medical Products Admin (NMPA) approval

May 2021 – First generic approval

An alliance agreement between the University of Pennsylvania and Novartis yielded an on-campus research center and two USFDA approved personalized cell-based therapies (Box 6.4).

Box 6.4. University of Pennsylvania/Novartis alliance yields first approved gene therapy for cancer

2012 – Penn and Novartis sign a global research and license agreement around chimeric antigen receptor (CAR) technologies.

2016 – As provided under the 2012 agreement, the Center for Advanced Cellular Therapies is built on a Penn campus.

2017 – USFDA approves a personalized cellular therapy (Kymriah) for the treatment of acute lymphoblastic leukemia in patients under the age of 25 years.

2018 – USFDA approval for the use of Kymriah for non-Hodgkin lymphoma.

2019 – Alliance agreement ends. A new narrowly focused agreement, which includes four clinical trials, is executed.

Patented technologies, whether developed in universities or public or private institutions, are utilized to attract companies/investors to further their R&D. In addition, startup companies are ordinarily formed based on some invention developed by an investigator in a university. The startup usually in-licenses the patent asset to a company, which uses its patent assets to attract investors or established companies to raise the funds necessary for moving products through the development and regulatory processes.

7 Technology transfer in biotechnology (continuum of agreements)

Technology transfer in biotechnology depends on various classes of well-structured agreements and strong IP foundations. This chapter highlights how academic institutions need Technology Transfer Offices with the capacity to manage IP assets and to facilitate commercialization through agreements ranging from non-disclosure agreements to exclusive licenses.

IP ownership

In biotechnology, various forms of agreement are utilized to drive the commercialization process, and in this regard IP, including patents and know-how, comprises a key element of any agreement. Thus, commercialization of biotechnology must be built on a strong foundation of IP with patents at the core to be successful. Furthermore, for an academic institution to effectively engage in the transfer of technology, it must have a mechanism in place to take ownership of its discoveries.

Technology transfer legislation

To enable academic institutions to legitimately take title to these assets, a country may promulgate national laws, such as the Bayh-Dole Act in the United States (and similarly focused laws and regulations adopted by many other countries including the United Kingdom, China, Japan, Germany, France, Austria, Denmark, Norway, Portugal, Spain and Finland), which establish paths for academic institutions to take title to government-funded inventions as well as develop technology transfer policies and practices to manage these inventions. In some countries, policies give the researcher ownership of their invention. These policies, often referred to as “professor’s privilege” or “research privilege”, can complicate matters, especially in terms of invention management, the relationship with a licensee or when further development of the invention occurs inside the institution and ownership stays with the inventor. In the absence of national law or to further specify IP rights management procedures and technology transfer processes, institutions may act to implement their own IP policies and practices.

Role of the Technology Transfer Office (TTO)

It is important that an academic institution has a robustly funded TTO with an adequate number of skilled professionals to empower it to take title to inventions and manage their transfer and licensing.[1] Such a system allows for academic discoveries to be protected by filing, managing and maintaining patent applications. Indeed, one of the ways a TTO adds value is by ensuring that the inventions and IP it seeks to license are high quality as a result of

1 Some publicly funded universities in the United States can take title to inventions but are required to establish external foundations or other entities to manage marketing, transfer and licensing on behalf of the university. Such requirements are not an obstacle to developing a high-quality TTO.

well-vetted IP policies and clear technology transfer procedures. Along with protecting IP, the academic institution must have the ability and financial and personnel resources to draw up contracts such that outside commercial partners can be granted valid rights and vested with clearly delineated obligations to develop and sell a product for the public good based on the institutional IP.

Technology transfer agreements

The academic institution technology transfer process includes a stepwise continuum of agreements. Many of these agreements work in concert with each other and, in some instances, a single agreement may incorporate what could be multiple agreements by granting licenses to a variety of IP as well as referencing other agreements. For example, an overall exclusive license may grant further licenses to patents, know-how and proprietary materials, all of which were developed by two or more academic institutions, with one institution taking the lead, as memorialized in an inter-institutional agreement (IIA). An IIA governs the management of jointly owned IP and may be attached as an appendix to an exclusive license agreement (ELA). In most countries each joint owner must obtain the written consent of the other joint owner(s) before licensing the joint invention and, therefore, whenever possible, it is important to enter into an agreement in advance of a joint collaboration to ensure all parties have a common understanding as to how joint inventions will be commercialized.

Material transfer agreements (MTAs)

Proprietary materials are materials which are not freely available and are only transferred under the terms of a material transfer agreement (MTA) that delineates the allowed use of such materials. In biotechnology agreements, proprietary genetic and other biological materials (for example, hybridomas, animals developed for disease models, cell lines, libraries, vectors) are often a necessary component for effectively transferring the technology from academia to industry for further development and commercialization. WIPO maintains a database of contracts, including technology transfer contracts, MTAs and licensing agreements, for such genetic and other biological resources, which can be consulted for up-to-date agreements relating to such transfers. Know-how and trade secrets are also important for the development and handling of the materials and may or may not be included in an ELA. In this regard, there is often the need for a strategic decision-making process to optimally include know-how and trade secrets in an ELA, importantly taking into account the balance between protecting proprietary information and leveraging these assets for commercial and competitive advantage.

Industry-sponsored research agreement (ISRAs)

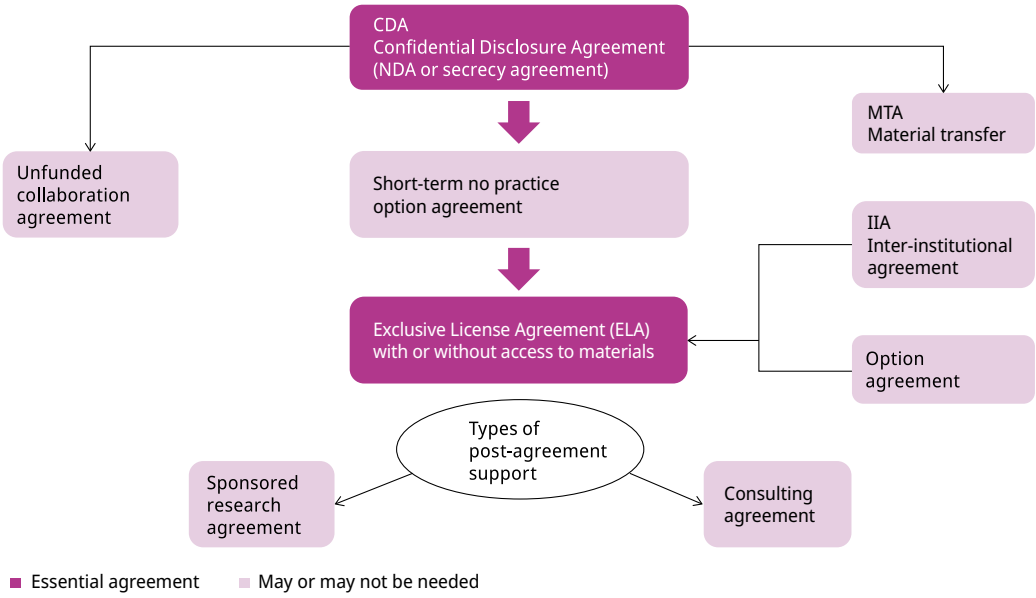
Along with a license to know-how or trade secrets, other means of conveying know-how include the execution of an industry-sponsored research agreement (ISRA) where the company/licensee financially supports research in the academic lab of the inventor. Alternatively, the licensee may engage the inventor as a consultant to assist in the transfer and application of the technology pursuant to a consultancy agreement, which often requires approval by the academic institution to avoid or manage any potential conflict of interest and to ensure the terms of the consultancy agreement do not conflict with the inventor's obligations to the academic institution.

Continuum of agreements related to technology transfer

The flowchart in Figure 7.1 shows a continuum of agreements, illustrating many of the typical agreements handled in the technology transfer process when moving an academic discovery from the academic institution to an industry licensee for commercialization. While the sequencing may vary slightly, the scheme shown in the chart is a generalized process that represents most cases. Almost every negotiation starts with a confidentiality agreement (called by a variety of names – secrecy agreement, confidential disclosure agreement,

confidentiality agreement or nondisclosure agreement) and culminates in a license agreement. There are many agreements that may also come into play along the way, including post-license agreements. The MTA is a common component of the initial conversations and due diligence done by industry around a biotech licensing opportunity with an academic institution, and is therefore shown in the main flow of the agreement process. Many biotech license agreements are more complex than non-biotech agreements and often require inclusion of materials and know-how.

Figure 7.1. The continuum of agreements in the technology transfer process



Nondisclosure agreement/confidentiality agreement

A nondisclosure agreement is often the first formal agreement in the technology transfer commercialization process; it may also be referred to as a confidential disclosure agreement or a secrecy agreement. A nondisclosure agreement can be crucial because licensing discussions often involve the disclosure of unprotected proprietary information, and such discussions may predate the filing of a patent application that covers such information. Furthermore, enabling disclosure may preclude or limit patenting in some countries. Industry is accustomed to signing these agreements.

There are, however, some complications that may arise at this point in the process. If discussions with industry are purely for licensing purposes, a one-way nondisclosure agreement protecting the institution's confidential information may be sufficient and advantageous from the institution's perspective as it prevents it receiving (or being "tainted" with) the company's proprietary information. In addition, the institution may not want to shoulder the liability or unnecessary burden of handling the confidential information of a third party. On the other hand, a two-way nondisclosure agreement may be necessary if the parties are discussing or negotiating a license that would, for example, involve joint R&D efforts, industry-supported research or a collaboration agreement. Some further considerations to keep in mind about nondisclosure agreements are summarized below.

