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INNOVATION IN REGULATORY SCIENCE: EVOLUTION OF A NEW SCIENTIFIC DISCIPLINE

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Regulatory science is increasingly recognized as an evolving science serving regulatory and other policy decisions. This article reviews the evolution of regulatory science and how various authors and organizations have defined it. The article identifies various tools, including Metrics for Evaluation of Regulatory Science information, peer review, risk assessment, scientific assessment, and economics. Subsequently, the article describes three phases of regulatory science consisting of the initial phase when decisions were made using inadequate scientific information, the exploratory phase when various tools were developed, and the standard operating phase when tools are used to reevaluate decisions made during the initial phase. The article concludes by indicating the need for transparency in regulatory science by identifying assumptions, judgments, and related processes during the regulatory science process.

Key words: Best available science; Regulatory science metrics; Definition of regulatory science; History of regulatory science; Regulatory science tools

INTRODUCTION

There is a long tradition on the interaction between science and policy. Prior to the late 19th or 20th century, the scientific community played an insignificant—if any—role in the societal decision process. Accordingly, governmental authorities, such as theocracies, emperors, kaisers, kings, and other rulers, were in charge of all decisions that established rules; hence, science was either not considered or played a minor role in the decision process. In many cases, religious leaders interpreted religion to cover rules regardless if they did or did not have scientific parts. Another key reason was during that period science was either insufficiently advanced or intermingled with beliefs—including superstition—thus making it difficult to cover all but a few subjects of societal interest.

Meanwhile, the advancement of various industries resulted in the desire of the public to regulate relevant aspects of their operations, including mining, manufacturing, agriculture, air pollution, drinking water, water pollution, and food safety—to mention a few. The legislators, regulators, and the public recognized that regulating these activities required the availability of relevant scientific information—or simply regulatory science.

Although in the US the office of the Comptroller of the Currency was established in 1863, probably the oldest regulatory agency in the US with interest in regulatory science was the *Bureau of Chemistry*, which was established in 1906 (29) with the responsibility to ensure that the public is protected from "manufacture, sale, [and] transportation of adulterated or misbranded, or poisonous or deleterious foods, drugs, medicines, and liquors." Eventually the Bureau of Chemistry became the Food and Drug Administration (FDA) whereby its mission was expanded, making it one of the most influential regulatory agencies in the US.

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Another major development was the formation of the United States Environmental Protection Agency (EPA), resulting in part from demands of the consumer advocacy and environmental movement. Many other regulatory agencies were established in the US in the latter part of the 20th century, including the Nuclear Regulatory Commission, Occupational Safety and Health Administration, Fish and Wildlife Service, Mine Safety and Health Administration, and Marine Fisheries Service.

A number of contested decisions of regulatory agencies are traceable to their history. The example of the EPA can be used to demonstrate the point. President Nixon established the EPA in December of 1970 by combining a number of organizations from various federal agencies. However, upon its formation, the EPA faced a number of legally mandated deadlines. Thus, during the early history of the EPA, many laws were enacted or reauthorized, including the Federal Insecticide, Fungicide, and Rodenticide Act (34); Safe Drinking Water Act (36); Toxic Substances Control Act (37); Clean Water Act (32); and Clean Air Act (31).

There were many other relevant events during that period. The passage of the Endangered Species Act in 1973 (33) mandated promulgation of regulations by the Fish and Wildlife Service of the United States Department of Interior and the National Marine Fisheries Service, an organization within the National Oceanic and Atmospheric Administration of the United States Department of Commerce. Based on a movement fighting all nuclear activities—particularly nuclear weapons—the then-powerful Atomic Energy Commission was divided into two parts: The first part took over the bulk of activities of that agency and was subsequently renamed, constituting the current Department of Energy. The regulatory responsibilities of the Commission were transferred mostly to the newly formed United States Nuclear Regulatory Commission with the EPA getting the regulatory responsibility for environmental radiation exposure. Other major events during that period included the passage of the Occupational Safety and Health Act in 1970 (35), mandating relevant regulatory activities to be performed by the Occupational Safety and Health Administration, an organization within the United States Department of Labor.

As we will see later in this article, these and many other laws mandated a deadline for the development of regulations by each affected regulatory agency. Given the shortage of available time, the agencies had to make decisions based on incomplete science. The term "regulatory science" was coined during this period with the objective to address the scientific needs of regulatory agencies.

