Introduction to Regulatory Science

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Edited by
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PREFACE

The desire to write a book on regulatory science primarily resulted from our teaching experiences for courses on Regulatory Science at the Biomedical Graduate Education Program at Georgetown University and the publication of several papers initiated through these courses. The evolution of regulatory science as a scientific discipline has encouraged our graduate students to write papers for scientific journals rather than social science journals. Such a project has been popular among graduate students for several reasons. It has motivated the students to study the topic's scientific backgrounds and learn existing related policies in detail. The publication helped advance their careers.

As described in this book, the origin of regulatory science can be traced to the Environmental Protection Agency (EPA) activities during its initial phases. The Institute for Regulatory Science was established in 1985, and Dr. Margaret Hamburg established a regulatory science program at the Food and Drug Administration (FDA) in 2011.

The evolution of regulatory science was significantly enhanced by the authors' interactions with distinguished individuals. These include: Norman Borlaug, Nobel Prize laureate and founder of the Green Revolution; Willard (Bill) F. Libby, Nobel Prize laureate at the University of California, Los Angeles; Hans Süss of the University of California, San Diego; Dixy Lee Ray, former Chairman of the Atomic Energy Commission; Frederick Seitz, former President of the National Academy of Sciences; Melvin W. Carter, past President of the International Radiation Protection Association; Matthew Meselson, US Presidential Advisor and Harvard Professor; and Norman P. Neureiter, US Presidential Advisor and the first Science Advisor to the Secretary of State Madeleine Albright. Their contributions are too numerous to be discussed here. Specific to regulatory science, William Ruckelshaus, the first Administrator of the EPA, developed important principles and confirmed the formulation of the *Ruckelshaus Effect*, which will be discussed in detail in several chapters.

This book is primarily intended as a textbook for university-level students as well as early practitioners of regulatory science. Given the diversity of the audience, we had to consider the practicality of applying the concepts as we designed the content and organization of the book. The book consists of three parts. The first part covers fundamental aspects of regulatory science, including how science is used in the three branches of government (the executive, legislative, and judicial branches). Although the book primarily relies on the US branches of government, it is hopeful that the US example applies to other countries. The second part covers regulatory science tools. The experience, particularly the program at Georgetown University, resulted in identifying potential tools and the unique structure of regulatory science. The third part summarizes the most used regulatory science branches, such as regulatory toxicology, regulatory microbiology, regulatory pharmacology, and regulatory ecology. As a discipline, Regulatory Science is still an evolving subject, and we hope to update this textbook in due course.

April 1, 2024

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Cooperating with a most distinguished professional society such as ASME was gratifying. They established a Peer Review Committee to oversee the peer-review process. The Executive Panel of that committee included past presidents of ASME: Charles Velzy, Ernest Daman, and Nathan Hurt. During the period of our involvement, the ASME Peer Review Committee included the following individuals: Gary A. Benda, President of US Energy Corp; Erich W. Bretthauer, former Assistant Administrator for Research and Development at the EPA; Robert A. Fjeld, Dempsey Professor of Environmental Engineering and Science at Clemson University; William T. Gregory III, private consultant; Peter B. Lederman, former Research Professor of Chemical Engineering and Environmental Policy at the New Jersey Institute of Technology; Jeffrey A. Marqusee, Technical Director of the Strategic Environmental Research and Development Program at the US Department of Defense; Lawrence C. Mohr, Jr., Professor of Medicine, Biometry, and Epidemiology and Director of the Environmental Biosciences Program at the Medical University of South Carolina; Goetz K. Oertel, former President and CEO of the Association of Universities for Research Astronomy; Glenn W. Suter II, Science Advisor at the National Center for Environmental Assessment of the EPA in Cincinnati; and Cheryl A. Trottier, Chief of the Radiation Protection, Environmental Risk, and Waste Management Branch at the US Nuclear Regulatory Commission.

Tony Scarpa of the National Institutes of Health (NIH) and his associates Dan Gerendasy and Don Luckett provided us with valuable information on peer review at NIH. Similarly, James Lightborne of the National Science Foundation (NSF) helped point us in the right direction to obtain information on peer review at the NSF. Marion Müller of the German Research Foundation (Deutsche Forshungsgemeinschaft; DFG), and Ruth Lee of the UK Research Council helped identify peer review information in their respective countries.

It is most important to note the existence of individuals within the government, particularly the US Department of Energy, who had the wisdom to appreciate the long-term implications of reliance upon credible and reliable science in the decision-making process. Those who supported

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CHAPTER 1

INTRODUCTION

A. ALAN MOGHISSI AND TOMOKO Y. STEEN

The application of science in policy decisions has a long tradition. However, as we know it today, the use of science for regulation only appeared around the eighteenth century. Consequently, popes, emperors, Kaiser, shogunates, and kings made all decisions sometimes regardless of the validity of the existing science. During the initial period of the modern scientific revolution, it was difficult to separate science from personal assumptions, superstitions, or personal judgments (Freudenberg, 2023). Most unfortunately, as we discuss later in this chapter, societal objectives or personal beliefs affect some decision-making in personal behaviors and even policy making still to this date.

