AN INTRODUCTION TO LEGAL, REGULATORY AND INTELLECTUAL PROPERTY RIGHTS ISSUES IN BIOTECHNOLOGY

Alessandro Stasi
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An Introduction to Legal, Regulatory and Intellectual Property Rights Issues in Biotechnology

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CONTENTS

PREFACE i

CONSENT FOR PUBLICATION i

CONFLICT OF INTEREST i

ACKOWNOLEDGEMENTS ii

CHAPTER 1 THE HISTORY OF BIOTECHNOLOGY AND THE LAW 1

INTRODUCTION 1

THE RISE OF MODERN MEDICINE 3

THE GREAT AMERICAN FRAUD 6

THE POISON SQUAD AND THE LEGISLATIVE HISTORY OF THE PURE FOOD AND DRUGS ACT 8

THE DISASTER THAT SHAPED THE FDA 17

CONCLUDING REMARKS 19

REFERENCES 22

CHAPTER 2 THE REGULATORY FRAMEWORK 24

INTRODUCTION 24

AN OVERVIEW OF THE FEDERAL REGULATIONS 26

FOOD AND DRUG ADMINISTRATION 28

DEPARTMENT OF AGRICULTURE 30

ENVIRONMENTAL PROTECTION AGENCY 33

CONCLUDING REMARKS 38

REFERENCES 39

CHAPTER 3 THE REGULATION OF HUMAN GENOME EDITING 40

INTRODUCTION 40

COMPETING FOR THE HUMAN GROWTH HORMONE 41

THE HUMAN GENOME PROJECT 44

THE LEGAL ISSUES OF GENE PATENTING 45

GENE PATENTS IN THE WAKE OF ASSOCIATION FOR MOLECULAR PATHOLOGY V. MYRIAD GENETICS 48

CONCLUDING REMARKS 57

REFERENCES 58

CHAPTER 4 LAW AND EMERGING GENOME EDITING TECHNOLOGIES 60

INTRODUCTION 60

FROM RECOMBINANT DNA TO NEW GENOME EDITING TECHNOLOGIES 61

THE FIRST CRISPR PATENT 65

Interestingly, the patent also states: 66

The patent describes the invention as follows: 70

Nucleic Acids 70

DNA-Targeting RNA 70

DNA-Targeting Segment of a DNA-Targeting RNA 70

Protein-Binding Segment of a DNA-Targeting RNA 71

Regarding the Utility Criteria, the Patent States: 75

PATENT BATTLE, SCIENTIFIC PROGRESS AND THE OBVIOUSNESS TEST 76

COURT RULING ON CRISPR GENE EDITING TECHNOLOGIES 78

Reasonable Expectation of Success 80

Specific Instructions 83

Treatment of Simultaneous Invention Evidence 83

CONCLUDING REMARKS 85

REFERENCES 85

CHAPTER 5 BIOTECHNOLOGY, PROPERTY AND THE HUMAN BODY 87
INTRODUCTION 87
DEAD BODY 88
LIVING BODIES AND SEPARATED BIOLOGICAL MATERIALS 89
Unique T-Lymphocyte Line and Products Derived Therefrom 90
Abstract 90
Unique T-Lymphocyte Line and Products Derived Therefrom 90
Field of the Invention 90
Brief Description of the Prior Art 91
SUMMARY OF THE INVENTION 92
Case History 92
EXPERIMENTAL PROCEDURES 93
PATENTING HUMAN GENETIC MATERIAL: THE UNUSUAL CASE OF JOHN MOORE 93
Introduction 93
Facts 94
Discussion 96
Breach of Fiduciary Duty and Lack of Informed Consent 96
Moore's Claim Under Existing Law 101
Should Conversion Liability Be Extended? 104
Disposition 108
PATIENTS TISSUE AND THE IMMORTAL HERITAGE OF HENRIETTA LACKS 108
CONCLUDING REMARKS 110
REFERENCES 110

CHAPTER 6 THE REGULATION OF GENETICALLY ENGINEERED PLANTS AND ANIMALS 111
INTRODUCTION 111
POLICY ISSUES IN GENETICALLY ENGINEERED ANIMALS 112
FDA STATUTORY AND REGULATORY AUTHORITY 113
ANIMALS WITH INTENTIONALLY ALTERED GENOMIC DNA 115
GENETICALLY MODIFIED FOOD 131
FOOD POLICY LAWSUITS 133
BACKGROUND 134
DISCUSSION 135
Subject Matter Jurisdiction 135
Notice and Comment 136
NEPA 137
GRAS Presumption 139
Labeling 141
CONCLUDING REMARKS 143
REFERENCES 143

SUBJECT INDEX 144

PREFACE

Technology is a useful servant but a dangerous master.

Christian Lous Lange, Historian

Biotechnology, a branch of science and a fast-growing source of developing technologies, has shown immense potential for its utility across all the dimensions of our lives. Its applications range from drugs and therapeutics, industrial, household applications, biofuels, and information technology to almost all resource-based sectors, such as manufacturing, aquaculture, agriculture, and forestry. Biotechnology offers outstanding potential to meet the growing demand for food and energy production in a sustainable way. Recognizing its economic and strategic value, countries have implemented a number of measures to generate a homegrown biotechnology sector and help science-based companies develop.

The chapters cover a multitude of themes and some of the most important legal issues arising in relation to biotechnology, including the historical development of a legal framework sufficient to protect public safety (Chapter 1), the current biotechnology regulatory system and the rules directing the primary agencies that regulate the products of biotechnology, namely the U.S. Food and Drug Administration, the U.S. Department of Agriculture, and the U.S. Environmental Protection Agency (Chapter 2), the regulation of human genome editing and its the impact on health research (Chapter 3), law and emerging genome editing technologies from recombinant DNA to CRISPR/Cas9 (Chapter 4), the development of legal principles to protect property rights in the human body and allow the efficient use of human tissue, organs, DNA, and cell-lines in medical research (Chapter 5), and legal issues arising from the use of genetic engineered plants and animals (Chapter 6).

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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CHAPTER 1

The History of Biotechnology and the Law

Abstract: The chapter explores the historical development of a legal framework for biotechnology regulation. It aims to provide an overview of the history of biotechnological practices and the development of modern concepts. It describes how people had used biotechnology processes for millennia, noting that the rise of modern medicine can only be traced back to the 19th century, when the progress of science and the advances in laboratory techniques contributed to the creation of a medical market. The chapter ends by analyzing the origins of the U.S. Food and Drugs Administration and the Food and Drugs Act of 1906.

Keywords: Biotechnology, Food and drugs administration, Food and drugs act, Meat inspection act, Patent medicines, Thalidomide scandal.

INTRODUCTION

The beginning of biotechnology dates back to the Paleolithic era, when mankind became able to manipulate the genetic makeup of organisms in agriculture and food production through selective breeding and domestication of animals, the cultivation of crops and fermentation techniques to produce products, such as beer, wine, bread, cheese and yogurt [1]. "The most primitive type of biotechnology is the cultivation of plants and the training (in particular the domestication) of animals. The domestication of animals stretches back over 10, 000 years, when our ancestors also started maintaining plants as a reliable source of food. The earliest examples of such domesticated plants are rice, barley and wheat. Wild animals were also controlled to produce milk or meat. The ancient production of cheese, yogurt and bread from micro-organisms is also reported. Various alcoholic drinks, such as beer and wine, were developed during this period, when the process of fermentation was first discovered. Later, it was discovered that micro-organisms, *e.g.*, bacteria, yeast or molds, hydrolyze sugars when they lack oxygen and are ultimately responsible for fermentation. This process results in the formation of products (food and drink). Consequently, fermentation was perhaps first explored by chance, since, in earlier times, nobody knew how it worked. During the prehistoric era, some civilizations considered fermentation to be a gift from their gods [2]."

Alessandro Stasi and Tan Weng Chiang David

Starting from BC 300 to 400, Greek philosophers became curious about human inheritance and the nature of reproduction. Plato, for instance, argued that inborn characteristics are inherited from both parents. His pupil, Aristotle, authored a number of well-known books where he stated that "children are born resembling their parents in respect not only of congenital characteristics but also of acquired ones. Moreover, this resemblance is true not only of inherited but also of acquired characters. For it has happened that the children of parents who bore scars are also scarred in the same way in the same place. In Chalcedon, for example, a man who had been branded on the arm had a child who showed the same brand letter, though it was not so distinctly marked and had become blurred [3]."

Hindu philosophers also contemplated the mechanism of human inheritance and hereditary characters. They noted that particular diseases might run in families, and children inherit their parents' characteristics. Rooted in these beliefs, the law of Manu says that "a man of base descents can never escape his origins".

The Middle Ages, a period that ranges from approximately 500 to 1500, "can be considered the dark age of biotechnology and law. Spontaneous generation remained the dominant explanation of the origin of living organisms, such as maggots originating from horsehair. A vinegar manufacturing operation in Orleans in the 1500s was the next development, marking an end to the dark ages of biotechnology development in Europe.