HISTORICAL OVERVIEW OF EVOLUTION OF REGULATORY SCIENCE

There is extensive literature on the perception of many investigators on how to make decisions based on uncertain scientific information. As expected, those involved in social sciences, law, and related disciplines have dominated the literature dealing with regulatory science. However, in recent years, the FDA has introduced the term "regulatory science" to describe its scientific activities. In writing this article, we made no attempt to cover the existing literature comprehensively. Instead, we provide an overview of the topic.

The emergence of the term "regulatory science" probably occurred shortly after the formation of the EPA in 1970. The term first appeared in an internal memorandum to describe the science used to develop regulations by that agency. Initially, the term was not accepted, the justification being that there is nothing unusual about science used in developing regulations (21). It was argued that "science is science" regardless of its application. However, the establishment of the Institute for Regulatory Science in 1985 (21) legally established an organization with that term in its title. The establishment of several regulatory agencies did not result in the recognition of the need for a new scientific discipline. Consequently, an admittedly less-than-comprehensive literature search in early 1985 did not find the phrase "regulatory science" in the literature to describe how science was used in the development of regulations, enactment of legislation, judicial decisions, or any other policy decision. In contrast, in March of 2014, an Internet search for "regulatory science" identified over 200,000 entries—indicating that it is extensively used not only in English but also in other languages, including German (*regulatorische Wissenschaft*) and French (*science de la réglementation*).

Initially, 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, as we shall see later, there were major problems and significant discourse in the society as a whole and dissatisfaction within the regulated community on how the subject was managed. The appearance of regulatory science discipline was—if not entirely but predominantly—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 a variety of policy activities, including regulatory decisions. A closer look at the subject indicates that regulatory science includes nearly all scientific disciplines. Moreover, it has been difficult to categorize relevant scientific information, particularly as related to the definition of regulatory science, its evolution, and its current status. In order 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 relevant published information. However, we recognize that the subject is complex, and the information that we have placed in a specific category may be disputed by the relevant authors. The studies dealing with the nature and application of regulatory science can be generally categorized as follows:

Group I

This group claims that regulatory science consists of the need for scientific approaches to comply with regulations. Although the number of papers and books in this category is not very large, apparently such a view is widespread, particularly within the regulated community. According to this group, various regulations need to be identified and their scientific basis evaluated. Subsequently, appropriate scientific procedures and methods are to be identified or developed to comply with the regulations.

1. The compilation of information in the book edited by Gad (10) demonstrates the views of various authors on how scientific disciplines, such as toxicology and pharmacology, can be used to comply with relevant regulations.
2. Petricoin et al. (26) 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 not be the same for all applications of genomic and proteomic microarrays but, instead, are likely to be highly dependent on context. The level of scientific rigor for microarray performance is likely to differ depending on whether the microarray is being used for early drug discovery and hypothesis generation or as a clinical device to make diagnostic, therapeutic, or prognostic decisions for patients.
3. Henry and Conrad (11) argue that only one set of standards and practices should be used to judge the quality of scientific work in a given 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 treatments for regulatory science would face severe scrutiny in light of that authority and would be difficult to administer.

Group II

Based on the experience of many individuals, this group claims that regulatory science consists of advising government agencies on scientific issues. This group correctly claims 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, there are also numerous committees and panels serving their respective governments. For example, Ilieva (12) reports that scientists involved in the regulatory process are experts assuming advisory functions, but they 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."

Group III

This group makes a distinction between regulatory science and conventional, research, normal, academic, and other science. According to this group, regulatory science is not the same as normal science or research science.