Regulatory science emerged as the public recognized the need to regulate large segments of medical practices, manufacturing processes, occupational safety, agriculture activities, food safety, air and water pollution management, protection of various species and other ecological elements, and numerous other activities (Jacobson, 2002). Air pollution regulations include limiting emissions from various operations and acceptable ambient concentrations of different chemical agents, whereas water pollution management includes establishing drinking water standards, among other things.

The oldest law to cover concerns over the composition of food, including drinks, is A*ssisa panis et sevisiae* (Assize of bread and ale), enacted in about 1266, which addressed the production and sale of bread and beer in Britain. The first law that prescribed the purity of food, including drinks, is known as *Reinheitsgebot* or purity law – or, more accurately, beer purity law – enacted in Bavaria in 1516. This latter law continued to be used in Bavaria and many other parts of Germany for several centuries and eventually was incorporated into the relevant laws of Germany.

In the United States, the oldest government agency interested in regulatory science was the Bureau of Chemistry, established in 1906. The responsibility of that agency was to ensure that the public was protected from the "manufacture, sale, and transportation of adulterated or misbranded, or poisonous or deleterious foods, drugs, medicines, and liquors." Recognizing the significance of the mission of the Bureau of Chemistry, it was eventually renamed the Food and Drug Administration (FDA). As expected, the FDA was substantially expanded and ultimately placed under the Department of Health and Human Services. One of the fundamental laws governing the operation of the FDA is the Food, Drug, and Cosmetics Act, initially passed in 1938.

Another critical regulatory agency with a broad regulatory mission is the US Environmental Protection Agency (EPA). The formation of the EPA was the result of the activities of many advocacy organizations. Eventually, the public recognized that the situation at that time was not reasonable or sustainable. In December of 1970, President Richard Nixon identified several segments (it was claimed to be 13 parts) of existing federal agencies and combined them to establish the EPA. As expected, after its formation, the EPA faced several legally mandated deadlines to develop regulations and enforce others that were already in effect. In addition, shortly after the formation of the EPA, several new laws were passed to enhance its mission, including the Federal Insecticide, Fungicide, and Rodenticide Act (USC-FIFRA 1972); Safe Drinking Water Act (USC-SDWA 1974); Toxic Substances Control Act (USC-TSCA 1976); Clean Water Act (USC-CWA 1977); and Clean Air Act (USC-CAA 1977). Our attempt to identify the number of laws that cover the authority of the EPA could have been more successful. Still, we have identified over forty laws ranging from the Atomic Energy Act to the Toxic Substances Control Act in this book.

An important issue facing the EPA's regulatory decisions was radioactive materials. The process started with the Manhattan Project during World War II, leading to the establishment of the Atomic Energy Commission (AEC). On August 1, 1946, President Harry Truman formed the AEC with the country's primary mission to develop nuclear weapons. Eventually, the mission of the AEC was expanded to include research and development of atomic energy, the application of radioactive materials in medicine and industry, and many other tasks. Included in the mission of the AEC was also the development and enforcement of relevant regulations. Later it was recognized that an agency would have a conflict of interest in simultaneously promoting and regulating the same activity. Eventually,

the AEC was divided into two agencies: The first agency took over the bulk of activities of the AEC and was called the Energy Research and Development Administration, which became the current Department of Energy (DOE). The regulatory responsibilities of the AEC were transferred to the newly formed US Nuclear Regulatory Commission (NRC). As if the problems were not complex enough, the regulatory responsibility for environmental radiation exposure was transferred to the EPA.

One of the oldest laws dealing with occupational safety traces its origin to the late 19th century, leading eventually to the passage of the Federal Mine Safety and Health Act in 1977, managed by the Mine Safety and Health Administration within the Department of Labor. Another law concerning major safety issues was the passage of the Occupational Safety and Health Act in 1970.Industrial workers and many other employees of scientific research organizations welcomed the passage of that laws. The law designated the Occupational Safety and Health Administration, an organization within the US Department of Labor for development and enforcement of relevant regulations.

A law with significant societal consequences was the Endangered Species Act (ESA) of 1973. Although a predecessor of that Act was passed in 1966, the 1973 law significantly impacted the regulatory process. The regulatory responsibility of the ESA was assigned to two agencies: the Fish and Wildlife Service within the US Department of Interior; and the National Marine Fisheries Service, an organization within the National Oceanic and Atmospheric Administration of the US Department of Commerce.

An agency not commonly recognized as a regulatory agency is the National Institute for Standards and Technology (NIST), located within the Department of Commerce. NIST was established in 1901 as the National Bureau of Standards (NBS). NIST creates standards often adopted by regulatory agencies and thus constitutes a part of the regulatory process.

Historical Overview of Regulatory Science

There is extensive literature on the perception by many investigators of the nature of regulatory science, what makes it unique, and how to apply existing science in writing regulations. Even to this date, social sciences

and the legal fields dominate in creating literature dealing with regulatory science.