Around AD 1630, William Harvey concluded that sexual reproduction existed in the lower organisms and that males contribute sperm and females contribute an egg in the process. Harvey's discovery that sexual reproduction existed in lower organisms was a major breakthrough in the field of biology. His discovery helped to pave the way for future discoveries about the reproductive process and the role of males and females in reproduction. In AD 1665, Robert Hooke observed the cellular structure of cork, and in the same period, the idea of spontaneous generation was disproven by the work of Francesco Redi, who, with a simple experiment, showed that maggots arose from uncovered meat, while covered meat did not reproduce maggots. Then in AD 1680, Leeuwenhoek observed the fermentation process of yeast through his first microscope.

Prior to the use of cowpox, the Moravians, a religious sect in North Carolina in the early 1700s, recorded in their detailed diaries the use of a small infection of smallpox to guard against a more serious case. This often resulted in death from an expectedly serious case. It was not until 1797, that Edward Jenner used a different living organism (cowpox) to protect people from diseases through inoculation. Louis Pasteur, in 1864, proved the existence of microorganisms and that they reproduced. Thereafter in 1865, Gregor Mendel demonstrated the

inheritance of traits from one generation to another in the pea plant, establishing the beginning of the field of genetics. Then in 1869, Johann Meische isolated DNA from the nuclei of white blood cells. It is noteworthy that the work of these scientists was beyond any regulatory mechanisms of the time.

The strong mercantile, commerce and regulatory interests in butter and cheese lead to the development of the New York Stock Exchange. The Exchange began when the Butter and Cheese Exchange of New York was created. On June 1, 1875, this Exchange became the American Exchange of New York, and then on April 26, 1880, it became the Butter, Cheese and Egg Exchange of the City of New York. Finally, on June 5, 1882, the Exchange changed its name to the New York Mercantile Exchange [4]."

The next major breakthrough in the field of biology came in 1859 with the publication of On the Origin of Species by Charles Darwin. In it, Darwin proposed the theory of evolution by natural selection, which is the idea that species can change over time through the process of natural selection. Darwin's work was based on his observations of the natural world, and he was able to provide convincing evidence that his theory was correct. Darwin's work helped to explain how species could change over time, and it had a profound impact on the field of biology. In the years that followed, Darwin's work was expanded upon by other biologists, and the theory of evolution became one of the most important ideas in the field of biology.

THE RISE OF MODERN MEDICINE

The 19th century was the culmination of the scientific discoveries of the Enlightenment period, and the English term "biology" was coined [4]. The rise of modern medicine can also be traced back to this period when the progress of science and the advances in laboratory techniques contributed to the creation of a medical market. From a regulatory perspective, the production of medicines did not follow any legal or commercial standard and the sale of so-called "patent medicines" became a major industry.

Patent medicines originally referred to medicines or *nostrum* ("our remedy" in Latin) that traditionally contained secret ingredients. These concoctions were generally advertised to consumers as over-the-counter products without regard to their actual effectiveness [5]. They often contained high doses of alcohol and narcotics such as cocaine, heroin or morphine and, some of them, were specifically advertised for infants.

Originating in England during the late 17th century as proprietary medicines manufactured under "patents of royal favor", these medicines became very

CHAPTER 2

The Regulatory Framework

Abstract: This chapter draws upon the role and responsibilities of federal agencies in regulating biotechnology products. It distinguishes the role of the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA) through statutory definitions. Special emphasis is placed on defining the role of the Animal and Plant Health Inspection Service (APHIS), the Agricultural Research Service (ARS), the Agricultural Marketing Service (AMS), the Food Safety Inspection Service (FSIS), and the Foreign Agricultural Service (FAS).

Keywords: Coordinated framework, Department of agriculture, Environmental protection agency, Food and drug administration.

INTRODUCTION

The regulation of biotechnology is a complex and ever-evolving area. There are a number of different regulatory regimes that govern different aspects of biotechnology, including the development of new products, the use of existing products, and the export of products. The term "biotechnology" was first coined in the 1920s by Karl Ereky, a Hungarian engineer and economist. However, the term did not gain widespread usage until the 1970s, when it was used to describe the new field of genetic engineering. Today, the term biotechnology is used to describe a wide range of technological applications that use living organisms or their products to perform specific tasks. These applications can be found in a variety of industries, including agriculture, food processing, pharmaceuticals, and environmental remediation.

According to the Organisation for Economic Co-operation and Development, biotechnology is "the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services."

From an international perspective, the most important international regulatory regime for biotechnology is the United Nations Convention on Biological Diversity (CBD), which was adopted in 1992 and came into force in 1993. The

CBD sets out a number of principles for the conservation and sustainable use of biodiversity, including the need to take into account the interests of indigenous peoples and local communities. Article 2 of the Convention, biotechnology is defined as: "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use."

The CBD has been ratified by 196 countries, making it one of the most widely-ratified international treaties. The CBD has three main goals, namely to conserve biodiversity, promote sustainable use of biodiversity and assure a fair and equitable sharing of benefits arising from the use of genetic resources. In order to achieve these goals, the CBD includes a number of provisions on topics such as access to genetic resources, technology transfer, capacity building, and benefit-sharing. The CBD also established the Ad Hoc Open-ended Working Group on Access and Benefit-sharing (WG ABS), which is responsible for negotiating a legally binding instrument on ABS.

After several years of difficult negotiations, the Parties to the CBD adopted, in 2000, the Cartagena Protocol on Biosafety. The Protocol is the first international legally binding agreement that aims to protect biological diversity from the potential risks posed by living modified organisms (LMOs) resulting from modern biotechnology. It represents an important tool for protecting biodiversity from the potential risks posed by modern biotechnology and establishes a clear regulatory framework that must be followed by all countries that are Parties to the Convention on Biological Diversity. This ensures that any risks associated with LMOs are properly assessed and managed, and that any releases of LMOs into the environment are carried out in a safe and responsible manner. Article 3 of the Protocol defines modern biotechnology as "the application of: (a) *In vitro* nucleic and techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or (b) Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection."

The Protocol seeks to protect biological diversity from the potential risks posed by LMOs resulting from modern biotechnology. It does this by establishing a regulatory framework for the safe transfer, handling and use of LMOs, including requirements for labeling and identification of LMOs, risk assessment and management, and monitoring and reporting. The Protocol applies to all LMOs defined as "living organisms that have been modified in a way that does not occur naturally by mating and/or natural recombination" but does not apply to LMOs used for food (*e.g.*, food ingredients, enzymes used in processing).

It also contains a number of provisions that are particularly relevant to agricultural LMOs, which are often developed for use in agriculture and food production. These include provisions on risk assessment and management, as well as specific requirements relating to the labeling of ALMOs intended for release into the environment.

It is interesting to point out that the Cartagena Protocol on Biosafety establishes a special procedure named "advance informed agreement", whereby exporting countries must provide importing countries with prior and informed consent before exporting LMOs for intentional introduction into the environment. In this regard, Article 10(6) specifies that the "lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the party of import, also taking into account risks to human health, shall not prevent a party from taking a decision, as appropriate, with regard to the import of the living modified organism in question."

AN OVERVIEW OF THE FEDERAL REGULATIONS

The regulatory framework for biotechnology is a set of regulations that govern the use of biotechnology in the United States. These regulations are designed to protect public health and safety, and to ensure that biotechnology is used responsibly. The framework is composed of ten main regulatory agencies which play a critical role in the development of biotechnology: Department of Health and Human Services (DHHS), Department of Agriculture (USDA), Environmental Protection Agency (EPA), Department of Commerce (DOC), Department of Defense (DOD), the National Science Foundation (NSF), Department of the Interior (DOI), National Institutes of Health (NIH), National Aeronautics and Space Administration (NASA) and Department of Energy (DOE). Each agency has its own set of regulations that apply to different aspects of biotechnology. The regulatory framework for biotechnology also includes several laws that govern the use of biotechnology, such as the Federal Food, Drug, and Cosmetic Act, the Federal Insecticide, Fungicide, and Rodenticide Act, and the Plant Pest Act.

The following passage from the "National Academies of Sciences, Engineering, and Medicine. Preparing for future products of biotechnology. National Academies Press, 2017" presents an overview of the biotechnology regulatory framework starting from the NIH guidelines of 1976.

"Federal involvement in the oversight of biotechnology is generally viewed as originating in the 1970s. Responding to concerns raised by scientists engaged in recombinant DNA research, the National Institutes of Health (NIH) published a

CHAPTER 3

The Regulation of Human Genome Editing

Abstract: With the progress of DNA sequencing technology and its falling costs, the number of gene patents is dramatically growing. This chapter aims to shed light on the regulation of human genome editing and its impact on health research. By analyzing legal provisions and cases, this paper assesses whether genetically modified forms of life meet the statutory requirements of utility, novelty, and non-obviousness under patent law. The nature of the patentable subject matter of living organisms and genes in the U.S. is also examined in detail.