1. Sheila Jasanoff (16,17) is one of the most articulate members of this group. She attempted to address the needs of regulatory science by making a distinction between "research science" and "regulatory science." She identified various categories of scientific information consisting of 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," consists of combining scientific information to address the needs of the regulator process. Finally, the third component that Jasanoff considered to be unique to regulatory science is its predictive nature. She also identified numerous highly contested decisions of regulatory agencies—notably the EPA. Jasanoff provided an overview of interaction between the scientists and regulatory agencies and how these interactions impact regulatory science.
2. Another member of this group is Rushefsky (28), who made a distinction between "normal science" and "regulatory science." He defined regulatory science as "science with specific and public policy implications or with public policy agenda."
3. Uchiyama (30) claimed that regulatory science is valuable and can be called "evaluation science" and suggested that regulatory science is neither basic nor applied research.
4. A center within the University of Colorado (3) provides an interesting distinction between "academic science" and "regulatory science." The information provided by the center compared the goal of academic researchers with science upon which policies are made. For example, the center claims that whereas academic science uses "published papers, presentation at professional meetings, regulatory science relies upon gray literature, baseline data, monitoring data, [and] regulatory documents."
5. Abraham (1) suggested that there are two cultures in regulatory science consisting of 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."
6. Funtowitz and Ravetz in a series of books and other publications (8,9) coined the phrase "post-normal science." They suggested that the level of uncertainty of science increases as follows: applied science → professional consultancy → post-normal science.
7. Melnyk (19) 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 for political and economic manipulation. Post-normal science is a concept for exploring alternative regulatory arrangements and how decisions can be enhanced both in terms of their democratic accountability and in the reduction of risks. Melnyk concluded 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 that diminish the willingness of actors to engage in dialogue and reach a mutual understanding.
8. Neff and Goldman (25) 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 evidence for the sole purpose of delaying health-protective regulation. Neff and Goldman concluded that while "sound science" as regulatory tools can be used to improve decision quality, they can also challenge the government's ability to safeguard the public's health and well-being.
9. Wagner (38) claimed that, "Science teases policymakers with the prospect of providing

definitive [scientific] guidance for regulatory decision making." She correctly identified problems in extrapolating animals exposed at high levels to a toxicant to humans at much lower levels. She also correctly identified the problem of transparency of "an agency's failure to explicitly identify the separate roles scientific research and values choices play in reaching a final regulatory decision," and "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 argued that the weight of evidence used in many regulations or extrapolation used in risk assessment is not science. An important issue identified by Wagner is the lack of transparency in the scientific aspects of the regulatory process.

Group IV

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 (40), the then-director of Oak Ridge National Laboratory, one of the major laboratories of what was then the Atomic Energy Commission and is now the United States Department of Energy. Weinberg 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 a number of issues that in his judgment fall into the category of trans-science. One of the examples was the effects of 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 levels prevailing in 1972. Even then, 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.
2. Rowland et al. (27) reported that obstacles to the wider use of physiologically based pharmacokinetic 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 lack of adequately trained researchers in PBPK modeling. However, according to the author, these obstacles can be removed if there is willingness in the pharmaceutical, regulatory, and academic communities to address them.
3. Freudenburg et al. (7) identified a pattern of argument they label "Scientific Certainty Argumentation Methods." According to Freudenberg, science is often characterized not by certainty, but 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 period of nearly 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 a report of the Institute of Medicine Drazen (13), the editor-in-chief of *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."
5. Doern and Reed (5) argued 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 subprocesses: regulation making and standard setting, product approval, overall compliance, postmarket monitoring, and management of the science base.
6. Demeritt (4) addressed problems related to the scientific aspects of global climate change. The author reported 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." The author recognized that

efforts to win public trust by basing policy on scientific certainty can actually increase public skepticism. Demeritt acknowledged that science does not offer the final word, and its public authority should not be based on the myth that it does, 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 that we can do for the moment."

7. Irwin et al. (15) 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. 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 that "regulatory science is concerned with how science can make predictions on the basis of uncertainties. The suggestion is that science in meeting the demands of policy has to transgress its own cognitive boundaries and limitations. It is the manner in which regulatory science approaches these challenges that supposedly lends it a different character to "academic science."
8. Wait and Maney (39) identified 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 paper, Asselt et al. (2) provided a comprehensive study addressing regulatory science aspects of nonionizing radiation (RF/EMF) and how these are impacted by uncertainties in the scientific foundation of risk assessment.
9. Mattes et al. (18) suggested that gaps in current scientific knowledge and practice limit the ability of regulatory agencies to carry out their mission. According to Mattes et al., the FDA has advocated a "Critical Path Initiative" to address Critical Path Research in applied and regulatory science. A key component of Critical Path Research is the participation and critical evaluations of the regulatory scientists who will later rely on the results obtained with these new tools as they are applied to the development of new pharmaceuticals.

WHAT IS REGULATORY SCIENCE?

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 established in the spring of 1985. The Institute for Regulatory Science 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 Institute for Regulatory Science has attempted to provide a definition that is applicable to scientific issues that must be addressed by all policy decisions. There were several attempts to define regulatory science as follows:

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 include 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 consists of application of science in policy decisions.

Accordingly, regulatory science includes regulatory pharmacology, regulatory toxicology, regulatory medical devices, regulatory hydrology, regulatory ecology, and regulatory atmospheric sciences—to mention a few. Given the evolution of regulatory science for several decades, it is not surprising that several definitions appeared by the same authors. In their book, Moghissi et al. (20) provide the following definition:

> 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.