One of the authors in this chapter coined the term “regulatory science” shortly after the formation of the EPA in 1970. The term was used for the first time in an internal memorandum to describe the science used to develop regulations by that Agency. Initially, the use of the term was not accepted. The justification being that there is nothing specific about science used in developing regulations (Moghissi et al. 2011). It was argued that “science is science” regardless of its application, and there was no need for creating the new term “regulatory science.” However, establishment of the **Institute for Regulatory Science** in 1985 (RSI 2013) legally established an organization with that term in its title for the first time.

Another surprising and interesting issue was the lack of recognition of the need for a new scientific discipline after several regulatory agencies were established. Consequently, in a literature search of the early 1980s, we did not find the phrase “regulatory science,” nor a description of how science was used in developing regulations, judicial decisions, or any other policy decision. In contrast, in June 2015, an Internet search for “regulatory science” identified about 250,000 entries, indicating that it is extensively used not only in English but also in other languages including German (r*egulierungswissenschaft*), French (*science réglementation*), Spanish (*ciencia reguladora*), Arabic (العلم التنظيمي), and Japanese **(**規制科学・レギュラトリーサイエンス**)**.

Initially, the scientific needs of the regulatory process had to be addressed in numerous scientific fields, such as toxicology, microbiology, pharmacology, chemistry, physics, biology, medicine, and several engineering disciplines. However, there were major problems, significant discourse within the scientific community, and dissatisfaction within the regulatory community on how the subject was managed. The appearance of a regulatory science discipline was in response to the desire for a more appropriate process to meet societal needs.

The advancements in science and technology within the last two centuries resulted in the availability of scientific information applicable to various policy activities, including regulatory decisions. A closer look at the subject indicates that regulatory science includes nearly all scientific disciplines. As described above, although the interaction between science

and the legal system is not new, there has been a substantial increase in policy decisions that are based on regulatory science.

In the US, several laws were passed after the regulatory community complained the "competent" agencies either relied upon poor science or disregarded science altogether. However, the formation of the Institute for Regulatory Science and establishment of similar institutes elsewhere showed that regulatory science is unique and requires special attention.

It has been challenging to categorize relevant scientific information, mainly related to the definition of regulatory science, its evolution, and its status. To evaluate the true definition or description of regulatory science, it is necessary to evaluate the existing literature in terms of the perception of the respective authors. In the following, we have attempted to categorize the relevant published information. However, we recognize that the subject is complex, and the relevant authors may dispute the categorization we have placed a specific work. The nature and application of regulatory science can, however, be generally categorized as follows:

Group I: There is a wide-spread belief that science as it has been known for about two centuries is no longer 'universal,' or 'normal' and one needs to recognize post-normal science. The vison of such 'post-normal' science is traceable to Thomas Kuhn who used words such as 'paradigm shift,' 'models,' 'patterns,' 'standards,' and 'prototypes.'

1. Funtowicz and Ravetz in a series of books and other publications (Funtowicz and Ravetz 1991, 1992) coined the phrase "post-normal science" in describing regulatory science. They suggested that the level of uncertainty of science increases, starting with applied science, followed by applied and regulatory science gaps, professional consultancy to post-normal science.
2. Melnyk (2005) considers changing policy and regulatory contexts in which science is situated to involve uncertainties, disputed values, high decision stakes, and urgent decisions. Scientists are more than just sources of objective facts but also sources of political and economic manipulation. Post-normal science is a concept for exploring alternative regulatory arrangements and how decisions can be enhanced in terms of democratic accountability and in the reduction of risks. Melnyk concludes that there are challenges to its realization in regulatory and policy circles, such as: 1) the dominant belief that decisions must be based on science, and that the science must disregard social,

economic, and cultural variables; and 2) the high economic stakes diminish the willingness of actors to engage in dialogue and reach a mutual understanding.

Group II: This group claims that regulatory science requires scientific approaches to observe regulations. Although the number of papers and books in this category is small, this view is widely spread, particularly within the regulatory community. According to this group, various regulations need to be identified in terms of their scientific basis and evaluated. Subsequently, appropriate scientific procedures and methods are to be developed to fulfill the regulations.

1. The compilation of information in a book edited by Gad (2001) demonstrates the views of various authors on how scientific disciplines such as toxicology and pharmacology can be used to fulfill relevant regulations.
2. Petricoin et al. (2002) report that determining the appropriate level of analytical and biological validation needed for each medical application of microarrays and their supporting computer-based bioinformatics systems raises new challenges. According to Petricoin et al., solutions to the regulatory challenges will differ for all applications of genomic and proteomic microarrays but are likely highly dependent on context. The level of scientific rigor for microarray performance differs depending on whether the microarray is for early drug discovery and at a hypothesis stage or is a clinical device to make diagnostic, therapeutic, or prognostic decisions for patients.
3. Henry and Conrad (2008) argue that only one set of standards and practices should be used to judge the quality of scientific work in each regulatory proceeding, regardless of why the work was conducted. Many of these hallmarks of scientific quality are incorporated into federal laws, rules, and policies. However, any system of differential treatment for regulatory science would face severe scrutiny based on authority. It would not be easy to administrate the regulation.