Keywords: Human genome project, Human growth hormone, Human genes, Myriad controversy, Recombinant DNA.

INTRODUCTION

The first living organism to be patented in the United States was a bacteria, specifically a strain of *Pseudomonas fluorescens*, in 1980. The patent was issued to Ananda Chakrabarty, a microbiologist who was working for General Electric at the time. Chakrabarty's invention is related to a method for treating oil spills using bacteria that had been genetically engineered to break down petroleum products. In particular, Chakrabarty's bacteria could degrade crude oil more rapidly than naturally-occurring bacteria. The U.S. Patent and Trademark Office initially rejected Chakrabarty's patent application, on the grounds that living organisms were not eligible for patent protection. However, the United States Supreme Court ultimately upheld the patentability of Chakrabarty's bacteria in a landmark decision, *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). The Court held that living organisms could be patented under U.S. law as long as they met the standard requirements for patentability, such as novelty, utility and non-obviousness.

Since the United States Supreme Court ruling in *Diamond v. Chakrabarty* that genetically modified forms of life are susceptible to patent protection, many institutions have attempted to claim ownership of gene sequences due to their commercial value and the number of patent applications containing individual nucleotide sequence claims significantly increased [1]. In 1978, only six months after the Chakrabarty case, researchers at the University of California, San Franci-

sco (UCSF) filed a patent application for the gene encoding human growth hormone. The patent was issued in 1982 and was directed to "recombinant DNA transfer vectors containing codons for human somatomammotropin and for human growth hormone". This was the first gene patent for the construction of a plasmid, and it involved an engineered hormone related to breast development in pregnant women. The invention, which listed Howard M. Goodman, John Shine, and Peter H. Seeburg as inventors, specifies, "A novel purification procedure of cDNA of the desired nucleotide sequence complementary to an individual mRNA species is disclosed. The method employs restriction endonuclease cleavage of cDNA transcribed from a complex mixture of mRNA. The method does not require any extensive purification of RNA but instead makes use of transcription of RNA into cDNA, with one or two restriction endonucleases, and the fractionation of the cDNA restriction fragments on the basis of their length. Novel plasmids have been produced, containing the nucleotide sequences coding for rat growth hormone and the major portions of human chorionic somatomammotropin and human growth hormone, respectively. Novel microorganisms have been produced, having as part of their genetic makeup the genes coding for RGH, the major portion of HCS and the major portion of HGH, respectively. The disclosed techniques may be used for the isolation and purification of growth hormones from other animal species and for the construction of novel transfer vectors and microorganisms containing these genes" [2]. The claims were directed to "recombinant DNA transfer vector comprising codons for human chorionic somatomammotropin" as well as "A recombinant plasmid vector comprising the nucleotide sequence coding for the growth hormone of an animal species and capable of transforming a microorganism, synthesized by a process" [2].

COMPETING FOR THE HUMAN GROWTH HORMONE

A few years after obtaining the patent, the University of California licensed its patent to Lilly and filed a patent infringement action against Genentech seeking $1.2 billion in back royalties asserting that the San Francisco Bay area company used its patented DNA to produce the blockbuster drug Protropin to treat growth hormone deficiency in children (the first biotech drugs brought to market) without prior authorization of the patent holder [3]. More precisely, the University of California claimed that professor Peter Seeburg, a few weeks after quitting his UCSF job in November 1978 to take a position at Genentech, stole several DNA samples used in the university lab. A 1999 Washington Post article observed:

"The men with foreign accents trod carefully through desolate hallways. They weren't supposed to be there, but the University of California at San Francisco had something they wanted, and they knew just where to find it. It was an hour before midnight on New Year's Eve, and nobody was around to see the deed unfold. The

men took the elevator to a ninth-floor laboratory. They retrieved vials and beakers, hauled the material downstairs, put it in their car and raced south toward the offices of a tiny new company not far from the azure waters of San Francisco Bay. A police officer pulled them over as they got to the doors of that company, Genentech Inc. They waved their employee badges and got past him. By the time the clock struck midnight on that evening two decades ago, Genentech's laboratory was freshly stocked with genetic material from the university. A few months later, Genentech announced that it had pulled off one of the most dazzling feats of modern science -- inserting human genes into harmless germs and getting them to produce a precious and much-needed substance, human growth hormone. Genentech was the first biotechnology company and an industry founder, demonstrating the potential of the new science. Yet if testimony unfolding in federal court here is true, that early milestone was tainted from the outset, and the biotechnology industry was born amid thievery and scientific fraud [4].”

This episode set off what is known as the first gene patent battle between the University of California, Lilly, and Genentech. The Federal Circuit Court addressed these issues in *Genentech v. Eli Lilly & Company and the Regents of the University of California.*

U.S. Court of Appeals for the Federal Circuit

Genentech, Inc., Plaintiff-appellant, v. Eli Lilly and Company, Defendant, and the Regents of the University of California, Defendant-appellee,

998 F.2d 931 (Fed. Cir. 1993)

“Genentech, Inc. appeals the judgment of the United States District Court for the Southern District of Indiana1 dismissing, as to the Regents of the University of California (“the University”), the declaratory judgment action brought by Genentech against the University and Eli Lilly and Company (“Lilly”). We affirm in part, vacate in part and remand for further proceedings.

This is one of several lawsuits filed in the federal courts of Indiana and California involving these parties, 2 relating to recombinant DNA technology used for the production of human growth hormone (“hGH”), a product having medicinal and therapeutic properties. The patent here involved is United States Patent No. 4,363,877 entitled “Recombinant DNA Transfer Vectors”, granted on December 14, 1982, inventors Howard M. Goodman, John Shine, and Peter H. Seeburg (“the '877 patent”). The patent is owned by the University.

The legal issues raised in this declaratory action relate to the infringement, validity, and enforceability of the '877 patent, and include charges by Genentech

CHAPTER 4

Law and Emerging Genome Editing Technologies

Abstract: *It is strange that only extraordinary men make the discoveries, which later appear so easy and simple.*

This chapter outlines the historical development of genetic manipulation, assesses the aspects that define genome editing technologies as breakthrough technologies and examines the recent trends in patent litigation. It investigates the ownership and licensing issues surrounding the revolutionary and highly lucrative CRISPR patents by focusing on the recent development in patent battles.

Keywords: CRISPR, DNA manipulation, Genome editing technologies, Obviousness test, Patent system, TALEN, ZFN.

INTRODUCTION

Within the last few years, new technologies have appeared that are intended to modify the genomes of living organisms from plants to animals. Some of these utilize restriction enzymes to introduce a DNA double stranded break at a targeted location such as zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs), and the clustered regulatory interspersed short palindromic repeats (CRISPR) associated systems [1]. These nucleases allow genetic material to be added, removed, or altered at particular locations in the genome, rather than introducing random changes as in the rDNA technology.

On the use of restriction enzymes and DNA manipulation, Di Felice *et al.* note:

"The many heuristic and applicative approaches employing restriction enzymes have proved fundamental for physical DNA mapping. Similarly, recombinant DNA technology, which has equally strong ties with these extraordinary molecular tools, had a revolutionary impact on molecular biology as well as on biomedicine and biotechnology. Shortly before the identification of the first restriction enzymes, Lederberg (1952) proposed to use the term 'plasmid' for any extrachromosomal element determining heredity or sex. A few years later the physical and chemical properties of plasmid DNA and its circular nature were extensively characterized and plasmids were also visualized by electron microscopy. In 1972 Cohen and coworkers inserted an exogenous closed-circular

DNA harboring sequences encoding the resistance against a given antibiotic into a bacterial strain. They selected the plasmid- containing population by screening for the ability to grow in the presence of the same antibiotic…

At the beginning of the 1970s, a tool for the specific fragmentation of DNA was still missing. Stanley Cohen, one of the major personalities in the field, had been experimenting with mechanical DNA fragmentation but the right kind of highly specific 'molecular scissors' became available only through the studies of Arber, Smith and. Work from Herbert Boyer's lab represented a landmark by providing an historical restriction enzyme, EcoRI…By joining DNA fragments from different organisms, the generation of the so-called chimeric DNAs became possible. The insertion of some X. laevis rDNA fragments into the pSC101 plasmid was one of the first examples. These experiments proved that it was possible to use bacterial plasmids to clone DNA from various sources; that the junction of DNAs from different organisms could take place after cutting them with restriction enzymes generating the same type of ends; and, last but not least, that this procedure did not affect the functionality of the plasmid itself which continued replicating and transcribing the harbored genes…

Restriction enzyme-mediated manipulation of DNA has opened the possibility to introduce targeted deletions of gene or promoter sub-regions, in order to compare the behavior of deleted templates with wild-type copies in terms of sub- strates for RNA transcription/processing and translation. The ability to cut and join gene pieces almost at will has provided tremendous momentum to basic knowledge on the nature, function and regulation of genes, and has led to remarkable biotechnological achievements. It became possible to deeply engineer genes *in vitro*, even human ones, transcribe them and give rise, by subsequent translation, to proteins of medical interest such as globins or insulin…These findings have greatly stimulated the research on site-specific manipulation of the genome, with emphasis on the development of endonuclease-based tools able to target and cleave virtually any sequence. This has led to two powerful systems: ZFN (zinc-finger nuclease) and TALEN (transcription activator-like effector nuclease) [2]."