Among the US government agencies, the FDA has led both the definition and application 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 component 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) addressing regulatory science issues. The following three definitions are similar and demonstrate reliance upon the mission of the FDA in defining regulatory science:

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 (6).
2. Regulatory science is the application of the scientific methods to improve the development, review, and oversight of new drugs, biologics, and devices that require regulatory approval prior to dissemination (14).
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 (23).

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

> Regulatory science is a scientific discipline consisting of the development and application of scientific methods, tools, approaches, and other relevant processes derived from various scientific disciplines used in regulatory and other policy decisions.

An abbreviated version of this definition would be "*regulatory science consists of the application of science in policy decisions.*"

APPLICATION OF REGULATORY SCIENCE IN VARIOUS BRANCHES OF GOVERNMENT

As the above definition indicates, regulatory science is used by all branches of government in policy decisions that include science, are based on science, or apply scientific tools.

Science in Legislation

In virtually every form of government, the legislative branch enacts laws that may or may not comply with requirements of science. One would hope that a reasonable legislative body would rely upon acceptable science.

Science in Executive Branch, Notably Regulatory Agencies

The primary target of regulatory science is the executive branch of the government. One of the key 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 safety, protection of human health, preservation of natural resources including the ecosystem, and the economy. A major part of regulatory science consists of evaluating an existing situation or condition, evaluating a proposed action, or prohibiting the continuation of an existing condition, to mention a few.

Science in Courts

There are many court cases that deal somewhat, predominantly, or entirely, 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 issues. Over the years, the advancement of science has provided unique tools to both prove and reject a legal claim. All industrial countries and many others with an operating legal

system must and do deal with scientific issues in their respective courts. In the US, increasingly, various courts must address scientific issues. Much 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 the final decision. In recent years, various courts have attempted to address legal issues that include science.

Regulatory Science Tools

As regulatory science evolved, the need for various scientific tools was identified and developed. During this evolution, many errors were made, and their corrections required significant efforts. The occurrence of the errors can be readily explained not only by the complexity of the subject but also by the influence of advocacy organizations. One of the key problems was the difficulties in communicating scientific issues among those involved in the regulatory process, as the education, training, and experience of these individuals included many disciplines ranging from physical and biological sciences, engineering disciplines, and medicine to social sciences and law. As regulatory science is evolving, so are its tools, particularly those that are known to be used by many regulatory science disciplines.

1. One of the key tools of regulatory science is identification of the levels of maturity and reliability of science, as well as the inclusion of areas outside the purview of science in the regulatory process. As described by Moghissi et al. (22), the concept of Best Available Science (BAS) and Metrics for Evaluation of Scientific Claims (MESC) provided the opportunity to develop Metrics for Evaluation of Regulatory Science Information (MERSI). The principles upon which BAS/MERSI are based consist of open mindedness, skepticism, universal scientific principles (USP), and transparency and reproducibility.

   These principles led to three pillars. The first pillar deals with classification of scientific information (SI) in terms of its level of maturity. This pillar includes proven SI, evolving SI, borderline SI, and identification of fallacious information. Note that regulatory science overwhelmingly uses evolving and borderline SI. Another pillar addresses the reliability of scientific information consisting of four categories starting with personal opinion and gray literature. The third category, independent peer review, is considered to be the primary source of SI to be applied to regulatory science needs. The fourth category in this pillar is consensus-processed SI. The final pillar identifies areas outside the purview of science, one of the primary reasons for the problems that decision makers have faced. Unfortunately, they did not consider the need for excluding information containing areas outside the purview of science from the SI used in their decisions.
2. Another significant tool of regulatory science is independent peer review. Elements of peer review include assessment of qualifications and independency (lack of conflict of interest) of reviewers, review criteria (questions provided to the reviewers), potential oversight of the process, and other details of the subject.
3. Risk assessment is also a major tool of regulatory science, as it is to be used in risk management, a key policy decision. Included are probabilistic risk assessment, health risk assessment, and ecological risk assessment.
4. Independent scientific assessment provides a tool to evaluate the scientific status of a subject of regulatory concern. There appears to be confusion between scientific assessment and peer review. Although the processes used to perform peer review and scientific assessment are identical, their objectives are different. Whereas peer review attempts to verify the validity of a scientific claim, scientific assessment is expected to address the status of science, particularly when there are contradictory scientific data and information, including those in peer-reviewed literature.
5. Scientific, including medical, communities have developed ethical requirements to be met by their respective members. The detailed description of regulatory science ethics is beyond the scope of this article. However, key regulatory science ethical requirements must be addressed in this article. All regulatory science documents must provide to the affected community not only assumptions, judgments, and similar parts but also potentially reasonable alternatives.