Group III: This group claims that regulatory science consists of advising government agencies based on scientific issues. They correctly claim that traditionally, many agencies have established science advisory boards, advisory panels, and similar groups that provide advice to the government. This group also considers scientific advice provided by almost 1,000 advisory panels established by various laws in the US to be the core of

regulatory science. In many other countries, numerous committees and panels serve their respective governments. For example, Ilieva (2004) reports that scientists involved in the regulatory process are experts assuming advisory functions but are also performers of specific behavior patterns peculiar to the research community. These [two] "positions discerned above have been an amalgam and rarely an object of reasoning; moreover, it has been sequestered behind academic walls" (Ilieva, 2004).

Group IV: This group distinguishes between regulatory science and other sciences such as conventional, research, standard, and academic. According to this group, regulatory science differs from 'normal' or research science. This is the group started just before 1990 and created programs called "Science & Technology Study" or "Science, Technology and Society." They analyzed "social construction of scientific knowledge (SSK)." One of the authors for this chapter was trained under this group by the founders (Sheila Jasanoff and Trevor Pinch).

1. Sheila Jasanoff (1990, 2010, 2011) is one of the most articulate members of this group. She addresses regulatory science's needs by distinguishing between "research science" and "regulatory science." She identified various categories of scientific information: knowledge production, knowledge synthesis, and prediction. She identified three components that separate regulatory science from research science. The first component consists of "knowledge production," designed to fill knowledge gaps to meet specific regulatory needs. The second component, "knowledge synthesis," combines scientific information to address the need for the regulator process. Finally, the third component that Jasanoff considers unique to regulatory science is its predictive nature. She also identified numerous poor decisions of regulatory agencies. Jasanoff provided an overview of the interaction between regulatory agencies and how these interactions impact regulatory science.
2. Another member of this group is Rushefsky (1986), who made a distinction between "normal science" and "regulatory science." He defined regulatory science as "science with specific and public policy implications or with [a] public policy agenda."
3. Uchiyama (1995) claimed that regulatory science is valuable, can be called "evaluation science," and suggested that regulatory science is neither essential nor applied research.
4. Abraham (2002) suggested that there are two regulatory science cultures: scientific culture and political culture. He implicitly

agreed that there is an "academic" science and claimed that there are no "norms and values held across academic science, let alone in regulatory science."

5. Neff and Goldman (2005) reported that despite the broad agreement that regulatory decisions should be based on evidence, interested parties have used the "sound science" mantle to demand extended research, analysis, and review of the evidence for the sole purpose of delaying health-protective regulation. Neff and Goldman conclude that while "sound science" such as regulatory tools can improve the quality of decisions, they can also challenge the government's ability to safeguard the public's health and well-being.
6. Wagner and Michaels (2004) claim that "Science teases policymakers with the prospect of providing definitive [scientific] guidance for regulatory decision making." They correctly identify problems in extrapolating animals exposed to a toxic agent at high levels to humans at much lower levels. They also correctly identify the problem of transparency of "an agency's failure to explicitly identify the separate roles between scientific research and value choices […] in reaching a final regulatory decision" and note that "The administrative system, which includes judicial review, is grounded in a commitment to provide the public, interest groups…with an accessible and understandable explanation for regulatory decisions." She argues that the weight of evidence used in many regulations or extrapolations used in risk assessment is not science. A critical issue identified by Wagner and Michaels (2004) is the lack of transparency in the scientific aspects of the regulatory process.

Group V: There is a widespread perception that there is nothing unique about regulatory science. The proponents of this group suggest that any scientific discipline has a subset that addresses the need for a regulatory process. Consequently, there is little, if any, the commonality between various scientific disciplines as applied to the regulatory process. For example, regulatory toxicology has no more in common with regulatory hydrology than toxicology has in common with hydrology.

Group VI: This group attempts to identify the unique nature of regulatory science primarily by describing uncertainties inherent in regulatory science.

1. One of the most thoughtful authors addressing the unique nature of regulatory science was Alvin Weinberg (1972), who was the Director of Oak Ridge National Laboratory, one of the major laboratories of the then Atomic Energy Commission and now the US Department of Energy. Weinberg describes the problem saying that "the scientist is expected to say whether a trip to the moon is feasible or whether the SST [supersonic transport] will cause additional skin cancer." The politician, or some other representative [individual] of society, is then expected to say whether society ought to proceed in one direction or another." "The scientist and science provide the means; the politician and politics decide the ends." Instead of using policies, Weinberg proposed an idea and coined the term "trans-science" to address scientific issues that he perceived to be difficult if not impossible to be answered by science or scientists. He identified several of the issues that in his judgment fall into the category of trans-science. One of the examples is the effects of exposure to low levels of ionizing radiation. He suggested that it would take about 8,000,000,000 mice to evaluate the increase of mutation rate of exposure to ionizing radiation at the low dose (less than 1 Gry) exposure prevailing in 1972. Even then, he said, the mutation rate of mice may or may not be valid for humans. Another example he used was in the field of engineering. According to Weinberg, the design of a large-scale engineering project is inherently uncertain:

> Unless one is willing to build a full-scale prototype and test it under the precise conditions. There is always the uncertainty of extrapolating to new and untried circumstances. Where the device being engineered is small, like a jet engine, a full-scale prototype is customarily built, and difficulties are worked out either on the prototype or on the early production models. But where the device is huge, like the Aswan Dam or a large bridge, a full-scale prototype is out of the question. Moreover, the service life of such devices may be as long as 100 years: even if a prototype were built, there would be little sense in waiting until weaknesses appeared in the prototype before starting on the next model. Thus, in every advancing technology there are inherent elements of scientific uncertainty which as a

matter of principle can never be totally resolved. In this sense, such technologies are or at least possess trans-scientific elements.

2. Rowland et al. (2004) report that obstacles to the wider use of Physiologically Based Pharmacokinetic (PBPK) modeling include uninformed management attitudes, suboptimal organizational structures, lack of user-friendly modeling software, lack of appropriate and easily accessible relevant physiological and related databases, and the lack of adequately trained researchers in PBPK modeling. However, these obstacles can be removed if there is willingness in the pharmaceutical, regulatory, and academic communities to address them.
3. Freudenburg et al. (2008) identify a pattern of argument they label "Scientific Certainty Argumentation Methods" (SCAMs). Science is often characterized not only by certainty, but also by uncertainty—meaning that the outcomes of scientific/technological controversies may depend less on which side has the "best science" than on which side enjoys the benefit of the doubt in the face of scientific ambiguity. The benefits of doubt may be distributed in ways that are not merely random: a series of risk-related controversies, over a century, indicate that industrial interests have often managed to delay or prevent legislative and/or regulatory actions even in "tough" cases—those where the preponderance of scientific evidence had indicated significant reasons for concern.
4. In an editorial in *Nature Reviews* (Anonymous 2010), the author suggested that investment in regulatory science is desirable.
5. Drazen (IOM 2010), the Editor-in-Chief of *The New England Journal of Medicine*, suggested that regulatory science is "a science that has been evolving and is continuing to evolve, but it's not as hard as we would like."
6. Doern and Reed (2001) argue that the study of science in government needs a viable mezzo- or middle-level framework to deal adequately with the analysis of science in regulatory governance. The suggested mezzo-framework centers on five sub-processes: regulation-making and standard-setting; product approval; overall compliance; post-market monitoring; and management of the science base.
7. Demeritt (2001) addresses problems related to the scientific aspects of global climate change. He reports that the defenders of

the global warming theory try "to emphasize the sound scientific basis for climate policy decisions and to downplay the inevitably partial interpretations and professional judgments that scientific understanding involves." He recognizes that efforts to win public trust by basing policy on scientific certainty can increase public skepticism." Demeritt acknowledges that science "does not offer the final word, and its public authority should not be based on the myth, because such an understanding of science ignores the ongoing process of organized skepticism that is, in fact, the secret of its epistemic success. Instead, scientific knowledge should be presented more conditionally as the best we can do now."

8. Irwin et al. (1997) provided a sociological framework for regulatory science. They identified five categories of regulatory science covering subjects ranging from "speculative research" to "regulatory compliance testing and regulatory submissions". Irwin et al. (1997) argued that "It is immediately apparent that regulatory science is likely to be very heterogeneous in character—in institutional, geographical and specialty terms." As we will see later, Irwin et al. were right by implying that regulatory science is interdisciplinary in its character. They also stated:

> [R]egulatory science is concerned with how science can make predictions based on uncertainties. The suggestion is that science, in meeting the demands of policy, must transgress its own cognitive boundaries and limitations. It is the way regulatory science approaches these challenges that supposedly lends it a different character to 'academic' science.

9. Wait and Maney (2006) identify the problem of scientific uncertainty in regulatory science. They suggest that "Uncertainty is not only an issue with measurement process but also with the scientific underpinning of regulations and standards…and the interpretation of data." In their study, van Asselt et al. (2007) provide a comprehensive study addressing regulatory science aspects of radio frequency, electromagnetic field (EMF), and how uncertainties in the scientific foundation of risk assessment impact these.
10. Mattes et al. (2010) suggest that gaps in current scientific knowledge and practice limit the ability of regulatory agencies to carry out their mission. The FDA has advocated a "Critical Path Initiative" to address gaps in applied and regulatory science. The

Predictive Safety Testing Consortium, one of the first consortia to address Critical Path gaps, is committed to cooperative research resulting in tools beneficial to both pharmaceutical development and regulatory science (termed Critical Path Research). A key component of Critical Path Research is the participation and critical evaluations of these regulatory scientists who will later rely on the results obtained with these new tools as they are applied to the development of new pharmaceuticals.

