

Regulatory Science: The Maturation of an Evolving Scientific Discipline

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Abstract

Regulatory science encompasses the participation of a large array of scientific disciplines involved in the regulatory process. Although each discipline addresses different phenomenology and exploits different methodologies, the common scientific core is the same: objective pursuit of verifiable and useful knowledge. This paper updates the definition and scope of the practice of regulatory science, starting with a concise historical overview. It then examines the different phases of regulatory science applications: initial, exploratory, and standard operating. The paper also reviews the definitions of regulatory science used by various agencies and provides abbreviated scientific definitions. The paper summarizes Best Available Regulatory Science (BARS) and Metrics for Evaluation of Scientific Claims (MERSC), along with key elements and tools of regulatory science: peer review; regulatory science ethics, including the so-called Jeffersonian principle; mathematical models; cost benefit analysis; and stakeholder participation. The paper concludes with a brief description of these key tools and elements, highlighting their importance in the field of regulatory science.

1. Introduction

Since the publication of our most comprehensive paper (Moghissi et al., 2014), the regulatory science discipline has significantly progressed in terms of fundamentals and tools. There is a long tradition of interaction between science and policy dating to the earliest civilizations.

However, prior to the sufficient evolution of relevant science, the scientific community played an insignificant—if any—role in societal decision processes. Accordingly, governmental authorities, such as theocracies, emperors, kaisers, kings, and other rulers, made decisions based on traditionally established rules. Hence, science was either

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not considered or played a minor role in the decision process. Often religious leaders interpreted religion to be the primary basis for rules because science was not only insufficiently advanced but was mixed with unfounded beliefs.

Industrial development led to the formation of agencies and private organizations that promoted the advancement of relevant science and technology and regulated health and safety of operations. The public, particularly legislators, recognized the need for the availability of relevant scientific information—or simply regulatory science.

In the United States, the office of the Comptroller of the Currency was established in 1863. However, the first U.S. agency with an interest in regulatory science was the Bureau of Chemistry, which was established in 1906 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.” The need for expansion of the mission of the Bureau of Chemistry led to the formation of the Food and Drug Administration (FDA), one of the most influential regulatory agencies in the United States to date. Today other U.S. regulatory agencies include the Environmental Protection Agency (EPA); the Occupational Safety and Health Administration (OSHA); Fish and Wildlife Service (FWS); Mine Safety and Health Administration (MSHA); National Marine Fisheries Service (or NOAA Fisheries); and the Nuclear Regulatory Commission (NRC). (FDA 2010)

The formation of additional regulatory agencies did not result in the recognition of the need for a new scientific discipline. As described in our previous paper (Moghissi et al., 2014), the term “regulatory science” was initially used shortly after the formation of the EPA in 1970, in an internal memorandum that described the science used to develop regulations by that agency. As expected, the term was not accepted, claiming that there was nothing unusual about science used in developing regulations—“science is science” regardless of its application. We struggled to describe and bound this emerging scientific discipline under one term. However, the Institute for Regulatory Science was established in 1985, using the term in its legal name.

The substantial increase both in numbers and complexity of FDA regulations led to the formation of the International Society of Regulatory Toxicology and Pharmacology in 1980. The primary objective of that society was to assist the regulated community in achieving compliance with FDA regulations. As a result, FDA eventually recognized the need for defining regulatory science.

The advent of a new regulatory science discipline was largely a response to societal needs for a more appropriate process. Initially, the scientific needs of regulatory processes 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 and significant

discourse in society as a whole and dissatisfaction within the regulated community on how the subject was managed. In their papers Moghissi et al. (2014) attempted to define regulatory science:

- **Group I** claimed that regulatory science consists of the need for scientific approaches to comply with regulations (Gad, 2018).
- **Group II** claimed that about 1,000 advisory panels to government agencies on scientific issues formed the core of regulatory science.
- **Group III**, led by lawyers, made a distinction between regulatory science, conventional research, academic, and other categories of science, stating that “a science teases policymakers with the prospect of providing definitive [scientific] guidance for regulatory decision making” (Moghissi, et al., 2014).
- **Group IV** attempted to identify the unique nature of regulatory science primarily by describing uncertainties inherent in regulatory science. Alvin Weinberg (1970), a renowned physicist and Director of Oak Ridge National Laboratory, 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.

Other attempts were made to provide definitions that address the application of science in all policy decisions, including the following:

- Regulatory science constitutes the scientific foundation of policy decisions.
- Regulatory science consists of scientific information that is applied to policy decisions, notably regulatory.