FROM RECOMBINANT DNA TO NEW GENOME EDITING TECHNOLOGIES

ZFNs are a class of engineered DNA-binding proteins generated by fusing a zinc finger DNA-binding domain to a DNA-cleavage domain and designed to cut at specific DNA sequences. They are comprised of zinc-finger DNA-binding domain that can recognize specific DNA sequences. These domains can be modified in order to bind and cleave specific DNA sequences producing the scissors required for modifying a complex genome [3]. Similarly, the TALEN system exploits a

fusion protein and consists of a DNA binding domain fused to a nonspecific FokI cleavage domain. Since TALEN effectors can be engineered to bind any desired DNA sequence, they are widely used for gene editing in live cells [4].

Until 2012, ZFN and TALEN systems were considered to be the most promising systems for genome editing. Both systems, however, have been shown to be time-consuming and less effective compared to the clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system.

The CRISPR system was first described as a as a general-purpose genome-editing tool in a Science paper published in 2008 by Erik Sontheimer and his postdoc Luciano Marraffini at Northwestern University in Evanston, Illinois. They showed how CRISPR protected bacteria by destroying invaders' DNA:

"Altogether, these data provide strong functional evidence that CRISPR interference acts at the DNA level, and therefore differs fundamentally from the RNAi phenomenon observed in eukaryotes and to which CRISPR activity was originally compared (29). A DNA targeting mechanism for CRISPR interference implies a means to prevent its action at the encoding CRISPR locus itself, as well as other potential chromosomal loci such as prophage sequences. Little information exists to suggest how crRNAs would avoid targeting "self" DNA, though the role of flanking sequences during CRISPR interference (24) could contribute to target specificity. From a practical standpoint, the ability to direct the specific, addressable destruction of DNA that contains any given 24–48 nucleotide target sequence could have considerable functional utility, especially if the system can function outside of its native bacterial or archaeal context. Furthermore, our results demonstrate that CRISPR function is not limited to phage defense, but instead encompasses a more general role in the prevention of horizontal gene transfer and the maintenance of genetic identity, as with restriction-modification systems [5]."

The scientists also filed a patent regarding the application of CRISPR loci interference to counteract horizontal gene transfer, but such application was rejected by the USPTO as it lacked any practical application and sufficient experimental demonstration [6, 7].

The discovery of the CRISPR as an effective genome editing technology was made in 2012 by the American biochemist Jennifer Doudna and the French microbiologist Emmanuelle Charpentier. They demonstrated that CRISPR/Cas9 endonuclease could be programmed to enable easy targeting and manipulation of living cells and organisms [6]. As professor Doudna writes:

CHAPTER 5

Biotechnology, Property and The Human Body

Abstract: The main objective of this chapter is to describe the development of legal principles which are used to protect property rights in the human body and allow the efficient use of human tissue, organs, DNA, and cell lines in medical research.

Keywords: Biological materials, Henrietta Lacks, Human-tissue-related inventions, John Moore, Ownership of human body, Patent claims on genetic material, Property in dead bodies.

INTRODUCTION

The questions regarding ownership and proprietary interests in dead bodies initially arose in the eighteenth century when American medical schools required cadavers for anatomy courses. During this period, dead bodies became economically profitable as their relevance in surgical training was established. The development of medical schools in the United States and Europe resulted in a demand for cadavers. This demand was met by grave robbers who stole bodies from graves and sold them to medical schools. In response to this problem, states began to pass laws that prohibited the sale of dead bodies. These laws were based on the belief that the human body is a sacred object which should not be bought or sold. As Prof. Hardcastle points out, "The legal status of cadavers, and rights to them, are not simply issues of historical significance; they have gained prominence, following a number of high profile inquiries into post-mortem practices. These inquiries highlighted the unsatisfactory development of the common law with respect to rights concerning human bodies and separated biological materials. In contrast to English law, U.S. courts have recognised property rights to protect dead bodies and biological materials removed from them. The creation of property rights in U.S. jurisprudence is not dependent on applying work or skill to transform the separated biological materials. Instead, the corpus of American authority has developed out of the unauthorised removal of organs and the potential protection afforded by the Due Process Clause contained in the Fourteenth Amendment of the U.S. Constitution [1]."

Alessandro Stasi and Tan Weng Chiang David

The legal principles which are used to protect property rights in the human body and allow the efficient use of human tissue, organs, DNA, and cell lines in medical research, have been developed over time.

DEAD BODY

The development of medical science led to new ways of using dead bodies and their parts. The use of dead bodies in medical research has been justified because it is necessary to develop new cures for diseases. With regard to dead bodies, Prof. Hardcastle notes:

"The Fourteenth Amendment protects an individual's right to property against deprivation by the state without due process. Any person alleging a deprivation by the state of any property right without due process possesses a civil cause of action under section 1983 of the Civil Rights Act. To assert a section 1983 claim, a party must establish: (1) that the alleged deprivation was committed by a person acting under colour of state law; and (2) that the deprivation infringed a right, privilege or immunity guaranteed by the U.S. Constitution. The question of whether an interest amounts to a 'property right' for the purposes of a section 1983 suit is a matter of state law.

The U.S. Court of Appeals for the Sixth Circuit has held that, under the Due Process Clause, family members do have property rights in separated biological materials. In *Brotherton v Cleveland*, the Sixth Circuit considered the constitutional validity of an Ohio statute that permitted a coroner to remove corneas from a deceased person, provided the coroner was not aware of any objections from close family members. During an autopsy procedure, the deceased's corneas had been removed against the wishes of his wife. The court reviewed the authorities dealing with analogous issues and noted that a majority of cases ruled that 'quasi- property' rights can exist in dead bodies. In this case, the court held that the 'aggregate of rights' given to a spouse under common law and the Uniform Anatomical Gift Act were sufficiently proprietary for constitutional purposes. These rights included the right to possess the body and to control its disposal.

In *Whaley v County of Tuscola*, the Sixth Circuit Court of Appeals considered the validity of a Michigan statute after the deceased's eyes had been removed without consent. The Sixth Circuit again held that the next-of-kin had a 'constitutionally protected property interest' in the dead body of a relative. In explaining the next-of-kin's interest, the court opined that the existence of a constitutionally protected property right does 'not rest on the label attached to a right granted by the state but rather on the substance of the right'. In this way, both *Brotherton* and *Whaley* emphasised that the rights of the family members should be viewed as a bundle of

rights in a proprietary sense. The Ninth Circuit Court of Appeals and several U.S. District Courts have adopted a similar approach to the Sixth Circuit.

The position adopted by the Sixth and Ninth Circuit Court of Appeals has not been widely embraced by other circuit or state courts. In *Georgia Lions Eye Bank Inc v Lavant*, the Georgia Supreme Court held that a statute permitting corneal removal was consistent with the U.S. Constitution because dead bodies are not constitutionally protected property. The court considered that the common law concept of 'quasi-property' did not have any constitutional dimension. Indeed, a substantial body of U.S. state court jurisprudence disagrees with the approach adopted by the Sixth Circuit. Such judicial reluctance to recognise property rights can be explained at least in part by the attitude of U.S. courts to the Takings Clause in the Fifth Amendment. This clause states that private property should not be taken for public use without compensation. Similar issues arise in an environmental context in relation to tradeable pollution rights under the emissions trading regime. U.S. courts have been reluctant to classify tradeable pollution rights as capable of constitutional protection. Again, this reluctance may be best explained as judicial concern over the consequences of applying the Fourteenth Amendment. The approach in *Brotherton* and *Whaley* does not, therefore, represent the more widely accepted position in current U.S. jurisprudence. In general, U.S. courts have not recognised that property rights are created following the separation of biological materials from a dead body [1]."