Group VII: As stated already, the first official regulatory science program was established under the leadership of Commissioner Margaret Hamburg of the US Food and Drug Administration (FDA) in 2011. The decision of Commissioner Hamburg led to major scientific efforts within the government, industry, and academia. For the sake of simplicity, the FDA-led regulatory science activities are referred to as medical regulatory science. A summary of these activities is included in the following section.

Regulatory Science in Health and Environmental Sciences

The establishment of the regulatory science program at the FDA including commitment of funds for the activities resulted in the significant expansion of educational and research projects. Several universities established master's and PhD programs (Moghissi et al. 2011). The FDA also provided a detailed definition of regulatory science. For obvious reasons, one should not be surprised that the FDA defines regulatory science as related to its mission. The FDA commissioned two workshops organized by the Institute of Medicine, a part of the National Academy of Science, National Academy of Engineering, and National Research Council dealing with regulatory science. Similarly, the FDA initiated a cooperative activity with the National Institutes of Health (NIH) and Defense Advanced Research Projects Agency (DARPA: https://www.darpa.mil/) addressing regulatory science issues. In this sub-section, we list several definitions of regulatory science proposed by different US governmental organizations. The first three definitions demonstrate reliance upon the FDA mission in defining regulatory science. The fourth definition is provided by the EPA.

1. Regulatory science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products (FDA 2010).

2. Regulatory science is the application of scientific methods to improve the development, review, and oversight of new drugs, biologics, and devices that require regulatory approval prior to dissemination (IOM 2012).
3. Regulatory science fosters the development, evaluation, and availability of new or improved tools, methods, standards, and applied science that support a better understanding and improved evaluation of product safety, quality, effectiveness, and manufacturing throughout the product life cycle (NIH 2012).
4. Regulatory science means scientific information including assessments, models, criteria documents, and regulatory impact analyses that provide the basis for the EPA's final significant regulatory decisions (EPA 2018).

Regulatory Science as a General Scientific Discipline

As described in this chapter, regulatory science is an evolving scientific discipline with applications of varied scientific knowledge to the regulatory process. In the US the evolution of the regulatory process probably started in the late 19th century, requiring the application of many scientific disciplines to regulate various cases. One of the earliest disciplines used in the regulatory process was toxicology. Eventually many applied toxicology disciplines were developed, including regulatory, environmental, forensic, and occupational toxicology to mention a few. Regulatory science covers all scientific disciplines that are used in the regulatory process. There are certain key elements and tools that are common to virtually all regulatory science disciplines:

The first step in describing regulatory science in a broader sense is defining its nature, areas of coverage, and other relevant subjects. Although the term "regulatory science" is widely used, there have been numerous attempts to define it. Before we provide a generally applicable definition, let us first provide a brief overview of available definitions. Probably the first organization entirely dedicated to regulatory science was the Institute for Regulatory Science (RSI) established in the spring of 1985. The RSI was established based on the desire of its founders to address the scientific needs of policy makers. The selection of the term "regulatory science" appeared to be logical as regulations constituted the bulk of policies. Since its establishment, the RSI has provided several definitions that are applicable to scientific issues that must be addressed by all policy decisions, including the following:

1. Regulatory science constitutes the scientific foundation of policy decisions.
2. Regulatory science consists of scientific information that is applied to policy decisions including regulatory, legislative, and judicial decisions. Consequently, any scientific discipline that is used in the regulatory process is likely to be a part of a regulatory science discipline.
3. Regulatory sciences consist of those scientific disciplines that constitute the scientific foundation of regulatory, legislative, and judicial decisions.
4. Regulatory science is an interdisciplinary and multidisciplinary branch of science constituting the scientific foundation and tools of policy decisions including legislative, judicial, and particularly regulatory decisions (Moghissi et al. 2013).

Obviously, regulatory science has become a well-established branch of applied sciences. Thus, based on the FDA, regulatory science may be defined as follows:

> Regulatory science is a scientific discipline processes that develops and applies scientific methods, tools, approaches, and other relevant processes derived from multiple scientific disciplines to regulatory and other policy processes, and decisions.

Similarly, the EPA's definition may be generalized as follows:

> Regulatory science means scientific information, including assessments, models, criteria documents, and regulatory impact analyses that provide the basis for significant regulatory decisions.

A generic definition is as follows:

> Regulatory science consists of various scientific disciplines used in the regulatory process.

A more abbreviated and simplified definition of regulatory science is:

> Regulatory science comprises a scientific segment of the regulatory process derived from various scientific disciplines.

Disciplines Included in Regulatory Science

As described above, regulatory science covers many scientific disciplines ranging from atmospheric sciences to zoology, including toxicology,

microbiology, pharmacology, chemistry, physics, biology, and medicine, all used in the regulatory process. Therefore, discussing a specific regulatory science discipline would require reasonably detailed descriptions of the discipline and the unique structure of regulatory science. The example of regulatory toxicology may be used to demonstrate the point. Numerous papers, textbooks (e.g., Gad, 2001), and a professional society are dedicated to regulatory toxicology (ISRTP 2016). In the future, textbooks should be published on specific regulatory science disciplines.