- The scope of the subject matter governed by the terms of the nondisclosure agreement should be limited to the specific information being shared and the purposes for which it is being provided (that is, the purposes for which the receiving party can use the disclosed information), each of which is typically expressly defined by the agreement. Beware of overly broad scopes for either of these definitions.
- The term of both the agreement and the receiving party's obligations under the agreement should be defined. The term of the agreement (that is, how long the parties can disclose information to each other) could continue for a year or more, meaning information will be

shared during that time. Obligations of confidentiality should run for an appropriate length of time for the subject matter being disclosed. For example, five years may be sufficient if the disclosing party intends to file a patent application on the disclosed information within that time, whereas a longer period may be required by a disclosing party if it intends to disclose trade secret information, or if the parties are negotiating and subsequently enter into a license agreement. However, the duration of confidentiality obligations is often unlimited, even if there are no further negotiations between the parties or a license agreement is reached, in order to protect the information of the disclosing party.

- The law governing the agreement should be, whenever possible, the jurisdiction of the academic institution's country, or the law that is usually applicable in the region – like a Swiss law in Europe – when it is not possible to reach an agreement under the national law of one of the parties. The jurisdiction should be known by and easily accessible to the academic institution so as to avoid facing an unknown legal framework and the costly burden of resolving a dispute in a foreign territory. Parties normally agree on a national jurisdiction without much friction, and often also opt to include a dispute resolution clause indicating the use of arbitration and mediation services, such as those provided by WIPO, before any legal action would be taken.

Material transfer and evaluation agreements/material and data transfer agreements (from institution to company)

MTAs and evaluation agreements are often precursors to an exclusive option agreement (EOA) or an exclusive license agreement (ELA). The commercialization of IP rights in biotechnology often necessitates access to, and the right to use, as part of an ELA, proprietary materials, such as cell lines, hybridomas, monoclonal antibodies, animal models, libraries and vectors, or proprietary methods. As part of a potential licensee's due diligence, they may ask to receive a sample of materials or details of methods for testing. The party supplying the materials/methods can (and should) include reasonable limitations on how they are used during the evaluation period. Thus, the materials/methods may be sent under an MTA and evaluation agreement which allows the company to test them for a limited time. The key provisions of such agreements are listed in Box 7.1.

Box 7.1. Key provisions to include in material transfer agreements and evaluation agreements

- The scope of the work should be clearly set out in an appendix detailing the permitted use of transferred materials/methods with retention of ownership by the provider, and guidelines around modifications, derivatives and ownership thereof.
- The group of people of the receiving party who are to have access to the materials should be restricted.
- Use of the materials on humans or for any commercial purposes whatsoever must be prohibited.
- An agreement to comply with all applicable regulations and guidelines around the use of animals, DNA and other biological materials should be included.
- There should be a clause specifying that no warranties will be provided by the institution.
- There must be full indemnification of the academic institution by the company recipient.
- The term of agreement should be clear, with a requirement to return or destroy materials at the end of the term.
- There should be provisions for the recovery of costs incurred by the institution in preparing and shipping materials.
- A provision should describe what would happen with regard to ownership and access to IP and data that might arise from studying the material (e.g., if an invention is made or valuable data are generated).

WIPO has issued a *Guide on Intellectual Property Issues in Access and Benefit-sharing Agreements*, which provides an introduction to the specific IP issues that arise in the context of MTAs, access and benefit-sharing agreements for genetic material, and material and data agreements.

Collaboration agreement/cooperation agreement

In addition to a transfer of materials, there may also be a need for collaboration (which may be unfunded) and cooperation between a company and the scientists in the academic institution to help a potential licensee assess the feasibility of the technology and materials. This is particularly so if the institution's technology is to be used in combination with the company's technology or existing research programs. Such unfunded collaboration arrangements may be embedded in an agreement such as a two-way MTA. These types of agreements generally allow for the exchange of materials between parties while carefully defining the terms of the agreement, the roles of each party, the uses of the materials, the limitations on modifications and derivatives, and the disposition of the materials at the end of the term.

These agreements differ from ISRAs, in that ISRAs involve funding for work to be done at the institution and are more commonly negotiated to further develop licensed IP. Unfunded collaborations that may be covered by agreements such as MTAs have no reporting, work scope or financial accounting obligations for either party, and any work carried out is funded by each party separately if required.

Short-term option/letter of intent

A letter of intent, also known as a short-term no-practice option, is a simple short-term agreement allowing a potential licensee (company) to option patent rights for a short period of time in order to assess a potential opportunity. The agreement allows the company time to perform its due diligence and evaluation prior to proceeding with a formal option agreement or exclusive license but does not give it rights to use the technology, except for the purposes of assessment. The company may be responsible for patent expenses incurred during the term of the agreement, which may include paying for time-sensitive actions such as the conversion of a provisional patent to a full-utility application in the United States, the filing of a Patent Cooperation Treaty (PCT) application, or the filing of applications in foreign territories. These agreements are particularly advantageous for startup companies that may need time to raise money as having time-limited exclusivity to IP rights is valuable for prospective investors in the company. Among the advantages of these agreements is that legal negotiation is not needed. However, rules on access to the patent-protected information should be included in any agreement, as well as restrictions on the group of persons who have access to the protected information. Other advantages of short-term no-practice options are listed in Box 7.2.

For institutions, a short-term no-practice option is an important first step in the process of obtaining an exclusive license and helps to focus and commit a prospective licensee.

Box 7.2. Advantages of a short-term no-practice option from the perspectives of both parties

Advantages to the company

- Simple agreement, no need to incur legal review costs.
- Helpful for fundraising, particularly for startup companies.
- Allows company input to ongoing patent prosecution, specifically the selection of foreign territories.
- No insurance needed as no use of IP.

Advantages to the institution

- Short-term commitment from potential licensee/opportunity to engage with potential licensee.
- Help matching patent decisions with needs of potential licensee.
- Source of patent reimbursement.
- Increased probability that company becomes licensee.

Exclusive option agreement

An EOA is an important step along the path to an ELA, particularly for small or startup companies that may need more time to develop their commercialization strategies and fundraise. Larger companies, by contrast, may bypass the step of taking an EOA and go directly to an ELA. An EOA typically lasts for one year with the ability to renew in six-month or one-year increments.

Under an EOA, unlike a short-term no-practice option, the company has the right to use the technology but may not engage in any commercial activities. Typically, a company uses the time during which it is bound by an EOA to test the technology in its own laboratories and to fundraise. The company also uses this time to determine an acceptable development timeline, which is necessary for justifying a future license agreement. An EOA typically contains an upfront fee, reimbursement of ongoing patent expenses incurred during the term of the license, and insurance (if taken out by the company) to account for any liabilities incurred out of the company's exercise of the EOA. An EOA may or may not spell out the future terms of an ELA, though EOAs often include "penalty clauses" if the company does not elect to negotiate and execute a license at the end of the option. For instance, the licensor may be reluctant to place its patent rights under a long-term option because it begins to eat into the patent term, or the company may use the time to identify an improvement that either blocks practice of, or enables the company to avoid infringement of, the academic institution's patent. To protect itself, the academic institution may include a provision requiring that the company grants it a commercial license, with the right for the academic institution to grant sublicenses, or provisions to block improvement IP and/or requiring the payment of a financial penalty if no license is executed.

Exclusive license agreement

ELAs are the main mechanism through which academic institutions grant the biotech industry rights to bring academic discoveries to the marketplace. Many of the recommendations throughout this *Primer* have their foundation in what is widely considered a good practice manual for the technology transfer community, a document entitled *Nine Points to Consider in Licensing University Technology* which was created in 2007 by a dozen preeminent academic institutions to help guide academic institutions in their licensing practice.[2] ELAs are of paramount importance in the biotech industry, where R&D timelines are lengthy and financial investments substantial. These time and financial costs make the exclusivity of ELAs necessary for the industry.

Furthermore, because therapeutics are typically regulated by government entities and the approval process requires disclosure of a significant amount of information regarding the drug, including its manufacture and administration, companies in the biotech industry need to rely on patents (rather than trade secret strategies) to protect their proprietary position. In industries with quick developmental cycles or products with thousands of components, patents may be less critical as companies can in many cases rely on trade secrets to maintain their proprietary position, and licensing strategies may include nonexclusive licensing. Also, as a result of their complex molecular structure, biotechnologically produced drugs might be more difficult to analyze and replicate by successor companies than chemical-synthetic drugs. In the case of biopharmaceutical products, the manufacturing method and production unit also determine the molecular structure. Therefore, biosimilars as successor products to biopharmaceutical drugs are only "similar" and not "identical". The manufacturing method could in turn be protected by a know-how trade secret.

This *Primer* lays out the criteria for an ELA that grants exclusive patent rights, transfers materials and involves inventions made by employees of two academic institutions with an agreement between the two entities codified in an IIA. An IIA typically gives one academic partner the lead responsibility for licensing and may specify terms that must be included in any license agreement executed. The important clauses of an ELA are set out in general terms in Box 7.3 and discussed in more detail below.

2 https://www.aau.edu/newsroom/press-releases/nine-points-consider-licensing-university-technology

Box 7.3. Elements of an exclusive license agreement

- Scope of IP rights granted
- Type of license granted (exclusive vs. nonexclusive, field of use, territory, sublicense, etc.)
- Diligence (delineation of timelines, obligations, etc., to ensure timely commercialization)
- Patent prosecution (important to ensure control over the process and seek meaningful patent protection)
- Reservation of rights (important for ensuring continued academic research)
- Indemnification (to protect against liability) in case the licensee violates the ELA
- Financial terms (expenses, royalties, sublicense fees, etc.)
- Term of the ELA and termination clauses (if required)
- Confidentiality obligations
- Information reporting and sharing requirements

IP rights

The most important clause in an ELA is the scope of the IP rights being granted by the licensor to the licensee. For example, does it include solely patent rights, or will know-how and copyrightable information also be included? Are there any co-owner rights that need to be considered? How is potential blocking IP (whether previously existing IP in the licensor's portfolio or improvements that may arise in the future) addressed?