LIVING BODIES AND SEPARATED BIOLOGICAL MATERIALS

Issues of ownership are also critical when patents involve human tissues and other biological materials taken from patients without their consent [2 - 4]. The U.S. courts have been grappling with the question of whether individuals have property rights in their own biological materials and, more specifically, in (discarded) human cells and organs. One of the more famous cases over biologic patents involved John Moore, a 31-year-old Coca-Cola salesman with a rare and deadly blood cancer called hairy cell leukemia. In October 1976, he underwent surgery to remove his spleen as recommended by his physician, Dr. David Golde of the University of California at Los Angeles (UCLA) Medical Center. After the surgery, Dr. Golde realized that Moore's T-lymphocyte cells had unique properties [5]. Moore's spleen, in fact, contained an immortal cell line capable of producing two strains of white blood cells that fight bacteria. With the help of the licensing office at the University of California, Dr. Golde successfully applied for a patent (No. 4,438,032) on the cell line naming himself as an inventor.

CHAPTER 6

The Regulation of Genetically Engineered Plants and Animals

Abstract: The recent advances in genetic engineering have enabled the development of new approaches to animal husbandry and agricultural production. Researchers have developed genetically modified laboratory animals to enhance specific characteristics and increase the efficiency of food production. At the same time, new and distinct varieties of plants have been produced with biotechnology. This chapter aims to investigate the legal issues that arise from the use of genetic engineering techniques in plants and animals.

Keywords: FDA regulatory authority, Food policy lawsuits, Genetically engineered animals, Genetically modified food, Intentionally altered genomic DNA.

INTRODUCTION

The recent advances in genetic engineering (including the application of CRISPR/Cas9 gene editing systems and other targeted genome editors) have enabled the development of new approaches to animal husbandry. Researchers have developed genetically modified laboratory animals to enhance specific characteristics and increase the efficiency of food production. At the same time, genetically engineered animals have been used as an effective tool for the development of new medical drugs and human disease models for screening drugs of clinical interest [1]. Finally, the use of transgenic mammary glands of animals as bioreactors can produce drugs at an industrial scale with high value for pharmaceutical use [2, 3]. As of the date of this book, the FDA has approved the following products: a GE goat that produces a therapeutic protein in its milk (Atryn), a GE chicken that produces a human biologic in the egg whites of eggs (Kanuma), a GE rabbit into which the DNA coding sequence for human Factor VII has been introduced to produce a protein necessary for blood coagulation (Sevenfact), a salmon that has been genetically engineered to grow faster than farm-raised Atlantic salmon (AquAdvantage) and a pig that produces α-Gal allergy-safe meat (GalSafe).

Alessandro Stasi and Tan Weng Chiang David

Genetic engineering of plants has been used for decades, and it has been shown to increase the efficiency of agricultural production. Genetically engineered (GE) plants have been produced to help meet the demands of the world's growing population. The use of genetic engineering in agriculture has produced plants that are resistant to insects and pests, tolerant to herbicides, and resistant to plant diseases. GE plants with these characteristics have been developed to increase crop yields, reduce the need for pesticides, and increase the efficiency of food production. The FDA has approved the use of genetically engineered plants in food production, including the use of genetically engineered soybeans, corn, canola, and cottonseed oil. The FDA has also approved the use of genetically engineered bacteria to produce rennet, an enzyme used in the production of cheese. Genetically engineered enzymes are also used in the production of bread, beer, and wine.

POLICY ISSUES IN GENETICALLY ENGINEERED ANIMALS

It is important to point out that genetic modifications in animals are regulated as new animal drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act). More precisely, Section 321(g) of the FD&C Act, includes "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals"; and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." Furthermore, Section 321(v) of the Act adds "The term new animal drug means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed, (1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof or (2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

This does not mean that GE animals are considered a drug [4]. The FD&C Act regulates the genetic modifications introduced into the animals' organism as a new animal drug because the genetic modifications are considered to be "articles (other than food) intended to affect the structure or any function of the body of man or other animals" under Section 321(g) of the Act. In other words, the FDA will assess whether the genetic modifications introduced into the animal are effective and safe [5].

Apart from the provisions of the FD&C Act, genetic modifications in animals are regulated under the Guidance for Industry # 187 titled "Regulation of Intentionally Altered Genomic DNA in Animals". Although non-binding, guidance documents have rule-like effects on regulated entities as they represent the current thinking of the FDA on a particular topic. With regard to guidance documents, Section 371(h)(1)(A) of the FD&C Act states that "The Secretary shall develop guidance documents with public participation and ensure that information identifying the existence of such documents and the documents themselves are made available to the public both in written form and, as feasible, through electronic means.

Such documents shall not create or confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the Food and Drug Administration. It also states, "For guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, the Secretary shall ensure public participation prior to implementation of guidance documents, unless the Secretary determines that such prior public participation is not feasible or appropriate. In such cases, the Secretary shall provide for public comment upon implementation and take such comment into account."

FDA STATUTORY AND REGULATORY AUTHORITY

The Guidance for Industry # 187 titled Regulation of Intentionally Altered Genomic DNA in Animals, provides recommendations for the regulation of animals with intentionally altered genomic DNA. The guidance applies to animals with alterations made using techniques, such as gene editing, gene targeting and genome modification. Animals that are not intended for use as food, such as laboratory animals and pets, are not included in the guidance.

The Guidance specifically "addresses animals whose genomes have been intentionally altered using modern molecular technologies, which may include random or targeted DNA sequence changes, including nucleotide insertions, substitutions, or deletions, or other technologies that introduce specific changes to the genome of the animal. This guidance applies to the intentionally altered genomic DNA in the founder animal where the initial alteration event occurred and the entire subsequent lineage of animals that contains the genomic alteration.

Intentional genomic alterations may be heritable or non-heritable (*e.g.*, those alterations intended to be used as gene therapy). Although much of this guidance will be relevant to non-heritable intentionally altered genomic DNA, this guidance primarily addresses heritable intentionally altered genomic DNA. For non-

SUBJECT INDEX

A

Acid 10, 21, 25, 48, 49, 50, 51, 90, 132, 134
  acetic 10
  amino 21, 49, 50, 51, 90, 132
  complementary ribonucleic 49
  deoxyribonucleic 48
  recombinant deoxyribonucleic 25, 134
  salicylic 10
Acid phosphatase 92, 93
  tartrate-resistant 92
Action 116, 118, 122, 138
  authorizing private 138
  enforcement 116, 118, 122
Activator-RNA 66, 69, 72, 73, 74
  cognate 73
    RNA hybridizes 66
Activities 52, 60, 90, 92
  colony-stimulating 90
  infringing 52
  neutrophil migration-inhibition 92
  nuclease 66
  risk analysis 27
Agency 26, 27, 28, 30, 33, 34, 114, 123, 124, 130, 134, 136, 137, 138, 140, 141, 142
  foreign affairs 33
  regulatory 26
Agricultural 24, 33, 38, 63, 111, 112
    advances 63
    marketing service (AMS) 24, 33
    production 111, 112
    products, regulating 38
    research service (ARS) 24, 33
Alcoholic drinks 1
Allegations 96, 100
  defective 96
  essential 100
Alterations 50, 53, 113, 114, 115, 127
  chemical 53
  genomic 113, 114, 115
  heritable genomic 114
  intentional genomic 113, 115, 127
  multiple genomic 114, 115
Altered genomic DNA 29, 111, 113, 114, 115, 116, 117
American civil liberties union (ACLU) 47
Analysis 75, 109
  genetic 109
  genomic 75
  meta-genomic 75
Animal 1, 24, 33, 113, 116, 118, 127, 128, 132, 134
   and plant health inspection service (APHIS) 24, 33, 116
   consumption 134
   disease 116
   domestication of 1
   genetic engineering of 118, 127
   plant health inspection service 132
   regulation of 113, 128
   transgenic 127
Antibiotic, synthetic bacteriostatic 14
Antithymocyte serum 93
Application 20, 24, 25, 57, 62, 64, 75, 78, 80, 109, 115, 127, 129, 139, 140, 141
  animal-drug 127
  commercial 78, 109
  gene-editing 64
  industrial 75
Archaea harboring 77
Artificial DNA-targeting-RNA 75
Atlantic salmon 119, 125
Authority 29, 33, 38, 53, 111, 113, 117, 118, 119, 121, 122, 127, 128, 129, 131, 132, 138
  assertion of 118, 122
  decision-making 138
  regulatory 111, 113, 117, 121, 129
  substantive rulemaking 53
Automated DNA sequencers 44