Regulatory Science Community

Many scientific, engineering, and related professions have defined their nature and identified their role in industry, government, academia, and elsewhere. A logical description of the regulatory science profession would include the role of regulatory scientists, regulatory engineers, and regulatory specialists in other disciplines like those of other professions. There are three groups with a potential interest in the scientific aspects of regulatory decisions:

1. The staff of regulatory agencies at all levels are involved in endorsing regulations; they apply them to licensing/permissions and enforce them.
2. The regulated community consists of the staff of industries affected by regulations based on or including science.
3. Scientists—individually as well as in their professional organizations.

Science in the Executive Branch: The primary target of regulatory science is the executive branch of the government. One of the critical characteristics of regulatory science is that it frequently attempts to predict future events and thus must contend with inherent uncertainties. Traditionally, the objective of a large fraction of regulatory science is evaluating virtually all areas that would impact society, such as the protection of human health or the preservation of natural resources, including the ecosystem, safety, and the economy. A significant part of regulatory science consists of evaluating an existing situation or condition, evaluating a proposed action, or prohibiting the continuation of an existing condition. Consequently, risk assessment and managing an assessed risk are prevalent aspects of regulatory science.

Science in Courts: Many court cases deal with scientific issues. Traditionally, in the legal system of many countries, both the defense and

the prosecution have the right to present expert witnesses who testify on relevant subjects—including scientific evidence. Over the years, the advancement of science has provided unique tools to either prove or reject a legal claim. All industrial countries and many others with an operating legal system must address scientific issues in their respective courts. In the US, an increasing variety of courts address scientific issues. Like many other countries, in the US there are local, regional, and federal court systems. The highest federal court in the US is the Supreme Court, located in Washington DC. According to the US system, many decisions—including some in local and regional courts—reach the US Supreme Court for conclusiveness. In recent years, various courts have attempted to address legal issues that include science.

Science in Legislation: In virtually every form of government, the legislative branch presents laws that may or may not require science. It is important that a reasonable legislative body relies upon good science.

Key Elements and Tools of Regulatory Science

As regulatory science has evolved, the need for various scientific tools has been identified and developed. Many errors have been made during this process, and their corrections required significant efforts. The occurrence of the errors has not only been due to the complexity of the subject but also the influence of advocacy organizations. One of the key problems has been the need for clarification in communicating scientific issues among those who were involved in the regulatory process. The education, training, and experience of these individuals has been in disciplines ranging from physical and biological sciences to engineering, medicine, social sciences and law. Regulatory science is still evolving, and so are its tools. The primary tools that are known to be used by regulatory science disciplines include:

I. Assessment of the Level of Maturity and Reliability of Regulatory Science: One of the key elements of regulatory science is the Metrics for Evaluation of Regulatory Science Claims (MERSC) derived from the Best Available Regulatory Science (BARS) concept. The BARS/MERSC system addresses the maturity and reliability level of science used in the regulatory process. Another critical and often violated requirement excludes non-scientific issues such as societal objectives, ideology, and faith in regulatory science.

II. Peer Review: Another significant element of regulatory science is independent peer review. The process requires addressing the qualifications and independence (no conflict of interest) of reviewers, review criteria (questions addressed to the reviewers), potential oversight of the process, and other subject details.

III. Scientific Transparency and Communication: Although the affected community values the transparency and communication of regulatory science to the public, the practice of accommodating how scientific information is described to the community so that the relevant communities understand the key issues has also been recognized.

IV. Regulatory Science Ethics: This tool has a significant impact for regulatory science as it describes the unique ethical requirements of regulatory science.

V. Stakeholder Participation: The laws in developing regulations should include their scientific foundation and public participation. Certain rules have specific stakeholder participation. However, the regulatory science process requires the identification of stakeholders and the need for interaction with them, particularly those who are directly or personally impacted by a proposed action.

VI. Risk Assessment: One of the relevant regulatory science tools is risk assessment, the key element of risk management. Within it plausible risk assessment, health risk assessment, and ecological risk assessment, for example, are included.

VII. Mathematical Models: Due to the unique nature of regulatory science, regulatory scientists are often forced to use mathematical models to quantify future risk events. Mathematical models are frequently the only available tool to estimate the consequences of an action or lack of an action. Despite their critical usefulness, the limitation of their results should be addressed.

VIII. Voluntary Standards: Professional societies and other scholarly organizations develop standards often based on scientific principles. Voluntary standards are another tool of regulatory science.

IX: Economics: Economics as a tool is based on the idea that a proposed action, management of a risk based on risk assessment, and other regulatory science activities require computation of their economic consequences.