Grant

In this clause the most important concepts are exclusivity, territory (worldwide or specific countries), field of use and right to sublicense. The patent rights granted are threaded into the grant clause through the definitions of the licensed products and licensed methods. A clear bounding of the extent of the patent rights conveyed is of critical importance as the grant should state exactly what rights are being given to the licensee. Many licensees wish to have access to improvements. The difficulty with granting rights to improvements is that the inventor may have funding and third-party obligations that will attach to new rights. Most exclusive licensees gain rights to the inventor's improvements by financially supporting research in the inventor laboratory, giving the company certain rights which may include the first right to negotiate a license to (this is more common in the United States), or ownership of (more common in European countries), improvements that are made under the industry-supported research agreement.

The field of use concept is of importance particularly if the invention being licensed has multiple uses and could be relevant to several industry sectors. For example, a therapeutic may have several applications for multiple diseases and may also have utility in, say, veterinary markets that fall outside of the licensee's core business. An agreement should allow a licensee exclusivity that aligns with its core business plans and capabilities. The agreement should not grant rights that exceed the licensee's capability in order to ensure that an academic institution's IP is fully developed, perhaps by another nonoverlapping licensee.

Diligence

The diligence timeline is often the most difficult part of a licensing negotiation but is essential for ensuring timely development and commercialization. A good diligence timeline is one that obligates the licensee to develop the technology to an agreed schedule. Failure to meet specific, clear and indisputable milestones results in termination or loss of exclusivity. Typically, a TTO in an academic setting will ask a potential licensee to provide an executive summary or brief development plan during a license negotiation to assist in assessing the capabilities of the prospective licensee. A potential licensee can also be asked to propose a diligence timeline to include in the ELA.

However, most potential licensees will resist the inclusion of diligence timelines in their ELAs, since no company wants to risk losing a license for failure to meet a developmental diligence milestone. Some licensees will say that it is too early to commit. In these circumstances, the

company may be bound by an EOA with a decided timeline that prevents the situation from continuing for too long without progress while the patent term reduces, the institution loses further opportunities and the public is potentially deprived of the benefit of a promising commercial innovation.

Without a diligence timeline, inventions may be put on the back burner if a company has other priorities or strategies. Even the cost of an annual maintenance fee and ongoing patent expenses are often not enough to ensure that licensees press forward with development. Furthermore, a lack of diligence requirements also prevents other potential licensees from developing products of the invention. There are alternative mechanisms and/or incentives that could be employed to encourage licensee compliance with diligence timelines, without overly penalizing innovation flexibility. These could include progressive milestones, renegotiation options or performance-based incentives to balance timely development with the realities of commercialization challenges.

Patent prosecution

In most cases, academic institutions will agree to pursue patent protection at the licensee's expense. While the academic institution will typically retain control over the patent prosecution, it will consider and incorporate input from the licensee as this may be critical to secure meaningful protection that supports planned commercial development. That said, it is desirable for the academic institution to retain ultimate control of patent prosecution for many reasons, including if:

- the licensee attempts to narrow the patent claims to avoid covering its commercial products (and thereby avoiding royalty obligations to the academic institution);
- the licensee develops a competitive portfolio and, as a result, a potential conflict of interest arises when attempting to prosecute both the academic institution's patents and its own patents;
- the licensee makes any misrepresentations or commits any other misconduct before the patent office with respect to a patent that is being pursued in the academic institution's name; or
- the ELA terminates and the rights are returned to the institution.

Reservation of rights

The academic institution should reserve the right to continue to use the licensed patent rights in academic research, which includes industry-supported research. The *"Nine Points to Consider"* document mentioned above suggests the following phrasing: "Institution retains the right, on behalf of itself and all other nonprofit academic research institutions, to practice the Licensed Patent and use Technology for any nonprofit purpose, including sponsored research and collaborations. Licensee agrees that, notwithstanding any other provision of this Agreement, it has no right to enforce the Licensed Patent against any such institution. Institution and any such other institution have the right to publish any information included in the Technology or a Licensed Patent."

Term of the ELA

The academic institution should reserve the right to terminate the ELA if the licensee does not fulfil its obligations (diligence obligations, for example). In addition, it may make sense to agree on the obligations of the licensee in case the ELA is terminated.

Indemnification

Academic institutions are not resourced for, nor is it fair for them to take on, the extensive liability associated with the licensee's development and sale of human therapeutic and diagnostic products. It is essential that the licensee bears this risk and carries appropriate levels of insurance, so the institution is fully protected from misfortune. However, in the industry setting, it is common for both parties to indemnify each other.

Financial terms

In negotiating an ELA, it is important for an academic institution to examine the totality of the consideration[3] provided by the agreement, and to avoid agreeing to one financial term in isolation. The financial aspects of an ELA are best communicated and negotiated through the use of a simple nonbinding term sheet to list and define the major financial components (Box 7.4) in order to facilitate timely negotiation and avoid focusing too heavily on one financial term. For example, a party might be willing to accept a modest upfront fee if the milestone payments are generous. It is also helpful to make fee-bearing milestone events requirements in the diligence section of the license agreement so that there is no ambiguity around the timing and completion of the milestone event.

Box 7.4. Key financial terms included in ELAs

- **Upfront fee**, including a percentage of equity if appropriate (see main text).
- **Sublicensing income percentage.** This percentage can step down as the licensee adds value to the invention through its investment in development. It is important to keep the definition of sublicensing income broad.
- **Annual maintenance fees.** These amounts should not be excessive as the licensor wants the licensee to invest its often-scarce funds in developing the product or technology; however, the amounts should be enough to make a licensee consider returning the license if it is not truly interested in developing the technology.
- **Royalty rates** may be established using a variety of methods. Comparable rates from other institutions for similar technology are helpful. It should be specified upfront when setting the royalty rate whether there is a combination product language and royalty stacking provisions. Such clauses may be appropriate to include but will almost certainly reduce the effective royalty rate. Royalty rate is usually based on the net sale of the product. Unlike sublicensing income, it comes in the later stages of development.
- **Minimum annual royalties** ensure that the licensee is actively marketing and selling the product or technology in question; these royalties may escalate over time.
- **Milestone payments.** Major developmental events such as the filing of an IND application, entry into various phases of clinical trials, regulatory approval and first commercial sale are all good milestones to which payments can be attached. Milestone payments represent value inflection points, and the licensor should share in some of the value creation along the developmental and regulatory pathway.
- **Full reimbursement** for past and ongoing patent expenses.

Academic institutions' licensing strategies may vary depending on whether the licensee is the academic institution's own startup or a third party. Most ELAs with smaller/startup companies are backloaded (that is, most payments will be at a later stage of the development process or at the royalty payment stage) as a startup company may not have the resources to accommodate a large upfront fee. In these situations, a licensor/academic institution may consider taking a low upfront fee or a modest amount of equity as partial consideration for the license agreement while bearing in mind the caveats below. Additionally, some TTOs may be resourced to manage the shares obtained from the license agreement, whereas others may not have the capacity and may also be precluded from taking equity.

From a company's point of view, it is better to avoid offering large amounts of equity that would give the TTO control or a voting seat on its board, because future investors in the company may not appreciate having bureaucratic institutions as shareholders. Additionally, a TTO would need to avoid taking shares to avoid potential conflicts of this kind. There may be additional complicating factors if an academic institution does not have a policy for handling equity or a treasurer's office to manage the shares. Acceptance of equity can raise issues relating to securities law (for example, insider trading) or whether the institution has fiduciary obligations to inventors.

3 "Consideration" is something that each party to a contract gives to the other party in exchange for that other party's promise or performance of the contract.

Nonexclusive license agreements

When an invention is a platform technology it is possible that it would be most effectively commercialized via widely granted nonexclusive licenses. Stanford University in the United States has had great success, in terms of both technology dissemination and licensing revenues, in nonexclusively licensing biotech inventions. As one example, in *A History of OTL*, Stanford's Office of Technology Licensing (OTL) recounts: "By August 1981, OTL started offering special, nonexclusive licenses to the new recombinant DNA technology. While there was not an immediate rush of interest, word spread through media coverage and our own intensive marketing efforts, and by the deadline – midnight on December 15 – Federal Express trucks were lined up outside the doors to OTL. When the deadline passed, 73 companies had signed agreements. By the end of that fiscal year, August 31, 1982, license fees from the new DNA technology had produced over $1.4 million in income. It is interesting to note that during the same period, all other technologies licensed by OTL together brought in just $1.1 million. While the percentage of income produced by the recombinant DNA licenses subsequently decreased to about one third of total income for the next several years, it then quickly overtook all other licensed technologies as the biotechnology industry caught fire."

Research agreements with industry and nonprofit foundations

In addition to receiving federal and state grants, a significant portion of many academic institutions' research budgets comes from for-profit and nonprofit entities. This is particularly the case in the biotechnology sector given the heavy investment that is required to translate basic research findings into clinical solutions. Each of these types of financial support are described below.

Industry-supported research agreements

An ISRA is an opportunity for a company, often a licensee, to provide financial support for an academic institution researcher to conduct work that is of interest to both parties (researcher and company) in the researcher's lab at the academic institution. The ISRA contains a clearly defined scope of work with a budget and a performance period. The researcher and the company agree on the scope of the work, which must have sufficient academic merit and not be merely work-for-hire work that could be contracted to a private research company (often the academic institution researcher has unique expertise that cannot be found elsewhere). The scope of work is appended to the ISRA and an appropriate budget is set out in the agreement.

Under the negotiated budget, the company pays the academic institution for both the direct costs of the research (salaries, equipment and materials) as well as "overhead" or "indirect" costs. These indirect costs include infrastructure expenses such as keeping the research buildings lighted and heated. In exchange for sponsorship, the company is given certain rights as determined during negotiations between the academic institution and the company.

Nonprofit grants

An increasing percentage of academic institutions' research budgets comprises financial support from nonprofit entities, primarily from foundations that have a particular disease or philanthropic focus (for example, the American Diabetes Association, Komen Foundation, Bill & Melinda Gates Foundation, etc.) and the research is intended to advance progress in related scientific disciplines.