2. The Evolution of Regulatory Science

In the early stages of regulatory science, there was a perception that scientists working in regulatory agencies constituted the regulatory science community. However, as regulatory science advanced, it became evident that many other scientists were engaged in regulatory science work. Eventually, it was recognized that the regulatory science community consists of three distinct groups:

1. The staff of regulatory agencies at all levels are engaged in the application of regulations to licensing and permitting and the dissemination and enforcement of regulations.
2. The regulated community, consisting of the staff of those industries affected by regulations, which themselves are based on or include science.
3. Scientists, individually and as representatives of their professional organizations.

During the last half of the twentieth century, particularly during the 1970s, many laws were enacted in the United States to address societal needs. In most if not all cases, the promulgation of regulations mandated by

these laws required scientific decisions. Two agencies were particularly instrumental in the evolution of regulatory science: the FDA and the EPA. At the time, the FDA—in existence for more than a century—was well established and its mission highly focused and well understood by the public. In contrast, the formation of the EPA was the result of significant political upheaval, and its mission was exceptionally broad. Furthermore, the needed scientific information was inadequate or nonexistent, and the administrator of the EPA was given significant latitude in making decisions.

The evolution of regulatory science in the United States occurred in three phases:

Formative Phase: Characterized by lack of sufficient scientific information to promulgate regulations, this phase lasted more than a decade for the EPA. Unlike the FDA, which completed this phase sometime in the 1970s or 1980s, the EPA took a different approach. EPA administrators relied on a process known by various terms including Best Available Information, Best Available Technical Information, Best Available Technology, or most appropriately Most Relevant Available Information.

Essentially managers used scientific information they believed to be the most relevant, ranging from peer-reviewed and credible scientific information to the opinion of credible individuals. In order to be protective of the health and environmental effects of pollutants, for example, they adopted a “conservative” approach, often significantly overestimating the human

health and environmental effects of pollutants. Independent peer review processes were rarely utilized during this period.

Exploratory Phase: This transitional phase started at the EPA about 1980 with the re-appointment of Administrator William Ruckelshaus and his successor, Lee Thomas. These administrators attempted to establish a scientifically acceptable process for the foundation of regulatory decisions. During this period, many decisions made by Congress mandated consultation with the National Academies of Sciences (National Academies). For example, the National Academies was tasked with a study for the FDA to develop and formalize processes to speed up the approval of drugs and medical devices and to withdraw drugs or limit their applicability when necessary.

Standard Operational Phase: Today regulatory science focuses primarily on applying scientific advancements, notably regulatory science tools, to decisions made during the initial phase. This phase aims to enhance the reproducibility of regulatory science findings by taking into account the assumptions and judgments involved in regulatory decision-making.

3. Regulatory Science as a Scientific Discipline

As the field of regulatory science continues to develop, its elements and tools are also advancing, particularly those used by various regulatory science disciplines. However, along this evolutionary path, numerous errors have been made within the

scientific process that require significant effort to rectify. These errors can be attributed to the complexity of the subject matter, as well as the influence of advocacy organizations. One major obstacle is the difficulty in effectively communicating scientific issues among the individuals involved in the regulatory process. This challenge stems from the fact that the education, training, and experience of these individuals spans a broad range of disciplines, including physical and biological sciences, engineering, medicine, social sciences, and law.

3.1 Definition of Regulatory Science Discipline

The FDA led both the definition and application of regulatory science since it defines regulatory science as related to its mission. According to the FDA, “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” (Food and Drug Administration (2010); and see Food and Drug Administration (2022). The EPA proposed a rule that included a definition for regulatory science: “Regulatory science means scientific information including assessments, models, criteria documents, and regulatory impact analyses that provide the basis for EPA’s final significant regulatory decisions” (EPA, 2018).

The FDA commissioned two workshops organized by the Institute of Medicine (2010), a component of the National Academy of Science, National Academy of

Engineering, and National Research Council. Similarly, the FDA initiated a cooperative activity with the National Institutes of Health (NIH) to address regulatory science issues. Three similar definitions (Moghissi et al., 2014) demonstrate reliance upon the mission of FDA. Definitions provided by NIH and Institute of Medicine are similar to the FDA definition:

“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” (Institute of Medicine, 2012).

There is widespread application of regulatory affairs addressing public health regulations. The subject is addressed by a professional society (Regulatory Affairs Professional Society, 2021) and covered by many educational programs.

3.2 Scientific Definitions

The FDA and EPA base their definitions of regulatory science on the various scientific disciplines to address their needs. For example, the FDA heavily relies upon regulatory toxicology in the development of drugs, food additives, and many other decisions. Similarly, EPA relies upon regulatory toxicology in evaluating dose response relationships. Various techniques of mathematical sciences are used by all regulatory agencies in evaluating data. Medical devices are developed and

evaluated by several engineering disciplines as are emission-control technologies from power plants and many other facilities. The definitions used by the FDA and EPA could be slightly reworded (*italics* are added) as follows:

Revised FDA Definition: Regulatory science is the science of developing new tools, standards, and approaches *derived from various scientific disciplines* to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

Revised EPA Definition: Regulatory science implies the systematic production of various types of scientific information, including assessments, models, frameworks, criteria, documents, and regulatory impact analyses – any of which provide the basis for EPA’s final significant regulatory decisions.