B

Bacillus thuringiensis 131, 132

soil bacterium 132
Bacteria, nitrogen-fixing 55
Bacterial defense 76
Bacterium, soil 131
Behavior, monopolistic 17
Beneficiaries 109
Benefits 4, 25, 35, 95, 96, 98, 99
financial 99
fringe 96
therapeutic 4
Beverages, alcoholic 5
Binding instrument 25
Biodiversity 25
conserve 25
protecting 25
Biofuels, potential 76
Biological diversity 24, 25, 26, 121
Biosafety 25, 26
Biotechnology 1, 2, 26, 27, 42, 24, 26, 27, 28, 33, 38, 39, 63, 106
company 42
development 2, 26
industry 42
processes 1
products 26, 27, 28, 33, 38, 39
regulating 24, 38, 39
research 106
revolution 27
tools 63
Blood 7, 111, 119
clots 119
coagulation 111
rushing 7
Board's 79, 80, 82, 85
fact-finding 82
finding 79, 80, 82, 85
judgment 85
ultimate conclusion 79
Bollgard cotton 132
Bone marrow 92, 94, 95
aspirate 94, 95
biopsy 92
Book-to-film sci-fi franchise 65
BRCA 46, 55
genes 46, 55
mutations 46
BRCA1 45, 46, 47, 50, 51, 52, 56
amino acids 51
breast cancer gene 46
gene 50, 51
polypeptide 51
BRCA2 46, 47, 50, 51, 54, 55, 56, 57
genes 46, 47, 50, 51, 54, 55, 56, 57
sequences 51
BRCA1 and BRCA2 genes 46, 47, 50, 51, 54, 55, 56, 57
on chromosomes 50
Breast 47, 48, 50
developing 50
Breast cancer 50, 55
developing 50
Breeding 25, 115, 118
traditional 25
Broad's claim on CRISPR 78
Bt genes 132
transplanted 132
Bt protein 132
Bt tomato 132
engineered 132

C

Cancer 5, 6, 47, 48, 50, 51, 89, 105, 108, 109
cervical 108, 109
deadly blood 89
ovarian 47, 48, 50
pancreatic 109
risk 47
Cartagena protocol 25, 26
Cas9 62, 66, 67, 70, 76, 77, 78, 80
gene editing 78
protein 66, 77, 80
system 62, 76
transgenic 67, 70
Cattle 7, 8, 18, 31, 133
dairy 133
swine 7
Ceiling crack 7
Cell-free systems 76

Chains 6, 10, 33
contaminated supply 10
nation's food supply 33
Chemical(s) 9, 27, 34, 35, 36, 37, 38, 56, 76, 101, 132
changes 56
insecticides 132
residue 35, 36, 37, 38
toxic 34
Chemistry, industrial 10
Chemotherapy 76
Children drinking 10
Chiropodists 5
Chloroform 13
Chloroplasts 68, 69
Chromatin target 81
Citrus fruits 17
Claims, product-by-process 58
Cleavage 41, 77
enzymatic 77
restriction endonuclease 41
Cloning, genomic 91
Clustered regularly interspersed short palindromic repeats (CRISPR) 60, 62, 63, 64, 65, 66, 76, 77, 78, 81
Code of federal regulations 29, 117, 137
Colony-stimulating factor 92
Commerce 3, 7, 29, 31, 32
foreign 7, 31, 32
Commercial 95, 106
biotechnology firms 106
firms, competing 95
Complementarity, base-pairing 68, 77
Complementary 48, 50, 66, 67, 68, 69, 70, 71, 72, 73, 74, 77
DNA 48, 50
nucleic acids 77
nucleotides 72
Composition 56, 57, 64, 134
chemical 56
genetic 64, 134
probiotic 57
Conditions 4, 6, 16, 17, 80, 112, 116, 117, 118, 120, 121, 127, 128, 129, 130, 131, 139, 140, 141
cellular 80
controlled 116
harsh 6
insanitary 6
medical 4
Conduct factory inspections 16
Confectionery 11
Conformational changes 80
Congenital limb deformities 19
Construction 41, 66, 126, 140
statutory 140
Constructs, expressing 132
Consumers 3, 11, 16, 17, 18, 28, 29, 30, 31, 32, 38, 142
demand 142
health and welfare of 31, 32
opinion 142
services 30
Convention on biological diversity (CBD) 24, 25
Conversion 100, 101, 102, 103, 104, 106, 107
law of 101, 102, 103, 106
liability 100, 104
theory 101, 104, 105, 107
Corneal tissue 102
Cosmetic act 15, 16, 20, 26, 29, 112, 119, 134, 136
Court of Appeal 42, 47, 88, 94, 96, 97, 102, 103, 108, 136
Covalent bonds 51, 52, 53
Cow's pituitary gland 133
Criminal regulations 5
CRISPR 62, 64, 77, 78
activity 62
array 77
Cas-mediated immunity 77
Cas systems 77
function 62
gene editing technologies 78
interference acts 62
system 62
technology 64
CRISPR/Cas9 62, 76, 78, 80, 81, 82, 84, 85, 111
endonuclease 62

gene editing systems 111
in eukaryotic organisms 78
system 78, 80, 81, 82, 84
system in eukaryotes 81, 82
systems 76
technology 85
CRISPR loci 62, 77
interference 62
CRISPR RNA 66, 69, 77
mature 66
precursor 77
Crops 1, 35, 55, 112, 132, 133
breed 133
insect-resistant transgenic 132

D

Damage 12, 33
environmental 33
Defendant's policy statement 143
Defense systems 77
Designations 4
generic 4
Development 1, 2, 3, 17, 19, 24, 41, 81, 82, 87, 88, 95, 107, 109, 111
breast 41
commercial 95
Device 13, 16, 18, 21, 126, 127
therapeutic 18
Diarrhea 4
Dietary 21, 29, 30
supplement health and education act (DSHEA) 21
supplements 21, 29, 30
Diethylene glycol 14, 15
Discretion 43, 116, 118, 128, 136, 137
agency's 137
court's 43
Diseases 2, 5, 8, 12, 16, 17, 33, 35, 108, 112, 114, 124, 126, 128, 131
curing 12
diagnose 16
fatal 128
plant 112
Dispute 44, 76, 84, 101, 104, 124
legal 76
two-party ownership 101
Distinguished federal civilian service award 19
DNA 3, 40, 45, 48, 49, 50, 51, 52, 53, 54, 56, 57, 60, 61, 62, 63, 66, 68, 69, 72, 73, 74, 76, 77, 78, 81, 91, 114, 116
altered 114
bacterial 76
chimeric 61
chromosomal 91
clone 61
demethylases 68, 69
encoding 72, 73, 74
eukaryotic 81
foreign 66, 77
genomic 116
harboring sequences encoding 61
isolated 3, 51, 52, 53
methyltransferases 68, 69
nucleases 66
nucleotides 49
plasmid 60
prokaryotic 81
sequencing technology 40, 45
synthetic 50
target in cell-free systems 76
DNA molecule 47, 49, 50, 52
chromosome's 47
natural 52
synthetic 50
DNA sequence 113, 114
changes, targeted 113, 114
DNA-targeting RNA 66, 67, 68, 69, 70, 71, 72, 73, 74, 75
double-molecule 69, 70, 72, 74, 75
encoding nucleotide sequence 75
functional artificial 74
guides 71
polynucleotide 67
Dried 17
fruits 17
vegetables 17
Drink manufacturers 10

Drug(s) 1, 5, 8, 9, 11, 12, 13, 14, 15, 18, 19, 20, 21, 22, 29, 38, 73, 76, 112, 118, 122, 124, 125, 126, 127, 128, 129, 134
act 1, 8, 9, 11, 12, 13, 14, 15
and cosmetic act 134
anticancer 76
anticholesterol 76
anti-nausea 18
authority 124
compound narcotic 12
hypothetical 128
narcotic 21, 22
regulations 14, 19
DsDNA 77, 91
cleave target 77
DXP pathway 76

E

Eating foliage 131
Economic incentive 106
Education act 21
Effects 18, 37, 38, 129
anti-emetic 18
binding 136
cumulative 37, 38, 129
endocrine 38
threshold 37
toxic 37
Efficacy, biomedical 5
Egg products 31, 32, 33
packaged 31
Egg(s) 2, 9, 30, 31, 32, 111, 120
packaged 32
processed 32
products inspection act 30
Electron microscopy 60
Emissions trading regime 89
Endangered 27, 61
species act (ESA) 27
DNA-binding proteins 61
Engineered plants 112, 115, 119, 123, 127, 131, 133, 137, 141
Environmental 24, 26, 27, 28, 33, 34, 35, 36, 38, 39, 116, 121, 129, 130, 131, 132, 133, 135, 137, 138, 139
assessment (EA) 130, 135, 137, 139
harms 130, 131
impact 131, 133, 137
impact statement (EIS) 121, 131, 135, 137, 138, 139
protection agency (EPA) 24, 26, 27, 28, 33, 34, 35, 36, 38, 39, 132
regulations, enforcing 34
remediation 24
risks 116, 121, 129, 130, 131
Enzyme(s) 21, 25, 60, 61, 66, 76, 77, 112, 119
chimeric endonuclease 66
disorder, rare 119
engineered nuclease 66
novel nuclease 66
polyketide synthase 76
restriction 60, 61
Epstein-Barr virus 93
Erythromycin 76
Ethical issues 108
Eukaryotic 78, 79, 80, 81, 82, 83, 84
cells 78, 79, 80, 81, 82, 83, 84
organisms 78
European molecular biology laboratory 109
Evidence 3, 79, 81, 82, 83, 84, 85, 107, 118, 125, 139, 141
empirical 107
factual 85
technical 141
Exercise 43, 97, 119, 126, 136, 137
bikes 126
discretion 136
Exposure, anticipated dietary 36
Expressed sequence tags (ESTs) 44