While a nonprofit grant is like an ISRA in that both often have defined scopes of work and the nonprofit grantor typically has the right to receive a copy of the results, the IP obligations are quite different because the nonprofit cannot directly commercialize the results. So, for example, rather than requiring that the academic institution gives the nonprofit granting foundation an option to negotiate a license (which would be of no use to the nonprofit), nonprofit grantors may expect anything from a simple report of the results to a share of the academic institution's profits derived from commercialization of the results.

Consulting agreements

A company may wish to engage an academic researcher in outside consulting work. Companies that have executed an ELA may seek assistance in implementing the licensed technology – in particular, they may seek assistance in implementing the know-how associated with the technology. Some licensees will elect an IRA while others will seek assistance from a researcher/inventor outside of the institution. Each institution will have its own policies governing consultation activities, but the parameters and caveats set out in Box 7.5 should always be considered. These are not comprehensive, nor should they be construed as legal advice but rather a list of some issues to consider.

Box 7.5. Parameters and caveats for consulting agreements

- A consulting agreement is a personal agreement between the researcher and the company. There are varying degrees to which institutions may be involved in these agreements. Some institutions will review the consulting agreements for conflicts of commitment and conflicts with institutional policies, some will assist with negotiations and some will keep the agreements on file.
- The consulting agreement should not supersede the researcher's obligations to the institution in terms of assigning agreements. The consulting agreement should clearly spell out the researcher's IP commitment to the institution.
- The consulting agreement should have a narrow scope so as not to overlap or conflict with the researcher's ongoing work at the institution.
- The consulting agreement should allow the researcher to confidentially share inventions made while consulting with the institution so that the institution may release or nonassert its rights to the invention, if appropriate. In many instances, however, the company will restrict the consultant's ability to share confidential information with any third party without its prior consent. This applies also to scientific publications by the researcher. In these situations, a university may ask to have patents disclosed upon publication so the inventor and company can obtain any nonassert or release letters from the institution. This is an important point for institutions as they have reporting obligations to third-party sponsors of research. The institution needs a mechanism through which it can ensure that it is diligently monitoring and reporting inventions that arise from research funding.
- The researcher should be indemnified by the company.
- The researcher should seek legal review from his or her own counsel prior to entering these personal agreements.
- Researchers are generally required to assign the IP generated during the consultancy to the company.

Licensing know-how and data/information ("nonpatentable information")

While patent protection is often essential for a technology to attract enough investment to make it to the marketplace, nonpatentable information can be just as important in terms of enabling others to effectively implement the technology. Know-how, or information that is not patented or patentable, is often bundled and jointly licensed with patents in biotech-related licensing agreements. This is usually done on a nonexclusive basis because of the difficulty in controlling access to know-how, the fact that researchers are incentivized to publish and the desire to advance science by sharing know-how.

Methods of protecting nonpatentable information

The main methods of protecting nonpatentable information are summarized in Box 7.6 and reviewed below together with considerations of how value is captured and incorporated in the context of biotechnology licensing agreements.

Box 7.6. Ways of protecting nonpatentable information

- **Trade secrets.** Nonexclusive examples of trade secrets in biotechnology are manufacturing processes, formulae and development research including preclinical data.
- **Copyright.** Collections of facts and information are one example of materials that can be copyrighted in biotechnology.
- **Court causes of action.** Examples include electronic databases and documents.
- Sui generis **rights.** Examples in biotechnology include plant breeders' rights, farmers' rights, protection of traditional knowledge; in the European Union, *sui generis* rights can cover databases.

Trade secrets

For companies, maintaining information as a trade secret can be a very effective and inexpensive way of protecting the value of nonpatentable information. However, this strategy is challenging, even inappropriate, for most academic institutions to adopt in view of their desire to publish, and, at least within the United States, to maintain their fundamental research exclusion (FRE) under the Export Administration Regulation (EAR) and/or International Traffic in Arms Regulations (ITAR) export control laws. "Fundamental research" is characterized as basic or applied research in science, engineering or mathematics, the results of which ordinarily are published and shared broadly within the scientific community, and for which the researchers have not accepted restrictions for proprietary or national security reasons. An academic institution can lose its FRE and subject its research enterprise to export control regulations (which are very onerous and expensive to implement) if it agrees to provisions prohibiting publication or dissemination of its research results. Therefore, protecting nonpatentable information via other means such as copyright or a contract may be preferable.

Copyright

The challenge of relying on copyright laws to protect nonpatentable information is that mere ideas alone are not protectable under copyright, only the expression of those ideas. However, in most countries, a database of facts may be protected by copyright as a "compilation" (that is, a "collection and assembling of preexisting materials or of data that are selected in such a way that the resulting works constitutes an original work of authorship" – see 17 USC 101). Academic licensing can involve granting rights to use a valuable database or other copyrightable expression of technical information. In the European Union, for example, databases are protected under EU law by Directive 96/9/EC on the legal protection of databases.[4]

Court causes of actions

While not widely relied on as a means for enforcement, trespass to chattels (that is, intentional taking of property without permission of the owner) and conversion are two possible causes of action that can be employed to pursue the improper taking of personal data. Case law is expanding to potentially cover intangible rights, such as electronic databases (virtual documents).

Sui generis rights

Sui generis rights are not available in the United States, but the European Union and several other countries recognize them for certain nonpatentable information. These rights prohibit the extraction or reutilization of any database in which there has been a substantial investment in obtaining, verifying or presenting the data contents. There is no requirement for creativity or originality, which are typically required for a work to be copyrightable.

4 Directive 96/9/EC of the European Parliament and of the Council of 11 March 1996 on the legal protection of databases, OJ L 77, 27 March 1996, p. 20–28, https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31996L0009.

Considerations when drafting the license grant

Once nonpatentable information has been protected, it may be included in biotechnology licensing agreements. The following are some key considerations to keep in mind when drafting the license grant and defining the scope of rights granted.

Basic grant clause

Parties to an agreement should carefully consider the scope of the license grant to ensure the grant clause is only as broad as is intended. For example, compare "Subject to the terms and conditions set forth in this Agreement, University hereby grants to Licensee a nonexclusive license to use the Nonpatentable Information"with this, more restricted, grant clause: "to use the Nonpatentable Information solely for the Licensed Purpose".

Bundling nonpatentable information with patent rights

Often, during the negotiation of a bare patent license in the biotechnology sector, it becomes evident that the prospective licensee also wants access to nonpatentable information, as well as tangible materials and other valuable resources. This can be advantageous from a licensor's standpoint as it can provide the licensor with a "royalty tail" (that is, continued consideration after the patent rights expire) and helps provide focus for the permitted licensed purpose. For example: "Licensee may use the Nonpatentable Information solely for the purposes of making, using, and selling Licensed Products covered by the Patent Rights." The scope of licensed products and/or licensed purpose might survive the expiration of the patent rights, depending on the term of the specific licensing agreement. In addition, contrary to registered IP rights, unregistered IP rights like know-how, protected as a trade secret, have, in principle, no limitation in time. When bundling nonpatentable information with patent rights, it is crucial to distinctly differentiate these assets in the licensing agreement and establish separate financial terms for each. This ensures clarity on the value and terms associated with licensing nonpatentable information, especially after the patent rights expire, allowing for transparent and equitable arrangements throughout the duration of the agreement and beyond.

If there is no intention to transfer or license nonpatentable information in a patent license, it is important to state as much in the disclaimer of warranties or grant clause section. The following is an example of such a statement: "For clarity, the rights granted pursuant to this Agreement pertain solely to the Patent Rights; if Licensee desires any right or license from University to use any information and/or tangible material associated with such Patent Rights (e.g., data, protocols, tangible materials, etc.), the parties may negotiate and either amend this Agreement, or enter into a separate agreement, to the extent such rights are available at the time of Licensee's request."

Defining the rights to be granted

In biotechnology agreements, it is important to clearly delineate the rights to be granted, including granting rights solely to what the licensor owns, and the scope of commercial rights the licensor wants to extend. Below are examples of such statements.

- **"Nonpatentable information".** Stock should be taken of what the licensor owns (check assignments, sponsor and employment agreements, and institutional or company policies) and rights should be defined carefully. As an example: "Nonpatentable Information means University's ownership interest (but, for clarity, excluding any patent rights) as a result of assignment by the Creators of the nonpatentable subject matter, including by way of example technical information, copyrightable works, processes, procedures, methods, protocols, techniques, designs, drawings and/or data, that satisfies all of the following: (i) it exists as of the Effective Date of this Agreement, and (ii) it is expressly identified in Appendix _ of this Agreement. University will have no obligation to keep Nonpatentable Information confidential or as a trade secret."
- **"Licensed purpose".** What commercial rights does the licensor want to grant and what does the licensee want to receive? For example, are the commercial rights solely for internal purposes? Or to make, use, sell, offer for sale and import products? Or solely for the purposes of training an algorithm? Consideration should be given to defining or enhancing

the definition of "licensed purpose" by excluding certain activities: "Notwithstanding the foregoing, Licensee may not use the Nonpatentable Information to do X or Y...."

Granting exclusivity

Before granting exclusive rights to nonpatentable information, the parties must carefully consider what it means to grant exclusivity. Unless otherwise defined, it requires maintaining full control over the dissemination of the nonpatentable information, which is often challenging to do in an academic context and may run afoul of export control laws and/or institutional policies. Other practical considerations include the desire to publish in the future, the ability to track dissemination of the nonpatentable information and challenges with prohibiting use of the nonpatentable information in future research, etc.

Closing potential royalty/consideration gaps

If the licensor will not be receiving all its consideration at the time of the transfer of the nonpatentable information, then it is also important to ensure that the license being granted is co-extensive in scope with the licensee's obligation to pay consideration in relation thereto. As an example: "Subject to the limitations and other terms and conditions set forth in this Agreement, University grants to Licensee a nonexclusive license with respect to the Nonpatentable Information to make, have made, manufacture and use Licensed Products for the sole purpose of offering for sale, selling, having sold, importing, exporting and distributing Licensed Products in the Field of Use and Licensed Territory solely in a manner that will trigger an Earned Royalty pursuant to Section X when such Licensed Product is sold, provided, distributed or otherwise transferred."