Revised Regulatory Science Definition: Regulatory science effectively ratifies and includes the applied versions of the various scientific disciplines that are used in regulatory and other policy decisions, including regulatory toxicology, regulatory pharmacology, regulatory ecology, regulatory engineering, regulatory microbiology, regulatory hydrology, and regulatory atmospheric sciences—to name a few.

Proposed Generic Definition: 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 to support regulatory and other policy decisions.

Abbreviated Generic Definition:

Regulatory science consists of an applied version of various scientific disciplines used in the regulatory process.

4. Structure of the Regulatory Science Discipline

The structure of regulatory science as a scientific discipline must be considered in relevant research and educational programs or any activity that would require an understanding of this evolving discipline. In the following, an attempt is made to categorize regulatory science programs in several areas:

Science in Legislation

In various forms of representative government, a legislative branch enacts laws – also known as statutes – that specify the general limits of the behavior of individuals, organizations, etc., that are acceptable by relevant communities. A law for example, might specify that automobiles must not exceed certain velocities as they traverse a road curve. The legislative body typically defers to an administrative component of government to determine exactly what the speed limit should be in order to minimize disaster – in daylight, at night, in rain, etc., while simultaneously maximizing traffic flow. This regulatory – that is, rule-making process requires a reliance on scientific laws that are consulted or derived for public policy purposes.

Science in Executive Branch

The primary user of regulatory science is within the executive branch of the government. Traditionally, one of the key objectives of regulatory science is to evaluate virtually all areas that would impact society, such as safety, protection of human health, preservation of natural resources including the ecosystem, and the economy, to predict future events and their inherent uncertainties.

Science in the Courts

All industrial countries and many others with an operating legal system dutifully deal with scientific issues in their respective courts. The legal systems of many countries permit both the defense and the prosecution to present expert witnesses who testify on relevant scientific subjects. Over the years, the advancement of science has provided unique tools to both prove and reject a scientific claim.

5. Best Available Regulatory Science

Given the complexity of regulatory science as a discipline, it should not be surprising that it has taken several decades to address one of the key aspects of regulatory science, its application to various scientific disciplines.

In this regard, the most recent study (Moghissi, et al. (2017) included a description of BARS and MERSC derived from BARS principles, including a summary of BARS/MERSC principles and examples in which these principles have led to the generation of tools of regulatory science. The application of BARS/MERSC characteristics shown in Figure 1 has been described in several publications. This paper contains an

abbreviated and slightly updated version of its description.

BARS is based on five principles. The **Open-Minded Principle** implies that the regulatory science community must be willing to consider all regulatory science claims, provided those who make the claim comply with the **Skepticism Principle** and provide evidence supporting their claim. In contrast, the **Ethical Rules Principle**—truthfulness, communicability, transparency, and morality—resulted from recognition of avoiding significant mishaps and other adverse events. **Outside the Purview of Science** comprises societal objectives such as conservatism, protection, and shared visions in regulatory decisions, which often go against the principles of the last pillar. It is important to note that being protective is not a scientific principle, but rather a part of the policy-making process. The **Reproducibility Principles** are addressed by several professional societies and are well established.

Reliability Pillar: Peer review provides a process for evaluating the reliability of gray literature and personal opinions, but concerns have emerged recently regarding the limitations of the peer review process. To address these concerns, the regulatory science field has introduced the verification of peer-reviewed scientific information as part of the reliability assessment. Since regulatory science often involves assumptions and related processes, a consensus process is frequently employed to reach conclusions. This process involves establishing a panel to address any discrepancies in scientific

assessments and reaching a consensus-based conclusion.