Evolution of Regulatory Science

Many regulatory science investigators have struggled with how to address the relationship between science and policy (Moghissi et al. 2014a, 2014b). There are those who claim that due to the uncertain nature of regulatory science, it is not only desirable but necessary to include societal objectives in regulatory science. During the initial phases of its operation, the EPA justified its scientific decisions based on its desire to be "protective of the population and the environment." However, one of the questions repeatedly raised was how protective is protective enough? As many segments of the regulatory science community felt that EPA decisions were too arbitrary. The US Congress mandated the National Academy of Sciences to review many activities of the EPA. Note that these reviews were performed independently by the National Academies (National Academy of Sciences, National Academy of Engineering, and National Academy of Medicine, including their research arms: National Research Council and the Institute of Medicine).

During the last half of the 20th century, many laws were passed in the United States, particularly during the 1970s, addressing the societal needs of people in the country through regulations. In most—if not all—cases, the promulgation of regulations mandated by these laws required scientific decisions. The evolution of regulatory science at least as used in the US occurred in three phases:

1. Initial phase
2. Exploratory or transitional phase
3. Standard operational phase

In the following discussion, we use two agencies to address the evolution of regulatory science: the FDA and the EPA. The FDA has a history of over a century and its mission is focused on the discussion. In contrast, the formation of the EPA was the result of significant political upheaval, and its mission is extensive. Furthermore, as in many cases, scientific information was needed to improve circumstances in the United States as shown below. The Administrator of the EPA was given significant autonomy in making decisions.

Initial Phase: This phase is characterized by insufficient scientific information for state regulations. In the case of the FDA, this phase was reasonably completed in the 1970s or 1980s. In contrast, during the initial phase of the EPA's history, which lasted about a decade, the

administrators used a process, including ***Best Available Information***, ***Best Available Technical Information***, or most appropriately ***Most Relevant Available Information***. The managers decided to use scientific information that they considered to be the most relevant, ranging from "peer-reviewed and credible scientific information" to the "opinion of an individual who, according to the opinion of EPA managers, was relevant and credible." For example, to protect one's health and environment from pollutants, they chose what they called the "conservative" approach, by often overestimating the pollutant's effects on human health and environment. During this period, the independent peer review process was virtually unknown.

Exploratory Phase: The next decade of the EPA's history could be appropriately called the transitional or exploratory phase. That phase started with the reappointment of William Ruckelshaus as Administrator by President Reagan and continued with his successor, Lee Thomas. These administrators attempted to move the scientific foundation of regulatory decisions from the initial phase to a process that would be scientifically more acceptable. Numerous decisions by the US Congress required consultation with the National Academies. At the FDA, this phase was marked by the study performed by the National Academies (NAS 1993), the development of processes to speed up the approval of drugs and medical devices, and the formalization of the process to withdraw drugs or limit their applicability.

Standard Operational Phase: One of the primary activities during the standard operating phase of regulatory science has been the reassessment of decisions made during the initial phase using scientific advancements (including regulatory science tools). Particularly, as many of the regulatory decisions rely upon partially reproducible and evolving science, the objective of this phase has been to enhance the level of reproducibility of regulatory science. For example, the information in this phase could be moved from slightly reproducible and evolving science to mostly reproducible and evolving science to fully reproducible and evolving science.

In recent years, the process of reevaluating approved drugs has significantly advanced. Accordingly, the FDA has required the withdrawal of several drugs and has also identified limitations in the usefulness of drugs. At the EPA, there are mandates in the Drinking Water Act and Clean Air Act to review relevant standards periodically. However, in most

cases, the standards have remained unchanged or have become more limited.

The Need for Recognizing the Unique Nature of Regulatory Science

Recognizing regulatory science as a legitimate scientific discipline has taken some time. There are those who claim that regulatory science is different from normal research or other scientific processes. The followings are several arguments that support or oppose regulatory science as a scientific discipline.

1. There is a wide-spread view that regulatory science consists of the application of various scientific disciplines in circulating specific regulations. Therefore, there is no generic regulatory science and thus there is no commonality among various scientific disciplines used in the regulatory process. What is being overlooked is that the unique nature of regulatory science includes the tools that are used by virtually all regulatory science disciplines.
2. Others claim that regulatory science inherently includes uncertainties and thus it does not qualify as science. What is being overlooked is that in most cases, the objective of scientific research is to reduce uncertainties in scientific knowledge. As science evolves the level of uncertainties is reduced based on the advancement of scientific knowledge.
3. Decisions based on uncertain information are not limited to regulatory science. Weather reports on adverse conditions are typically associated with various levels of uncertainty. The predictions on the pathway and the severity level of hurricanes such as Irene and Sandy changed with time based on the information resulting from evolution of the hurricanes. If one accepts arguments about regulatory science as described in this chapter, the legitimate question would be: Is meteorology a scientific discipline?
4. Some argue that regulatory science as described above is, in fact, a compilation of many disciplines and thus it does not qualify as a scientific discipline. Based on that argument, one can ask if chemistry is a scientific discipline. There are many disciplines included in chemistry: analytical chemistry, biochemistry, environmental chemistry, electrochemistry, combustion chemistry,