Restrictions in view of human-derived data

If the nonpatentable information includes the right to have access to any data derived from humans, then consideration must be given to whether further transfer by the licensee is permitted in view of internal review board approvals or existing patient consent forms. Typically, permission to transfer patient-related information is granted on a per licensee (that is, a specifically identified entity) basis. In addition, data aggregation and data mining technology are continually advancing, resulting in an increased risk that personally identifiable information may be matched to a dataset. Therefore, it may be important to prohibit the licensee from conducting such data mining (for example, "Licensee has no right to, and shall not attempt to, identify the patient source of any ... provided or licensed hereunder").

In any case it is important to distinguish between anonymized and nonanonymized data. When a person is identifiable, strict privacy and data protection regulations must be respected. In the European Union, for example, the General Data Protection Regulation (GDPR)[5] regulates principles for the collection, processing and transfer of personal data as well as the rights of persons concerning their data. The GDPR is the toughest privacy and security law in the world and is directly applicable in all EU member states. However, though it was drafted and passed by the European Union, it imposes obligations on organizations anywhere, so long as they target or collect data related to people in the European Union. The regulation came into effect on May 25, 2018, and can levy harsh fines against those who violate its privacy and security standards, with penalties reaching into the tens of millions of Euros. For almost all activities concerning private data, such as collecting, processing and transferring of personal data, the prior consent of the individual is required and must be documented. Third countries, such as Switzerland and Japan, have adopted similar data protection laws to facilitate transfer of personal data with the European Union.

Assessing and capturing value

An important aspect of biotech licensing agreements that include nonpatentable information is assessing and capturing the value of said information.

5 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation, GDPR), OJ L 119, 4 May 2016, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679.

- **Assessing value.** Factors to consider when assessing the value of the nonpatentable information may include the sum of research expenditures which led to the creation of the information; reproducibility or other sources for the data set (uniqueness and exclusivity); manner and difficulty of aggregation; value of time saved in recreating data/information or finding another source (known as the first mover or accelerated scale-up theory); whether data/information are validated or published (validation can increase value depending on application); quality of the data or information (this includes relevance, accuracy and type); testing the licensee (that is, if data/information were removed from the patent/data/information deal, would the licensee still take the deal?); and contractual provisions to include regarding the data/information's ownership and/or value (for example, "University owns the data/information and University has expended significant resources gathering, assembling and compiling the data/information, and the data/information is the valuable property of University").
- **Capturing value.** The parties should consider modeling the consideration obligations on the licensor's ability to police whether the licensee has extracted value and to enforce the contractual rights. If it is relatively easy to assess value but difficult to enforce, requiring the consideration upfront or on an annual fee basis could be an option. If it is more difficult to assess value but relatively easy to enforce, basing the consideration on equity, earned royalties and/or success fees could be a strategy if negotiating it in this form would result in a significantly higher payout. The choice of approach largely depends on visibility into product development and ability to enforce.

Termination considerations

There are unique termination considerations when licensing nonpatentable information. It is important to define the terms of the agreement, as well as the term of the licensee's obligation to pay if consideration is to be paid later. If the nonpatentable information is being licensed with patent rights, it is necessary to consider whether the licensee's obligation to pay with respect to the licensed nonpatentable information should run longer/shorter than the term of the patent rights. If the agreement terminates prior to the natural expiration of whatever term the licensor places on the licensee's ability to use the data and the obligation to pay consideration for such use, there should be a requirement to confirm the destruction of the nonpatentable information. Alteration of the payment obligation (for example, by way of a payment step down) could be considered if the nonpatentable information becomes publicly available. It is also important to consider whether the licensee could sublicense the right to sell licensed products (but not sublicense the nonpatentable information) or assign the license agreement (or its assets) to avoid an obligation to pay ongoing consideration.

There are a host of laws and regulations applying to the transfer and use of data that must be considered on termination of an agreement, particularly when the license included access to human-derived and personal information. These include, for example, the European Union's GDPR; California's Consumer Privacy Act (CCPA); Brazil's Lei Geral de Proteção de Dados; and South Africa's Protection of Personal Information Act, as well as regulations governing personally identifiable information and protected health information. Other considerations include internal review board permissions, patient consent forms, data privacy laws and trade secret regulations (See "Privacy and export control laws and regulations are not uniform".)

Financial research support from foundations and nonprofits

As noted above, funding from charitable foundations and nonprofit organizations can supplement other internal and external financial sources and can bring several advantages. These include support for applied (versus basic) research for a specific therapeutic or diagnostic goal; finance for investigations into conditions affecting underserved populations; and introductions to key external networks of researchers, patient advocacy groups, companies and investors.

Contract terms will vary depending on the sponsoring organization. Typically, the academic institution is allowed to own inventions and control licensing. However, some funders' terms can undermine any licensing effort and discourage commercial interest. If the funder demands co-ownership of inventions, approval of the licensee/licensing terms or the right to

terminate a license under certain scenarios, it may be impossible to find interested companies. Foundations pay few or no indirect costs, which can burden the research institution. Some foundation sponsors expect a share of any license income. Overall, however, these kinds of issues can usually be resolved and the benefits of accepting funding from charitable foundations or nonprofit organizations outweigh the risks or challenges.

8 Biotechnology in the time of COVID-19

COVID-19 placed biotechnology in the global spotlight, prompting unprecedented collaboration in vaccine development. This chapters looks at how academic institutions pivoted to support rapid research and technology transfer through time-limited non-exclusive royalty-free licenses and at how patent pools and licensing partnerships facilitated access to technologies.

The arrival of COVID-19 in late 2019 brought biotechnology, specifically vaccine science, development, production and access, into the world's spotlight in an unprecedented way. Once health officials began to understand the transmissibility and lethality of the virus and governments realized its potential to devastate economies, it became clear that the old way of doing business would not be effective in meeting the challenge. This spurred novel collaboration, with 170 countries actively engaging in developing hundreds of vaccines, antibody therapies and inhibitory small molecule drugs, diagnostic tests and specialized protective devices, all aimed at preventing transmission, identifying infected individuals and reducing suffering, morbidity and death from COVID-19 infection.

With respect to vaccines, three types were created: protein subunit vaccines, vector vaccines (DNA vaccines) and mRNA vaccines. The timing for mRNA vaccines was especially fortunate because several companies, in particular Pfizer (and its partner BioNTech) and Moderna, had already been looking at this innovative approach to stimulate a safe, effective immune response. Other companies like Merck had long experience with both traditional vaccines and antiviral medications (antivirals). The clinical effectiveness of different interventions has varied depending on the technology, company and government involved with development.

Funding to develop, manufacture and distribute COVID-19 therapies has come from corporate companies, governments, charities, non-governmental organizations (NGOs) and other sources. In some instances, the funding was used for R&D efforts or to underwrite manufacturing scale-up before completion of phase III clinical trials. The latter was to ensure the rapid deployment of therapeutics in the event of successful trials. In many cases, governments paid significant amounts to pre-purchase the drugs or vaccines. Although the benefits have not been evenly distributed within their borders, for developed and wealthier countries, the effort has been a remarkable success.

The need for developed innovation ecosystems

The same cannot be said for less-developed countries. There are many reasons for this, including financial and political reasons as well as lack of suitable infrastructure, manufacturing capability, raw materials for vaccine production, researchers and know-how, and ineffective distribution and delivery. However, some efforts have been made to address these deficiencies. To support equitable and humane medical intervention, a number of initiatives aimed to ensure universal access to COVID-19 therapies. Several for-profit companies signed an Open COVID Pledge in which they pledged to make their IP available free of charge. Other groups or companies pledged not to pursue infringers during the pandemic. Several

companies engaged in broad sublicensing to facilitate production of less-expensive biologics or other drugs. Patent pools were established or broadened to make them relevant to COVID-19. Over 90 leading universities in the United States and other countries, led by the Association of University Technology Managers (AUTM),[1] agreed COVID-19 licensing guidelines[2] which were promoted to IP owners worldwide to facilitate the sharing of technology during the pandemic. For technology or products needing little investment to bring to market, for example, personal protective equipment or a standard diagnostic test, companies, universities and charities either gave the products or the specifications to make them for no cost.

Limited nonexclusive royalty-free license

TTOs realized that a paradigm shift was necessary to support efforts to bring a swift end to the crisis, especially in developing and least-developed countries. The COVID-19 licensing guidelines developed by the AUTM aimed to facilitate rapid pandemic responses by licensees and to make the execution of associated transactions a top priority. In its guidelines AUTM urged that, for most technologies, where legally possible, parties should consider time-limited, nonexclusive royalty-free licenses in exchange for the licensees' commitment to rapidly make and broadly distribute products and services to prevent, diagnose, treat and contain COVID-19 and protect healthcare workers during the pandemic (that is, while COVID-19 was defined as a public health emergency of international concern by the World Health Organization (WHO)). These licenses could subsequently convert to a more typical commercial license as appropriate, and they also had to preserve the licensor's freedom to publish and use the IP for teaching and research.

Licensing pools and patent pools to facilitate access to a suite of patented technologies

The COVID-19 pandemic also highlighted other existing technology transfer mechanisms, including licensing pools and patent pools. Licensing pools and patent pools can be an efficient means for licensors to out-license their technologies, as well as for potential licensees to in-license technologies from multiple entities in a single transaction, and can help to connect patent holders seeking to license their patented technology with candidate users seeking to use patented technology.

