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BIOTECHNOLOGY & NANOTECHNOLOGY REGULATION

B. DAVID NAIDU

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Biotechnology & Nanotechnology Regulation

Regulation Under Environmental, Health, and Safety Laws

B. DAVID NAIDU

2014 Edition

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Editorial Offices
121 Chanlon Rd., New Providence, NJ 07974 (908) 464-6800
201 Mission St., San Francisco, CA 94105-1831 (415) 908-3200
www.lexisnexis.com

MATTHEW BENDER

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About the Author

B. David Naidu is a partner in the New York office of K&L Gates, LLP. He has extensive transactional, litigation and regulatory compliance experience involving a diverse set of environmental areas. He has advised clients in mergers and acquisitions, divestitures, real estate leases and financing, as well as has represented clients in complex multi-party litigation. His advice to clients has covered a broad range of issues, including the federal Superfund statute, brownfield redevelopment, eminent domain, natural resource damages, Clean Water Act, Clean Air Act, chemical and waste management statutes and regulation

Preface

When I began this project in 2005, regulatory agencies in the United States offered only a limited amount of information as to how nanotechnology and nanomaterials would be regulated under environmental laws. Thus, at that time, it made sense to look at biotechnology as a model for how this other new and emerging technology would likely be regulated. But now, in 2013, a number of different regulatory agencies have issued policy papers or guidance documents outlining their regulatory stance toward nanotechnology. Nonetheless, the policy positions of these agencies still need to be fully developed. Therefore, biotechnology—due to its longer regulatory history—continues to provide a good comparison for those seeking to understand the current and potentially future regulation of nanotechnology. Moreover, the controversies that have surrounded certain uses of biotechnology, such as genetically modified foods, offer insight into the pitfalls that can challenge a new technology in terms of rapidly shifting—and potentially severely negative—public opinion and the ramifications for regulatory action.

This book covers a diverse number of laws that affect a wide-ranging set of industries and that are administered by a variety of agencies. It can be correctly pointed out that the topics discussed are worthy of books themselves. And there are, in fact, books solely covering most of the topics discussed in this book, including, but not limited to, risk analysis, regulation of foods, regulation of drugs, regulation of medical devices, and laws dealing with chemicals. However, this volume is intended to offer the reader a uniquely comprehensive view of the overall scheme of environmental, health, and safety laws as they apply to both biotechnology and nanotechnology. From a practitioner's perspective, there are many sections of the book that detail the specific steps that must be taken in order to obtain approval for a product, while offering insight into the perspective that the applicable regulatory agency or agencies may adopt. In addition, and likely of interest to academics, the book discusses not only the regulations themselves, but also the historical context in which they were created, and offers an understanding of the political dynamics and economic realities that inevitably shape the laws that are developed.

While research and writing is a lonely exercise, many of my friends provided encouragement during the long process. If I were to list each person, I fear I would miss someone. Thus, I can only say, you know who you are. However, there are a number of people who directly assisted me with this project, and I am deeply grateful for all their efforts. With respect to my original manuscript published by Oxford University Press, I would like to thank Hetal Dhagat, Dawn Munson, Deborah Low, Mandy Lundstrom, Jonathan Barron, Phil Seliger, and Nicole Behesnilian for their research and editing assistance. Barbara Tanzer was most helpful in finding journal articles and other secondary sources. I am especially grateful to Rebecca Halford Harris, Roger Pitt, Paul Stimers, Eric Stone, Suzan

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Finally, I would like to thank my parents Karikutla R. Naidu and Elizabeth Naidu for their love of learning and teaching, which they instilled in me. And certainly the most important person in this entire process is my wife Andrea J. Stein, without whose unfailing love, support, and encouragement I could not have completed the original manuscript or subsequent update. I dedicate this work to her and our boys, Ravi and Kieran

List of Acronyms

ALJ	administrative law judge
ANDA	abbreviated new drug application
ANSI	American National Standards Institute
AOSCA	Association of Official Seed Certifying Agencies
APH(3')II	aminoglycoside 3'-phosphotransferase II
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
ASTI	American Society for Testing and Materials International
ATP	adenosine-5'-triphosphate
BET	Biotechnology Evaluation Team
BLA	biologics license application
BRS	Biotechnology Regulatory Services
BSE	bovine spongiform encephalopathy ("mad cow" disease)
Bt	*Bacillus thuringiensis*
CAIR	Chemical Assessment Information Rule
CBER	Center for Biologics Evaluation and Research
CDER	Center of Drug Evaluation and Research
CEQ	Council of Environmental Quality
CESQG	conditionally exempt small quantity generator
CFSAN	Center for Food Safety and Applied Nutrition
CIB	Compliance and Inspection Branch
CIR	Cosmetic Ingredient Review
CJD	Creutzfedlt-Jacob disease
CNT	carbon nanotube
CPSA	Consumer Product Safety Act
CPSC	Consumer Products Safety Commission
CRT	cathode ray tubes