F

Fat 9, 21
beef 9
low 21
Fatal septicemia 131

Fatty alcohols 76
FDA 14, 16, 21, 28, 29, 117, 120, 126, 127, 128, 143
agent 14
approved application 120, 128
authority 21, 127
enforcement action 117
food safety modernization act 29
intervention 126
jurisdiction 16
policy 28
regulated growth hormone 126
regulations 29, 117, 127, 143
Federal 7, 26, 29, 30, 33, 34, 38, 42, 43, 103, 132
antitrust laws 43
circuit court 42
government's role 38
insecticide 26, 34, 38, 132
law 29, 33, 103
meat inspection act 30
meat inspector 7
seed act 33
Federal food 14, 20, 21, 26, 29, 38, 112, 134, 139
drug, and cosmetic act (FFDCA) 14, 20, 21, 26, 29, 38, 112, 139
Fermentation techniques 1
FIFRA regulations 36
Financial assistance 30
Fish and wildlife service 120
Food 10, 11, 12, 13, 15, 16, 17, 28, 29, 30, 35, 36, 38, 112, 124, 125, 134, 139, 140, 142
additional 36
additives 1, 6, 8, 9, 10, 17, 19, 20, 21, 24, 26, 28, 29, 32, 33, 35, 38, 111, 112, 113, 118, 119, 121, 122, 124, 125, 126, 129, 130, 133, 134, 134, 135, 137, 138, 139, 140, 141
allergies 133
and drug administration 1, 19, 24, 28, 29, 38, 113, 118, 133
and drugs act 1
drug, and cosmetic act (FDCA) 20, 21, 29, 118, 119, 121, 122, 124, 125, 126, 129, 130, 134, 135, 139
engineered 137, 139, 141
industry 6, 8
legislation 8
manufacturers 10
natural 17
nutrition and consumer services (FNCS) 33
packaged 21
particular rDNA-developed 134
processed 35
producers 134
production 1, 26, 28, 32, 111, 112
quality protection act 29
rDNA-engineered 139
rDNA-modified 138
rDNA-produced 134, 135
supplemental 33
tolerance 35
Food safety 11, 24, 28, 30, 32, 33, 121, 132
inspection service (FSIS) 24, 32, 33
legislation 11
Force 122, 123
and effect of law 123
of law 122
Foreign 24, 30, 33, 66
agricultural service (FAS) 24, 30, 33
DNA elements 66
Fragmentation, mechanical DNA 61
Free exercise clause 135
French microbiologist 76
Freshwater 120, 128
culture facilities 120, 128
tanks 120
Fruit, canned 17
Fungicide 34, 132
Fusion protein 62

G

Gene(s) 40, 41, 45, 47, 48, 55, 56, 61, 67, 75, 106, 113
cloned 106

coding 41
downstream 75
encoding 41
engineer 61
expression 45, 67
manipulating 56
patenting 45
sequences 40, 47, 48, 55
therapy 113
Gene editing 62, 64, 65, 78, 81, 113
pushing CRISPR 78
systems 81
Genentech's 42, 43
complaint 43
laboratory 42
Genetically engineered salmon 120
Genetic 46, 47, 52, 66, 81, 112, 113, 127, 140, 142
diagnostic laboratory (GDL) 46, 47, 52
engineering of plants 112
manipulation techniques 127
modifications 81, 112, 113, 140, 142
reprogramming 66
Genetic material 42, 60, 87, 102, 118, 119, 125, 136, 139
derived 119
transferred 136, 139
Genome(s) 60, 61, 62, 63, 65, 66, 77, 113, 114, 115, 116, 117, 119
edit crop 63
editing 62
elephant 65
goat's 119
mammoth 65
modification 113
Germs, harmless 42
Glycosylation 91
Government 7, 10, 11, 28, 30, 44, 116, 119, 121, 124, 126, 128, 129, 130, 131, 137, 138
agencies 116
federal 7, 28, 30, 137
inspection 7
regulation 10, 128
Granulocyte-macrophage colonies 92
GRAS 134, 135, 136, 137, 138, 139, 140, 141
rebuttable presumption of 137, 138
presumption 137, 139, 141
Growth 41, 92
factors 92
hormone deficiency 41
Gynecological tumors 106

H

Hairpin 68, 73
Hairy-cell leukemia 92, 93, 94
Health 4, 5, 9, 12, 26, 28, 31, 32, 33, 35, 43, 44, 95, 98, 99, 103, 109, 130
agricultural 33
crisis 4
Inspection Service 33
insurance 109
risks 35
services 103
Helicoverpa zea 132
Histone 68, 69
acetyltransferases 68, 69
deacetylases 68, 69
HMG-CoA reductase pathway 76
Hormone, engineered 41
HPV genome 109
Human 35, 40, 41, 45, 47, 48, 53, 92
chorionic somatomammotropin 41
chromosome 45
dietary risk 35
erythroid colonies 92
genes 40, 47, 48, 53
Human genome 40, 41, 44, 45, 87, 90, 106, 109
T-lymphoblast 90
Papilloma virus (HPV) 109
project (HGP) 40, 44, 45
sequence 45
somatomammotropin 41
therapeutic products 106
tissue-related inventions 87
Huntington's disease 44

I

Immune interferon 90
Immunoelectrophoresis 92
Immunoglobulin 93
Immunosuppressant 76
Industry 6, 10, 24, 29, 78, 113, 115, 133
  dairy 133
  food processing 6
Infectious waste 103
Information 20, 21, 47, 48, 49, 50, 53, 54, 56, 57, 109, 113, 114, 115, 117
  genetic 54, 56, 109
  protein-coding 48
Insects, killing target 132
Isolated DNA coding 51
Isopentenyl pyrophosphate 76

J

Jurisdiction, exclusive regulatory 32

L

Laboratory 1, 3, 113, 116
  animals 113, 116
  techniques 1, 3
Legal 105, 125
  theories 105
 treatise 125
Legislation 27, 28, 118, 126, 137
  unified biotechnology 27
Legislative 122, 123
  authority 123
  rules 122, 123
Leukemia 89, 105
  hairy cell 89
Leukocyte count 92
Limb regeneration 64
Litigation lottery 106
Livestock production 33
Living modified organisms (LMOs) 25
Lymphokines 92, 93, 95, 102

M

Management, resource 33
Manipulation 60, 61, 62, 66, 118
  enzyme-mediated 61
  genetic 60, 66, 118
Manufacture lymphokines 102
Measurable terminal deoxynucleotidyl transferase 93
Meat 1, 7, 8, 10, 30, 31, 32, 63, 111
  allergy-safe 111
  inspection Act 1, 7, 8
  products 7
  restore decaying 10
Meat food 7, 31
  industry 31
  products 7, 31
Medical device amendments (MDA) 20, 21
Mitigation 16, 112, 114, 124, 126, 130
  environmental 130
Modification 35, 66, 67, 68, 69, 70, 91, 118, 122, 135, 142
  rDNA 135, 142
Modifying polypeptides 67, 70
Modulating transcription 67, 70, 75
Molecules 27, 50, 68, 70, 133
  fluorescent 68
  mRNA 50
  protein 133
  synthetic nucleic acid 27
  tracrRNA 70

N

National 26
  aeronautics and space administration (NASA) 26
National environmental 27, 116, 121, 129, 130, 131, 135, 136, 137, 138, 139, 143
  policy act (NEPA) 27, 116, 121, 129, 130, 131, 135, 137, 138, 139, 143
  protection Act 135, 136, 137
Natural 48, 56, 73
  DNA 48, 56

nucleic acid sequences 73
Nature 37, 40, 45, 48, 52, 53, 54, 55, 56, 61, 64, 83, 85, 91
chemical 53
Nature-based 57, 58
combination 58
product limitation 57
Neutrophil migration inhibition factor 90
NIH-funded research 27
Non 17, 114
heritable altered genomic DNA 114
official drugs 17
Notice-and-comment procedures 122, 137
Nucleases 60, 61, 81
effector 61
zinc finger 60, 81
Nucleic acid 25, 67, 68, 69, 70, 73, 75, 78, 139, 140
encoding 68
mitochondrial 69
proteins 139, 140
Nucleotide(s) 49, 50, 51, 52, 53, 54, 67, 68, 69, 70, 71, 72, 73, 74, 75, 113, 114
insertions 113, 114
intervening 73
linker 73
sequences 52, 53, 67, 69, 70, 71, 73
Nutrition labeling and education act (NLEA) 21