Patent pools

Patent pools are one approach to allowing licensors to combine self-selected patent assets, typically in a specifically defined technology, to facilitate licensing of the bundled patent assets to industry via a single license.[3] Often, the patent pool is set up as a distinct entity from the licensors and serves as a liaison between the licensors and the licensee. This strategy can reduce the number of agreements and thus transaction costs (compared to licensing from each patent owner), enabling companies to obtain convenient, transparent and efficient access to technologies. Patent pools can be set up either as nonprofit entities (wherein the focus may be to improve access to technologies and/or drugs in underserved communities or low- and middle-income countries (LMICs)) or for-profit entities (wherein the goals often include increasing dissemination and monetization of IP assets). Given the significant effort and the many millions of dollars in investment required by companies, it is important to ensure that contributions to these pools remain voluntary. It is also important for patent pools and associated licensing programs to have a comprehensive portfolio of assets such that licensees have reasonable confidence that they can gain access to the technologies they need for a given use. Finally, there must be no restrictions of access to the patent pool for antitrust reasons.

Since the 1990s, some companies have developed patent pools and licensing strategies for certain technologies and standards that are widely used in consumer electronics, video and

1 AUTM is a nonprofit organization dedicated to bringing research to life by supporting and enhancing the global academic technology transfer profession through education, professional development, partnering and advocacy.
2 https://autm.net/about-tech-transfer/covid19/covid-19-licensing-guidelines
3 Patent pools are often modeled on the "Sewing Machine Trust" of the mid-19th century, where a group of innovators agreed to pool their patents and agree to terms such that a consumer could buy a machine with features owned by different patentholders, and proceeds were distributed by the patent pool to the patentholders.

information technologies, radio-frequency identification (RFID) and power management. MPEG LA, founded in 1997, developed a patent pool strategy to facilitate adoption of the MPEG-2 standard required for digital television applications (for example, DVDs) by offering a "one-stop" license for the required technologies. MPEG LA has continued to develop licensing programs for additional MPEG standards, and has also developed patent-pool-based licensing and standards programs for wireless power, electric vehicle charging, video coding and other technologies. MPEG LA now holds licensing-related rights to thousands of patents owned by hundreds of patent holders in 100 countries and has over 7,200 licensees.

Efforts to form centralized patent pools for the biotechnology sector have been less successful. In 2012, MPEG LA launched Librassay®, a one-stop patent licensing program in the field of molecular diagnostics, but that program is not currently offering licenses. Using a different model, MPEG LA recently began to offer a drug development and design program for cell-targeting oligonucleotides, which appears to be an internally developed set of technologies as opposed to an externally sourced pool of patented technologies.[4] In 2017, MPEG LA proposed developing patent pools for CRISPR-Cas genome editing using the foundational techniques of CRISPR-Cas9 technology,[5] although ongoing patent disputes among potential contributors has delayed progress. The classic patent pool model may not prove useful for biotech innovations, due in part to the lack of modular standards and the often distinct needs of each user.

Licensing pools/licensing partnerships

Licensing pools or licensing partnerships are another approach allowing users access to a suite of separately owned patented innovations in order to accomplish a goal (say, to carry out a treatment campaign or a research program). This approach utilizes voluntary licensing and, if possible, voluntary patent pooling. When a need has been identified – for example, a treatment need that has been defined by a disease, a patient population, a proposed dosage amount/regimen and an intended geographical field of use – the licensing pool or partnership can negotiate with patent holders to license the medicines and technology needed to meet the need. The licensing pool or partnership can then sublicense the right to make any patented assets to meet the identified need. In some cases, a voluntary patent pool may have already put some country-specific patent assets at the disposal of the licensing pool or partnership. The Medicines Patent Pool (MPP) is an international organization that has pioneered this approach, and some of its successes are described in Box 8.1.[6]

Box 8.1. The Medicines Patent Pool

MPP is a Swiss-based nonprofit organization established by Unitaid in 2010 to facilitate access to quality-assured affordable medicines and other health technologies in LMICs through public health-oriented licensing and technology transfer. MPP works in partnership with industry, WHO and other international organizations, governments, community and civil society organizations, patient groups, disease experts and others.

MPP has agreements with 20 patent holders including many leading pharma companies, such as AbbVie, BMS, Merck, Gilead, Pfizer and ViiV/GSK, covering medicines to treat HIV, hepatitis C, tuberculosis and, most recently, COVID-19. It holds licensing agreements with 58 manufacturing companies across 16 countries to develop generic versions of patented medicines for use in LMICs and, as of 2022, MPP licensees had supplied 30 billion doses of treatment in 141 countries.

How it works

MPP identifies innovative medicines needed in LMICs from a public health perspective where licensing and technology transfer can improve access. It negotiates licenses with patent holders and then sublicenses the rights to manufacture these treatments to generic pharmaceutical companies. MPP also supports development and technology transfer where relevant, and works with partners to facilitate access in LMICs.

4 https://www.mpegla.com/wp-content/uploads/IAM-article-June-2-2020.pdf
5 https://www.via-la.com/mpeg-la-invites-crispr-cas9-patents-to-be-pooled-in-a-one-stop-license
6 https://medicinespatentpool.org

Key features of MPP licenses

- Public health oriented;
- Nonexclusive – licenses to multiple manufacturers to facilitate competition, allowing for further innovation by facilitating the development of new or adapted formulations such as fixed-dose combinations that meet public health needs;
- Licenses can include the requirement for royalty payment to patent holders;
- Transparent – all MPP agreements are available on the website;
- Broad geographical scope, to enable as many people as possible to benefit.

An example

During the COVID-19 pandemic, MPP signed separate agreements with three patent holders of COVID-19 antivirals (Pfizer, MSD and Shionogi) to make generic versions of their products available in a total of 119 countries. The voluntary license agreement between MPP and Pfizer covered Pfizer's COVID-19 antiviral treatment candidate PF-07321332, which is administered with low-dose ritonavir. The license agreement allowed MPP to grant sublicenses to qualified generic manufacturers to supply the drug combination to 95 countries, including LMICs and some upper middle-income countries in sub-Saharan Africa. Pfizer agreed to not receive royalties on sales in low-income countries and to waive royalties on sales in all countries covered by the agreement while COVID-19 remained classified as a public health emergency of international concern by WHO. The license can be viewed at https://medicinespatentpool.org/licence-post/pf-07321332.

MPP also signed an agreement with the Spanish National Research Council to facilitate access to a COVID-19 diagnostic assay (Box 8.2).

Box 8.2. The COVID-19 Technology Access Pool

A variety of licensing agreements can be utilized in furthering the transfer of know-how, including through the COVID-19 Technology Access Pool (C-TAP). C-TAP was devised by WHO to provide a single platform for developers of COVID-19 vaccines, tests, devices and medicines to temporarily share data, know-how and technologies with quality-assured manufacturers. The operational model is based on public health-oriented, transparent, voluntary and nonexclusive licenses, which could be issued through MPP, or other C-TAP partners such as Open COVID Pledge, United Nations Technology Bank and Unitaid.

The first license agreement for a COVID-19 diagnostic assay was facilitated by MPP in November 2021 (https://www.who.int/news/item/23-11-2021-who-and-mpp-announce-the-first-transparent-global-non-exclusive-licence-for-a-covid-19-technology and https://medicinespatentpool.org/licence-post/elisa-antibody-technology). The license for the serological antibody diagnostic test was signed between MPP and the Spanish National Research Council (CSIC) and covers all related patents and the biological material necessary for the manufacture of the test. The test checks for the presence of anti-SARS-CoV-2 antibodies developed in response to either infection or vaccination (https://www.who.int/initiatives/covid-19-technology-access-pool/csic-license). CSIC provides all know-how to MPP and/or to prospective licensees as well as training. The license is royalty-free for LMICs and will remain valid until the date the last patent expires.

In May 2022, C-TAP signed two licensing agreements with the United States National Institutes of Health (NIH) for the development of 11 innovative therapeutics, early-stage vaccines and diagnostic tools for COVID-19 (https://www.who.int/initiatives/covid-19-technology-access-pool/us-nih-licenses). The NIH licensing agreements were assessed by the C-TAP Technical Advisory Group. There are clauses that allow the NIH to issue licenses with notification to the licensee and the opportunity for licensees to address the need for the licensed product or licensed services in lower-income countries for use in neglected diseases. [7]

7 See C-Tap: https://www.who.int/initiatives/covid-19-technology-access-pool

There are ways that companies can be encouraged to volunteer their technologies, especially in times of public health emergencies such as COVID-19. Such agreements can be beneficial for companies, allowing them to increase their knowledge of the effect of their product in LMICs where they have no, or limited, presence.

In short, the global health response to the COVID-19 pandemic has been inspiring, astonishing and hugely successful and, at the same time, an alarming wake-up call. On the one hand, extremely effective therapies were developed and approved in record times and widely, though unevenly, distributed, saving lives and protecting critical economic structures. On the other hand, from the point of view of governments, international organizations, the medical and research establishment, disadvantaged populations and even the average citizen, there have been multiple failures to ensure access to life-saving treatments for all those in need, many of which could have been prevented. Pandemic preparedness, despite warnings in recent decades, was inadequate. Investment in key areas of biotechnology as well as international cooperation has been lacking and must be increased. This concerns not only the development of biotechnological innovations but also the exchange of data, such as sequence information for viruses, to enable researchers to develop vaccines and medicinal products. There is no adequate framework for ensuring that a patient in a poor country receives, in a timely fashion, the same effective medical intervention as someone in, for example, the United States, Europe or Japan.