CSFAN	Center for Food Safety and Applied Nutrition
CTFA	Cosmetic, Toiletry and Fragrance Association, Inc.
CVM	Center for Veterinary Medicine
DEFRA	British Department for Environment, Food and Rural Affairs
DNA	recombinant deoxyribonucleic acid
EA	environmental assessment
ECB	European corn borer
EIS	environmental impact statement
ELA	establishment license application
EPA	Environmental Protection Agency
EU	European Union
EUP	environmental use permit
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
FFDCA	Federal Food, Drug, and Cosmetic Act
FHSA	Federal Hazardous Substances Act
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FONSI	finding of no significant impacts
FPLA	Fair Packaging and Labeling Act
FPPA	Federal Plant Pest Act
FQPA	Food Quality Protection Act
FSIS	Food Safety Inspection Service
GM	genetically modified
GMO	genetically modified organism
GRAS	generally recognized as safe
GRASE	generally recognized as safe and effective
HCS	Hazard Communication Standard
HT	herbicide-tolerant
IGF-1	insulin-like growth factor
INAD	investigational new animal drug
IND	investigational new drug
IRB	institutional review board
IRM	insect resistance management
IUR	Inventory Update Rule

IWGN	Interagency Working Group on Nanoscience, Engineering and Technology
LHAMA	Labeling of Hazardous Art Materials Act
LQG	large quantity generator
LVE	low volume exemption
MCAN	Microbial Commercial Activity Notice
MRI	magnetic resonance imaging
MSDS	material safety data sheet
MWNTs	multiwalled nanotubes
NADA	new animal drug application
NAS	National Academy of Science
NDA	new drug application
NEHI	Nanotechnology Environment and Health Implications
NEPA	National Environmental Policy Act
NF	National Formulary
NGO	nongovernmental organization
NIH	National Institutes of Health
NIOSH	Nanotechnology Research Center
NMFS	National Marine Fisheries Service
NNI	National Nanotechnology Initiative
NOC	Notice of Commencement
NRC	National Research Council
NSET	President's National Science and Technology Council
NSF	National Science Foundation
NSPS	new source performance standards
NTF	Nanotechnology Task Force
NTRC	NIOSH Nanotechnology Research Center
OCED	Organisation for Economic Cooperation and Development
OMB	Office of Management and Budget
OSH Act	Occupational Safety and Health Act
OSHA	Occupational Safety and Health Administration
OSTP	Office of Science and Technology Policy
OTC Monograph	over the counter monograph

PBN	premarket biotechnology notice
PEL	permissible exposure limit
PG	polygalacturonase gene
PHSA	Public Health Service Act
PIP	plant incorporated protectant
PLA	product license application
PMA	premarket application
PMN	Pre-Manufacture Notice
PPE	personal protective equipment
PPPA	Poison Prevention Packaging Act
PQA	Plant Quarantine Act
RAC	Recombinant DNA Advisory Committee
rBST	recombinant bovine somatotropin
RCRA	Resource Conservation and Recovery Act
R&D	research and development
rDNA	recombinant deoxyribonucleic acid
ROS	reactive oxygen species
SAP	Scientific Advisory Panel
SARA III	Superfund Amendments and Reauthorization Act of 1986
SNUN	Significant New Use Notice
SNUR	Significant New Use Rule
SPF	sun protection factor
SQG	small quantity generators
SWNTs	single-walled carbon nanotubes
TERA	TSCA Experimental Release Application
TME	test marketing exemption
TSCA	Toxic Substances Control Act
TSDF	treatment, storage, and/or disposal facility
UNEP	United Nations Environment Programme
USDA	U.S. Department of Agriculture
USP	United States Pharmacopeia
UST	Underground Storage Tank
UVA	ultraviolet A
UVB	ultraviolet B

VCRP	Voluntary Cosmetic Registration Program
WTO	World Trade Organization

Chapter 1

INTRODUCTION TO REGULATION OF BIOTECHNOLOGY AND NANOTECHNOLOGY

Synopsis

§ 1.01 Introduction

The twenty-first century may be shaped in significant measure by the development of two different technologies: biotechnology and nanotechnology. A broad range of industries and products are impacted by both of these technologies, including medicine, medical devices, food and food additives, pesticides, cosmetics, other consumer products, chemicals, and many others. When it comes to the law, the fundamental question that each technology presents is the same: are the environmental, health, and safety laws that were formulated mainly during the latter half of the twentieth century both adequate to protect us from the risks associated with these technologies and permissive enough to allow us to obtain the benefits these technologies have to offer?