O

Occupational safety and health administration (OSHA) 27
Oil 40, 54, 55, 112, 139
capacity for degrading 55
cottonseed 112
crude 40, 54
Operation 2, 95, 100, 103
vinegar manufacturing 2
Orphan drug act 29
Osteoporosis 106
Outreach programs 34
Ovarian cancer susceptibility gene 46

P

Pain 5, 15
abdominal 15
intense 15
Pairs 49, 55, 56, 77
additional nucleotide 56
nucleotide 55
Patent(s) 1, 3, 4, 5, 6, 12, 40, 41, 42, 43, 44, 45, 46, 48, 51, 52, 53, 54, 55, 56, 60, 65, 78, 89, 93, 95, 102
and trademark office's (PTO) 46, 53
biologic 89
gene 40, 41, 45, 48
isolated DNA 53
issue Myriad's BRCA 46
lucrative CRISPR 60
medicines 1, 3, 4, 5, 6, 12
Pathways 21, 76
biosynthetic 76
fatty acid synthesis 76
metabolic 76
mevalonate 76
People's freedom 92, 128
restricting 128
hairy cells 92
leukocytes 92
Perishable agricultural commodities act 33
Pesticide 34, 35, 36, 37, 38, 112, 131
chemical 131, 37
eligible 36
regulating 36, 38
Pests 112, 132, 134
cotton 132
repel 134
Phytohemagglutinin 93
Plant(s) 1, 3, 6, 7, 32, 33, 55, 60, 63, 64, 78, 111, 112, 132, 133, 134, 139
cotton 132
crop 132
domesticated 1
gene-edited 64
incorporated protectants (PIPs) 132
leguminous 55

living 63
meatpacking 6, 7
pea 3
pests 32, 33
protection Act 132
tomato 132
Plasmid(s) 41, 54, 55, 60, 61, 69, 77, 90
additional 55
bacterial 61
containing population 61
Policy 18, 27, 28, 30, 101, 102, 104, 107, 112, 113, 134, 135, 136, 137, 138, 139
decisions 107
goals 102
guidance 27
implicates 101
issues 112
official 137
public 30
Polio vaccine 109
Polyketides 76
Polymorphonuclear leukocytes 92
Polypeptides 9, 67, 68, 70, 90, 91, 92
inactive Cas 9, 67, 70
macromolecular 90
Post-traumatic stress disorder (PTSD) 5
Poultry products 30, 31
inspection act 30
Power 12, 128
curative 12
regulatory 128
Problems 14, 33, 34, 55, 81, 84, 87, 104, 127
agricultural 33
environmental 34
Procedures, containment 27
Process 1, 2, 3, 25, 27, 48, 49, 52, 53, 56, 58, 77, 88, 98, 123, 126, 127, 130, 136
decision-making 98, 123, 130
endonucleases 77
fermentation 2
reproductive 2
synthetic 48
Production 3, 5, 24, 33, 42, 49, 90, 91, 112, 120, 133, 134
amino acid 49
boosting milk 133
crop 33
Products 1, 10, 11, 12, 16, 21, 24, 28, 29, 31, 39, 40, 47, 48, 83, 103, 105, 114, 126, 142
mosquito-related 114
natural 47, 48
petroleum 40
tobacco 29, 126
Prokaryotic systems 80, 82
Property 42, 50, 60, 102,
chemical 60
law 102
natural bonding 50
therapeutic 42
Property rights 87, 88, 89, 110
protected 88
Prophage sequences 62
Protection 17, 18, 27, 33, 34, 89, 104
constitutional 89
consumer drug 17
environmental 33
Protein(s) 44, 48, 49, 50, 61, 66, 68, 69, 70, 77, 80, 90, 92, 111, 132, 133, 139
activities 66
binding sequence 68, 70
coding genes 44
crystal 132
folding 80
production 50
therapeutic 111
toxin 132
Protein-binding segment 66, 67, 68, 69, 70, 71, 72, 73, 74, 75
hybridize 72
Protospacer adjacent motif (PAM) 68, 77
Pseudomonas fluorescens 40
Public health 20, 21, 26, 28, 30, 35, 38, 103, 126, 129
pesticides 35
protecting 20, 30
Public interest organizations 133
Pyruvate, converting 76

R

Radioactive thymidine 93
Ramifications 65
Recombinant DNA 40, 41, 42, 61, 119, 127
  transfer vectors 41, 42
Reform act 38
Regulating 11, 90
  cell functions 90
  traffic 11
Regulations 21, 22, 26, 28, 29, 30, 31, 32, 33, 38, 90, 113, 114, 117, 130, 139, 140, 141
  additive 139
  cell 90
  development 28
  foreign 33
Regulatory 28, 29
  affairs 29
  system for biotechnology 28
Reluctance 89
  judicial 89
Research 27, 30, 95, 96, 97, 98, 99, 100, 101, 102, 105, 106, 107, 110
  genetic 110
  synthetic nucleic acid 27
Reverse transcriptase 91
Ribonucleases 80
Ribosome-lamellar complexes 93
Riboswitch sequence 68
Rice 1, 63
  produced disease-resistant 63
Rights 88, 89
  quasi-property 88
  tradeable pollution 89
Risk assessment 25, 26, 33
  environmental 33
Risks, medical 97
RNA 41, 49, 62, 66, 67, 68, 69, 73, 75, 77, 80, 90, 91, 127
  designed 75
  double-stranded 66, 80
  guided silencing 66
  interference (RNAi) 66
  messenger 49, 90, 91
  phenomenon 62
  polynucleotides 69
  recombinant 127
  single-guide 69
  trans-acting 66
RNA-directed 65, 77
  system 77
  target DNA modification 65
RNA molecules 67, 69, 70, 72, 73, 80
  hybridize 72
Rodenticide act 34, 132

S

Safety 11, 19, 28, 30, 32
  galled consumer 11
  of meats 30, 32
  regarding thalidomide's 19
  risks 28
Salmon 111, 118, 119, 120, 126, 127, 128, 130
  engineered 118, 120, 128
Sequence(s) 44, 46, 48, 49, 50, 51, 66, 67, 68, 69, 70, 71, 73, 77, 116, 119, 132
  coding 132
  genome-targeting 77
  of DNA nucleotides 49
  tags, expressed 44
Serum protein electrophoresis 92
Sheep erythrocytes 93
Silencing, crRNA-guided 77
Single-letter DNA changes 63
Splenectomy 92, 94, 99, 100
Streptococcus pyogenes 66
Supreme court decision 57
Surgical training 87
Synthesis pathway 76
  polyketide 76
Synthetic food products 32
Systems 10, 19, 21, 22, 61, 62, 65, 80, 81, 82, 83, 101, 102, 109
  bacterial adaptive immune 65
  engineering CRISPR-Cas9 81

immune 101, 102, 109
prokaryotic protein 81
restriction-modification 62
ribozyme 82

T

TALEN 61, 62
effectors 62
systems 61, 62
Target 62, 66, 67, 68, 69, 70, 71, 77
DNA 66, 67, 68, 69, 70, 71, 77
sequence, nucleotide 62
Targeting 66, 77
arbitrary genes 66
crRNA 77
Techniques 25, 45, 63, 82, 90, 92, 111, 113, 119, 126
gene-editing 126
genetic engineering 92, 111
transgenic 63
Technologies 24, 42, 60, 62, 63, 65, 66, 78, 82, 84, 85, 106, 113, 114, 127, 134, 135, 138, 142
effective genome editing 62
gene-manipulation 63
genome editing 60
hybridoma 127
rDNA 60, 134, 135, 138, 142
recombinant DNA 42, 60
Teratogenicity 18
Thalidomide 18, 19
induced birth defects 19
related birth defects 19
Therapeutic effect 18
Tissues 44, 103, 108, 132
brain 44
cancerous 108
Tools 60, 61, 63
effective genetic engineering 63
endonuclease-based 61
extraordinary molecular 60
Tort theory 101
Toxicity 14, 15, 37, 66, 81, 133
post-natal 37
tests 14, 15, 133
Toxins 76, 131
TracrRNAs 66, 69, 70, 72, 74, 77, 80
activating 77
Transcription 41, 49, 60, 61, 65, 75, 77
activator-like effector nucleases (TALENs) 60, 61
termination segment 75
Transcriptional repressors 68, 69
Transgenes 66
Transgenic mammary glands 111
Transmission electron microscopy 93
Treatment 16, 18, 94, 95, 97, 98, 102, 107, 108, 109, 112, 114, 124, 125, 126
medical 97, 102, 125

U

USDA agencies 32
USPTO's Patent Trial and Appeal Board 78

V

Vaccines 30, 109
Veterinary 28, 29
medicinal products 29
medicine 28, 29
Vomiting 15

X

Xenotransplantation 64

Y

Yeast, infectious 64

Z

Zinc finger nucleases (ZFN) 60, 61, 81

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