The necessary infrastructure of education, personnel, facilities and distribution does not exist in many countries, especially LMICs, and until it does, pandemic response in these countries will be ineffective. There is a lack of understanding on the part of key stakeholders concerning the science of biotechnology and how therapies are funded, developed and manufactured. In an interconnected world, future pandemics are likely. Hopefully, the biotechnology community and its myriad stakeholders will have learned from what went right or wrong with the response to COVID-19 and better confront the next threat. In the European Union, for example, the COVID-19 pandemic has led to the creation of the “European Health Union” with the objective to improve EU-level protection, prevention, preparedness and response against human health hazards and to collectively respond to cross-border health crises.[8] Similarly, the mRNA Technology Transfer Hub, co-led by WHO and MPP, was established in July 2021 in response to the flagrant inequities in access to COVID-19 vaccines in LMICs. It is aimed at improving health and health security through sustainable mRNA manufacturing capabilities in and for LMICs. It is based around a technology transfer “hub” located in South Africa, which will provide technology development, training and transfer to “spokes” in LMICs across the world. Currently, there are spokes in 15 LMICs (Argentina, Bangladesh, Brazil, Egypt, India, Indonesia, Kenya, Nigeria, Pakistan, Senegal, Serbia, South Africa, Tunisia, Ukraine and Viet Nam). The program is focused on mRNA vaccines against COVID-19 at present, but it is also designed to stimulate the development of other mRNA vaccines against important diseases that threaten LMICs, thereby ensuring that the capacity built by the project is sustained and available to combat future pandemics.

8 EU Commission, European Health Union: Protecting the health of Europeans and collectively responding to cross-border health crises.https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en

9 Cross-border collaborations: challenges and opportunities

International biotechnology collaborations have increased with globalization, enabling researchers to combine expertise from divergent jurisdictions on complex multidisciplinary problems. This chapter looks at how these partnerships face significant challenges, including cultural differences in negotiation approaches, varying legal frameworks across jurisdictions, inconsistent IP ownership laws, and differing privacy laws and regulations.

There are as many areas of collaboration in biotechnology as there are biotechnology areas. Since technology has made the world globalized, international research collaboration has gained momentum. With the increasingly complex and fast-changing global issues of today, researchers have found great benefit from international multidisciplinary expertise. International collaboration enables researchers to share their knowledge and combine perspectives to solve complex problems that are increasingly cross-disciplinary in nature. The need for collaboration has increased even more because of the global struggle to address the COVID-19 pandemic.

While globalization has enabled an ever-increasing amount of collaboration across borders, challenges nonetheless exist. The availability and affordability of therapeutics and vaccines in LMICs are among the key challenges. Other challenges for collaborations include overcoming language barriers when working with people from foreign countries or addressing issues specific to the local community and managing the complexity and transparent enforcement of IP rights.

Being mindful of cultural differences when pursuing international agreements is important because culture in large part determines the rules for creating an agreement, and how an agreement is carried out in practice. In some cultures, the goal of a business negotiation may be a signed contract between the parties. Other cultures tend to consider the goal of a negotiation to be not merely a signed contract, but also the creation of a relationship between the two parties. Therefore, the preliminaries of a licensing agreement, in which the parties seek to get to know one another thoroughly, are critical.

Methods of communication also vary among cultures. Some emphasize direct and simple methods of communication while others rely heavily on indirect and complex methods. These cultural differences can be as complex as the legal framework under which agreements are formulated or as simple as the meanings attributed to a particular word. For example, in some contexts an American will take “yes” to mean “I agree”, while someone from Japan in the same context might take it to mean “I understand”. To avoid some of the cultural challenges in licensing agreements, the process should begin with standard templates and model agreements that are acceptable to all parties.

Considerations applying to cross-border collaborations and jointly owned IP

Some examples of challenges that can arise when licensing IP that is jointly owned by entities located in different jurisdictions where the laws of each may conflict in terms of patent, copyright and other IP (such as trade secrets) law and/or privacy laws are given below. Many (but not all, for example, privacy laws) of these issues can be addressed proactively by expressly defining either in a collaboration, IP rights management principles agreement or other IP management agreement, how co-owned IP, if any, will be managed and which laws apply.

- **Patent laws are not uniform.** Patent laws vary among countries, and this can impact the handling of jointly made inventions. Examples include the statutory and case law definitions of who constitutes an "inventor" and whether exploitation of a jointly owned invention requires consent of the other joint owners. In the United States, for example, the default position is that joint owners can independently exploit their respective interests in the joint invention without any obligation to obtain permission from or report to the other party, whereas in most other jurisdictions, such as the European Union, Japan, the United Kingdom, Australia, China, Spain, etc., all joint owners must consent to the grant of a license to the joint invention. Other examples are the enforcement of jointly owned IP in court (US law, for instance, requires that all owners join the lawsuit, while in other countries any one of the joint owners may enforce the jointly owned patent) and filing obligations (for example, some countries, such as India, Italy, Singapore, South Korea, Turkey and the United Kingdom, have laws requiring their residents to file patents on their inventions in their country first). Furthermore, patent laws vary as to the kinds of biotech inventions that can be patented ("patentable subject matter") in a country. As a result, it is important to identify precisely what technologies are covered by enforceable patent rights in a given country, and how the patent rights term in an agreement should be defined.
- **Laws and policies for ownership of IP at foreign institutions are not uniform.** Many countries have developed laws and policies that enable academic institutions to take title to inventions made at academic institutions. However, these laws and policies are not uniform, making the administration of cross-border, jointly owned IP challenging. A single academic institution's ability to take the lead and manage the patenting and licensing under the terms and conditions of an IIA or an IP rights management principles agreement is of critical importance to the commercial viability of the technology. Without an IIA in place, it is highly unlikely that one institution would spend money filing patents on an invention which will be difficult or impossible to license. No company wants to have to negotiate with two separate parties or negotiate with an individual researcher who might, as in some foreign institutions, be the co-owner of the patents. The clarity of ownership provided by laws such as the Bayh-Dole Act in the United States, and by extension the patent policies developed by institutions, is of vital importance for the successful commercialization of academic institution research.
- **Privacy and export control laws and regulations are not uniform.** Differences in data protection (for example, GDPR vs. CCPA vs. the California Privacy Rights Act (CPRA)), privacy and export control (for example, EAR; ITAR; EU Regulation 428/2009) laws from one country to another must be considered. This requires collaborators to have or retain adequate expertise to address these issues. As explained above, the GDPR, drafted and passed by the European Union, is one of the strongest privacy and security laws in the world. It applies to individuals and entities located anywhere in the world if they are collecting data on people residing in the European Union. In some cases, it may be necessary to consider the data protection laws of a state or province. For example, the CCPA provides residents of California with more control over their personal information, including what information companies retain, what they use it for and whether they can sell such personal information. This law applies to any entity that meets certain thresholds in terms of gross annual revenue or the extent to which it buys, receives or sells the personal information of California residents, households or devices. The CPRA also places limits on data collection, retention and use. Complying with these data privacy laws becomes more and more important, since the digitalization of the healthcare sector leads to huge amounts of data that can be used to develop, for example, drugs and therapies. Thus, the secondary use of data needs to be regulated and addressed adequately to make use of this "data ecosystem".

- **Accepted practices can vary among ecosystems, leading to conflicting expectations.** Each territory often has its own unique set of best practices and policies. Differing default assumptions (that is, parties go into the negotiation having misaligned expectations of what "standard" terms and conditions consist of) can lead to protracted negotiations. Additional rounds of draft exchanges are involved in these negotiations, which delays the contemplated collaboration and decreases the likelihood of executing it successfully.

Cross-border collaborations between academic institutions and for-profit entities

Many of the challenges presented by cross-border collaborations between academic institutions and for-profit entities are similar to those outlined above. There are, however, some additional issues to consider.

- **Patent laws applying to exploitation of joint inventions differ.** In some countries, a joint owner does not need prior consent to commercialize the joint invention (that is, to manufacture and sell products) although they must get permission from the other joint owners to license the joint invention. This advantages companies over academic institutions that do not commercialize their discoveries. As a result, incentives to participate and share ideas and nonpatentable information are diminished. In most other jurisdictions, joint owners do need the explicit consent of the other owners, which can be a limiting factor in the commercialization of technologies. To avoid unnecessary obstacles to fast dissemination and access to the market, parties are often adopting IP rights management principles agreements and mandating that one of the parties take the lead with respect to technology transfer-related activities, with the obligation of regular reporting on outcomes of such activities.
- **"Standard IP rights" granted under ISRAs vary.** Customary IP terms that an academic institution is willing to grant to a company sponsor can vary by territory and this can lead to misunderstandings and protracted negotiations. For example, most US academic institutions are reluctant to (and often cannot) assign ownership of IP to a for-profit entity. However, there are some territories wherein academic institutions are willing to do so and, as a result, expectations between an academic institution and a for-profit entity at the commencement of a cross-border collaboration negotiation are often misaligned and require substantial communication as their respective starting positions may be far apart.
- **IP ownership and tax laws are not uniform.** Various corporate laws applying to for-profit entities can also vary significantly by country. Examples include works-made-for-hire (some countries have addressed ownership in their statutes, while entities in other countries must address ownership via an employment or other contract), liability and tax laws.
- **Export control concerns.** Personal data and genetic information can sometimes be subject to export control review.[1] It is important for the academic institution to consult a trade lawyer prior to sending data outside the United States.

Impact of international regulations on cross-border collaboration

Cross-border collaboration in the biotechnology sphere, while attractive, requires careful consideration and compliance with international regulations. One overarching international regulation that has an impact on biotechnology cross-border collaborations is the Nagoya Protocol of the Convention on Biological Diversity (CBD).[2] The aim of the protocol[3] is the implementation of one of the three objectives of the CBD: the fair and equitable sharing of benefits arising out of the utilization of genetic resources, thereby contributing to the conservation and sustainable use of biodiversity. It sets out obligations for its contracting parties to take measures in relation to access to genetic resources, benefit-sharing and compliance.

1 Export controls are laws and regulations that regulate and restrict the release of critical technologies, information and services to foreign nationals, within and outside of the United States, and foreign countries for reasons of foreign policy and national security.
2 Convention on Biological Diversity (CBD), https://www.cbd.int/abs/doc/protocol/nagoya-protocol-en.pdf.
3 Nagoya Protocol on Access and Benefit-sharing, https://www.cbd.int/abs/.