Because research into, and manufacture of, products using genetic modification began nearly two decades before nanomaterials reached the marketplace, regulators and stakeholders in biotechnology have had almost two additional decades to wrestle with the critical question of how to balance these competing interests while also developing a regulatory structure that is neither too permissive nor too restrictive. Nonetheless, as will be evident in subsequent chapters, regulators are still struggling with these issues in the biotechnology field. As technology advances, and new products that were previously only theoretical possibilities become reality, agencies must stake

out policy positions in previously uncharted territory—and modify the regulatory structure accordingly.

As for those working in the field of nanotechnology, they too must now also confront the issue of whether the laws enacted decades ago are adequate and appropriate to regulate products that not only did not exist at the time of their enactment, but were unlikely to have even been contemplated. To their benefit, however, these people have the biotechnology experience from which to learn. That is, they can see how the regulations have shifted and changed in the face of new products made possible due to biotechnology advances as well as public concern about the risks of these new technologies.

To address this fundamental legal question, this book provides a review of the major laws and regulations that govern biotechnology and nanotechnology in certain key fields. These include a number of key environmental health and safety laws, as well as other laws that do not traditionally fall under the rubric of "environmental laws," such as the Food, Drug, and Cosmetic Act. Each of these laws has spawned a complex and detailed regulatory program administered by a number of different agencies. Any attempt to explain such a complex set of laws and regulations—especially one concerning a subject matter as technical as that addressed in this book—requires a degree of simplification. As a result, it is presumed that the reader, if he or she is interested, will in conjunction with reading this book also review as appropriate the relevant statute, Code of Federal Regulations, or agency policy position paper.

Another important point concerning the law governing these technologies relates to the use of guidance documents, agency policy statements, and even draft guidance documents in this book to outline an agency's position. These types of documents are not necessarily predictive of agency behavior, even though many agencies use them as "firm" policy, because it has been well settled that an agency is not bound by such statements. These documents merely serve as an agency's current interpretations of applicable statutes or regulations. An agency is free to choose different standards, procedures, or policies provided they meet the applicable statute and regulations. Yet despite the limitations of such documents, in those instances in which the agency has not released final rules or regulations but has, in fact, issued guidance documents or interpretative statements that specifically address the applicability of the underlying statute to biotechnology or nanotechnology, those guidance documents and interpretive statements are discussed. The reader is cautioned to remember the limitations of such documents.

The organization of the book reflects the view that, before reviewing the statutes and regulations applicable to these technologies, it is necessary to

examine certain background issues. As detailed below, Chapters 2 through 4 lay out the groundwork for the chapters that follow—offering historical background and discussion of the theoretical underpinnings of the regulatory structure with respect to biotechnology and nanotechnology. Chapters 5 through 10 focus on specific industry sectors and the particular issues that arise in the regulation of each. This is not to suggest that statutes in one section are applicable only to that section. For example, the Occupational Safety and Health Act applies to a vast number of industries, and is not simply limited to the chemical manufacturing industry.

Chapter 2 offers a starting point for the discussion and provides those not familiar with the historical development of biotechnology or nanotechnology with some basic information, including some nontechnical definitions for specific nanomaterials referenced in other chapters. Additionally, it will offer examples of how these technologies are currently being used.

Chapter 3 offers a survey of the various factors (*e.g.*, health and environmental risks, economic and ethical considerations, and public opinion) that have influenced discussions of biotechnology and nanotechnology. The risks discussed in this chapter serve as the basis for the way biotechnology and nanotechnology are currently regulated. The biotechnology discussion in this chapter focuses in particular on agricultural biotechnology because it is that area (as opposed, *e.g.*, to medicines or medical devices) that has generated the most significant controversy. The risks described in this chapter are divided into human health risks and environmental risks. In examining human health risks, the chapter focuses on two elements: toxicity (*e.g.*, food allergens) and exposure (*e.g.*, bioaccumulation and persistence in the environment and pathways into the human body). As to environmental issues, Chapter 3 examines the potential adverse consequences (*e.g.*, impacts to microbial and aquatic communities) associated with products made from these technologies if they are released into the environment. The chapter will then focus on other factors that influence how a product is regulated—namely, the economic and societal impacts of the product, any uncertainty associated with what is known about the product, and public perceptions. Finally, the chapter will provide a brief discussion of an alternative mechanism for regulation: the application of a stringent version of the precautionary principle.

Chapter 4 provides a discussion on the evolution of the regulatory structure governing biotechnology and the current regulations governing nanotechnology. Because of the longer historical time line for biotechnology, it is possible to examine the early efforts at regulation in the late 1970s and compare them with the later regulatory structure imposed in the