Furthermore, they should include conclusions that may be derived for alternative assumptions, judgments, and similar parts in a language understandable to a knowledgeable nonspecialist.
6. Other tools of regulatory science include voluntary standards developed by professional societies and other scholarly organizations, public and stakeholder participation, and economics, notably cost–benefit analysis.

EVOLUTIONARY PHASES OF REGULATORY SCIENCE

During the initial phases of regulatory science, there was a perception that scientists within the regulatory agencies constituted the regulatory science community. However, as regulatory science evolved, it became clear that many other scientists were involved in regulatory science.

A closer look at the subject indicates that there are three groups with potential interest in the scientific aspects of regulatory decisions:

1. The staff of regulatory agencies at all levels who are involved in promulgating regulations, who apply them to licensing/permitting, and who enforce them
2. The regulated community consisting of the staff of those industries that are affected by regulations that are based on or include science
3. Scientists—individually, as well as their professional organizations

As stated above, during the last half of the 20th century, a large number of laws were enacted in the US, particularly during the 1970s, addressing the societal needs of the US. 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, 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. In contrast, as stated above, the formation of the EPA was the result of significant political upheaval, and its mission was exceptionally broad. Furthermore, as in many cases, the needed scientific information was inadequate or nonexistent, and the administrator of the EPA was given significant latitude in making decisions.

Initial Phase

This phase is characterized by lack of sufficient scientific information to promulgate regulations. In the case of the FDA, this phase was reasonably completed sometime in the 1970s or 1980s. In contrast, during the initial phase of the EPA's history that lasted more than a decade, the administrators used a process that has been known by several terms, including Best Available Information, Best Available Technical Information, Best Available Technology, or most appropriately, Most Relevant Available Information (MRAI). In effect, the managers decided to use scientific information that they conceived to be the most relevant, ranging from peer-reviewed and credible scientific information to personal opinion of an individual who, according to the opinion of EPA managers, was relevant and credible. For example, in order to be protective of the health and environmental effects of pollutants, they chose what they called the "conservative" approach and thereby overestimated—and often significantly overestimated—the human health and environmental effects of the pollutant. During this period, the independent peer-review process was virtually unknown.

Exploratory Phase

The next period of evolution of regulatory science could be appropriately called the transitional or exploratory phase. At the EPA, that phase started about 1980 with the appointment of William Ruckelshaus and 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 Congress required consultation with the National Academies. At the FDA, this phase was marked by the study performed by the National Academies (24), 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 is the reassessment of decisions made during the initial phase using scientific advancements, notably regulatory science tools. In particular, as many of the regulatory decisions rely upon regulatory science information that includes assumptions and judgments, the objective of this phase is to enhance the level of reproducibility of regulatory science.

A description of the current status of various regulatory decisions is beyond the scope of this article. However, it is worth mentioning that, in recent years, the process of reevaluation of the approved drugs has significantly advanced. Accordingly, the FDA has required the withdrawal of a number of drugs and has identified limitations of usefulness of other drugs. At the EPA, the Clean Air Act requires periodic reevaluation of standards for numerous air pollutants, including ozone, nitrogen oxides, and particulate matter. Similarly, there are mandates in the Drinking Water Act to periodically review drinking water standards.

CONCLUSIONS

Based on the information included in this article, it has taken some time to recognize regulatory science as a legitimate scientific discipline.

1. The term "regulatory science" is justified, as scientific aspects of the regulatory process are dominant despite the fact that regulatory science also covers legislative and judicial branches of government.
2. Regulatory science includes all scientific, including engineering, disciplines that are used in policy, notably regulatory decisions.
3. At least in the US, regulatory science has passed its initial phase. Although the need for developing new regulatory science tools cannot be ruled out, it is likely that for the immediate future the currently available tools are sufficient for regulatory agencies to operate in the standard operating phase.
4. The regulatory agencies would benefit from complying with the key ethical requirement of regulatory science related to transparency. They should provide the affected community and the general public with their assumptions, judgments, and related decisions. They should also describe if they have included a societal issue in their decisions. Finally, all of these have to be made available to the public in a language that is understandable to the recipients.

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