The protocol was adopted in October 2010 in Nagoya, Japan, and enacted in October 2014. By October 2020, it had been ratified by 128 parties – 127 United Nations member states and the European Union. The United States has not ratified the Nagoya Protocol. One of the challenges with the Nagoya Protocol is the lack of uniformity in its implementation among member states. For example, some countries (such as China, India, South Africa and Brazil) have instituted patent disclosure requirements for genetic materials that are referenced and/or utilized in the invention, whereas others have opted to go with access and benefit-sharing contractual agreements to comply with national regulations governing genetic materials.

Even though the Nagoya Protocol requires that countries designate a focal point, there are many jurisdictions in which there remains a lack of clarity as to who owns a genetic resource – the country, the locality, an indigenous community or an individual, for instance. And further, in some jurisdictions there is a lack of clarity as to whether a synthetic biological material or a digital genetic sequence falls within the myriad national regulations. Sorting through the morass of regulations and laws that govern genetic resources (some of which are not only costly and burdensome but may result in criminal prosecution depending on the jurisdiction) can disincentivize collaboration and thus commercialization.

10 Utilizing genetic resources for economic growth

Biotechnology uses genetic resources for societal benefit. This chapter gives an overview of how international treaties and countries can foster economic growth by creating frameworks that provide legal protection for inventions while encouraging conservation, funding relevant research, while establishing effective technology transfer offices and facilitating knowledge transfer to commercial entities.

Biotechnology is distinctive in that it manipulates natural or synthetic genetic resources. Such resources were historically governed by the doctrine of the common heritage of mankind until 1992, when the Convention on Biological Diversity (CBD) recognized the authority of sovereign states to determine access to the genetic resources within their territory. Nevertheless, certain categories of genetic resources with special importance are still governed as global public goods by specialized legal instruments and access and benefit-sharing systems.[1] For instance, the WIPO Treaty on Intellectual Property, Genetic Resources and Associated Traditional Knowledge, adopted on May 24, 2024, establishes a mandatory patent disclosure requirement that requires patent applicants to disclose the country of origin of the genetic resources and/or the Indigenous Peoples or local community providing the associated traditional knowledge, if the claimed inventions are based on genetic resources and/or associated traditional knowledge.[2] Plant genetic resources for food and agriculture are also governed under the International Treaty on Plant Genetic Resources for Food and Agriculture[3] because of their importance for food security. Such frameworks governing access to genetic resources and the sharing of benefits arising from their utilization connect the benefits arising from their use with incentives for conservation policies.

Thus, conservation policies are not necessarily pitted against deriving maximum social value from these products by developing and commercializing them, but rather are intended to be mutually supportive and reinforcing. Laws and regulations that encourage commercialization in this space can coexist with regulations that aim to conserve public goods. Responsible patenting and licensing of inventions that arise from these materials can and likely will contribute to the economic growth, as well as the conservation, of countries rich in biodiversity. Countries can ensure that their laws protect inventions that give rise to novel products and technologies that can address health, food security and environmental challenges faced by their populations. Countries can also fund relevant research in academic institutions and public research institutions in the life sciences. They can ensure that these institutions are equipped with TTOs capable of assessing the commercial value of this research. Finally, countries can create a legal framework that enables the transfer of inventions, related know-how and new varieties of plants that arise from the use of these genetic resources to entities that are equipped to further develop them into products that can benefit the public. Sensible policies in these areas lay the groundwork needed for private investment without which these technologies would not be developed.

1 e.g., the Nagoya Protocol.
2 https://www.wipo.int/treaties/en/ip/gratk/
3 https://www.fao.org/plant-treaty/en/

Many countries have recognized the economic benefits of their genetic resources and the role that academia-to-industry technology transfer plays in securing these benefits. Considering this, they have implemented systems conducive to effective technology transfer between academic institutions and the biotechnology industry. However, inconsistencies in policies regarding genetic resources and incomplete legal infrastructure for technology transfer have sometimes stymied their ability to derive the benefits associated with technology transfer. Understanding biotechnology technology transfer agreements is a first step in addressing these inconsistencies. Therefore, WIPO makes available a specialized online database of genetic resource-related contracts with IP clauses and specialized licensing tools for innovations related to genetic resources and data through its Traditional Knowledge Division.

11 Humanitarian goals versus for-profit activities

In biotechnology, addressing global health needs requires both charitable and commercial approaches. This chapter looks at how developing treatments for endemic diseases in underserved populations may be best addressed through foundation-funded initiatives, while other biotechnology products require for-profit investment and expertise. Creative solutions can combine both models through strategic licensing approaches.

Addressing global health needs requires different approaches and stakeholders in the biotechnology sector to make meaningful contributions in more than one way. Consider endemic diseases like malaria or Chagas' disease. If the goal is to provide an underserved population with a low-cost therapy that does not require temperature-controlled distribution and can be administered by medical personnel with minimal skills, the most effective strategy to assist might be driven by a charity or foundation with funding sourced from donors, NGOs, intergovernmental organizations (WHO, for example) or governments rather than from companies or investors. Conversely, some biotechnology products are unlikely to be developed without the involvement of the for-profit sector and stakeholders in small, medium or large companies as well as sophisticated investors. Neither model is wrong, as both have a place in improving global health care.

Sometimes, but not always, the models can cooperate or overlap, so it is critical for all parties in the biotechnology innovation ecosystem to acknowledge which route – charity or for-profit entity – they are choosing. Expecting a foundation or NGO to invest millions in clinical trials or produce a highly complex vaccine may be unrealistic. Conversely, assuming that a biotechnology company will be willing to operate with low or no profit margin is equally mistaken. Finding a creative way to cooperate and utilize both approaches is difficult but possible. As an example, the Gates Foundation allows grantees that make a therapeutic discovery that can serve different populations depending on the indication, to set up two licensed fields, one which will address underserved populations in, for example, Africa, and another to incentivize investment and corporate efforts in development, clinical trials, manufacturing and distribution.

The COVID-19 pandemic raised questions about academic licensing of patents and technology that can address diagnosis or treatment of COVID-19. These can be dealt with by first determining whether the license will be used for charitable purposes or for revenue generation, and then by utilizing the following common licensing tools:

- field of use limitations
- geographic limitations
- time limitations.

The licensor may consider granting a royalty-free or low-cost license for the duration of the pandemic, for use only for vaccines targeting COVID-19 antigens but not antigens associated with other infectious diseases, and for sale or distribution in underdeveloped and developing countries. This approach addresses immediate humanitarian needs but leaves open other uses and initiatives which will depend on traditional, profit-based investment and effort.

Conclusion

Technology transfer

Technology transfer is an evolving practice even in countries with established systems, and particularly in the field of biotechnology. The biotechnology technology transfer ecosystem from university laboratories to public use is unique in that it requires constant interaction between academia, funding organizations and industry as well as NGOs, governments and communities for whom the technology is meant, supported by diligent protection of IP and proper policies that support technology transfer. It is the consistent funding support provided by the public and private sector and funding organizations for biotechnology research that gives rise to foundational technologies which are leveraged to develop the innovative biotechnology products consumed today. However, while funding is essential, it is not sufficient. For biotechnology technology transfer to meet its ultimate goal of broadly disseminating the fruits of research through commercialization, proper government policies must be in place, in particular, policies that spur risk taking and require proper stewardship of IP resources. In addition, cost-benefit analysis demonstrating all benefits – not just improved health but benefits in various sectors – of intervention versus costs might help persuade governments to prioritize certain products and secure funding. Just as with licensing agreements in other technologies, biotechnology technology transfer requires consideration of overall institutional and governmental policies, the expectations of various stakeholders and the demands of the day.

Complexity and risk

The risky nature of any biotechnology enterprise, often involving decades of R&D and billions of dollars of investment, needs certain basic elements to flourish – strong and predictable protection of the intellectual assets that serve as the basis for this industry, a streamlined, science-based regulatory apparatus and an integrated system of funding from various sources with a technology transfer system that appreciates the complexities of the technology.

An additional layer of complexity is that biotechnology patent assets are rarely transferred in isolation. Licensees often contract with the lead researcher on the licensed technology to retain their experience and knowledge of the technology. As a result, biotechnology licenses may cover a variety of elements needed to practice the invention and further develop the discovery, including know-how and biological materials. Experience has shown that the path to commercialization with private entities often requires exclusive licenses, but the COVID-19 pandemic has made clear that this “business as usual” model cannot always provide the tools needed to combat a disease. Meeting the challenges of the pandemic required all stakeholders to be creative. For TTOs this may mean flexibility in licensing by providing royalty-free, nonexclusive licenses for a limited time. For governments it may mean providing additional resources, implementing supportive policies and easing barriers in cross-border collaborations. Cost-benefit analysis could help demonstrate to governments that their funding is not simply an expenditure, but also an investment not only in health but in other sectors as well. And for companies it may mean seeking out nontraditional partners and participating in patent pools or licensing partnerships to ensure affordability and availability in resource-limited settings.

Capital intensiveness

It should be also kept in mind that both R&D and commercialization efforts in biotechnology are very capital intense and have a longer gestation period than other domains. The variety of template agreements, suggested clauses and pooling mechanisms included in the WIPO Contract Database [1] provide the preliminary tools to address these challenges. The templates have resulted in the commercialization of many biotechnology products and are presented for technology transfer professionals to consider. It is important, however, to note that these template agreements are merely examples, and it is common for TTOs and institutions to modify them to meet their needs.

1 https://www.wipo.int/tk/en/databases/contracts/list.html

A primer on *Technology Transfer in the Field of Biotechnology* aims to help biotechnology innovation stakeholders understand the environment needed for sustainability, legal certainty, and effective technology transfer in this sector. It also considers challenging issues such as the role of intellectual property in the creation, protection, commercialization, and transfer of research outcomes from laboratories to public and private users.

Whether working in university to transfer research outcomes from laboratories to end-users or in other settings such as business, manufacturing, government agencies, independent research institutes, non-governmental or intergovernmental organizations, or public–private partnerships, this essential *Primer* illustrates the intricate pathways through which biotechnology innovations travel.

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