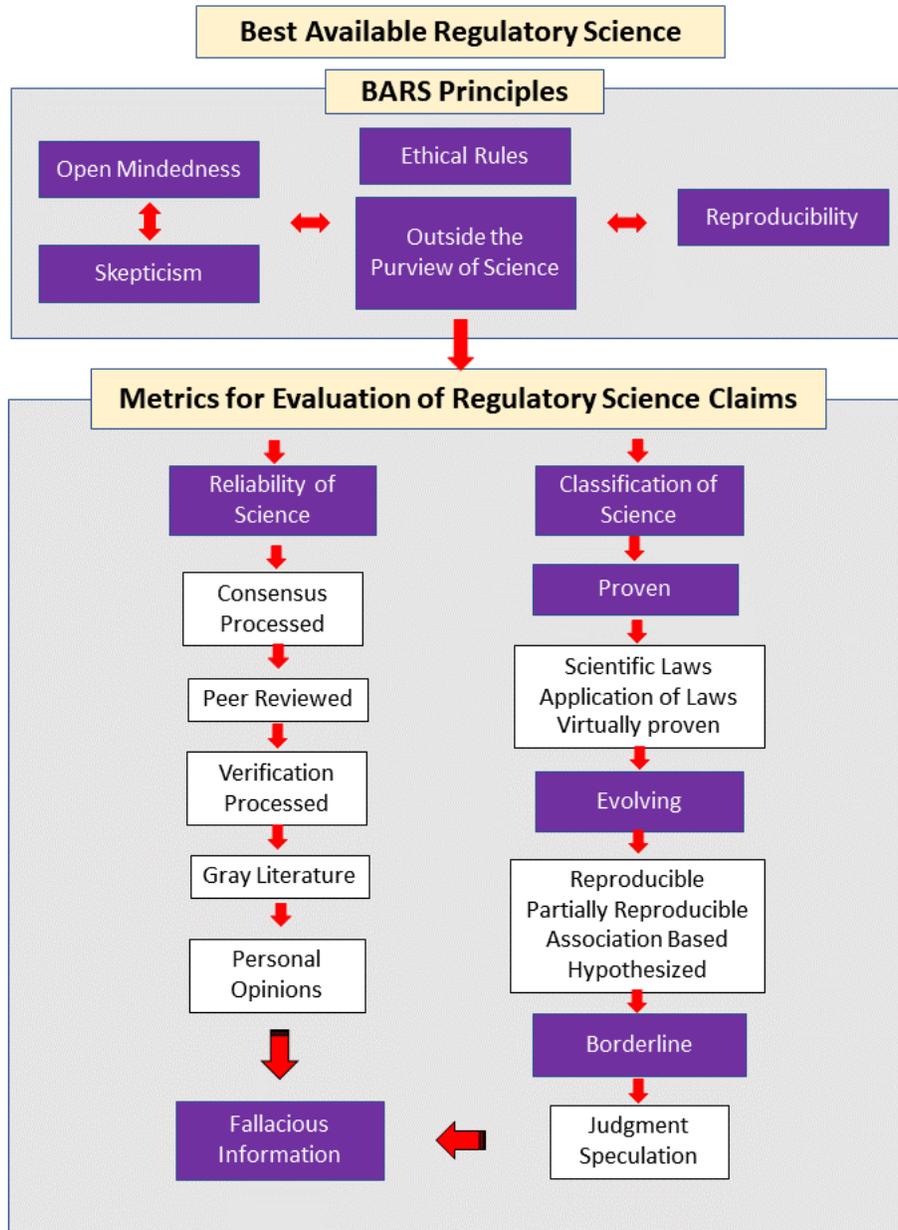


Figure 1. Best Available Regulatory Science and Metrics for Evaluation of Scientific Claims

Classification Pillar: This pillar focuses on Proven, Evolving, and Borderline science. Proven science consists of scientific laws and their reproducible applications. Evolving

science ranges from reproducible to hypothesized – with decreasing reproducibility, such as assumptions and judgments made in the absence of data.

Borderline science solely consists of judgment and speculation.

Elements and Tools of Regulatory Science

This section includes elements and tools of regulatory science derived from fundamentals of regulatory science including BARS/MERSC and those from other disciplines. As regulatory science evolves, other elements and tools are likely to be added.

5.1 Independent Peer Review

Independent peer review is a key tool for evaluation of the reliability of a scientific claim and the most reasonable and most widely accepted process for evaluating scientific claims. (Moghissi, et al., 2013). Peer review is used in scientific publications, in various funding agencies such as NIH and the National Science Foundation (NSF), and in scientific assessment documents commonly used in the regulatory process. Elements of peer review include:

- Assessment of qualifications and independence (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

Regardless of its objective, peer review requires a process to identify a peer reviewer and the review criteria. A peer reviewer is an individual who can answer questions identified in review criteria without significant study. In effect, the reviewer

must know the subject that is being reviewed well. Review criteria arise from key questions identified by the decision makers such as managers of journals, funding agencies, or policy makers/regulators with the objective to evaluate the validity of a relevant scientific claim.

5.2 Publication of Scientific Claims

Many government funding agencies in the United States, Europe, and elsewhere require that published reports resulting from their funding must be publicly accessible. However, the availability of open-access publications has significantly impacted scientific publications and led to the development of predatory journals that typically publish any paper if the authors pay the publication fee. For the results of a study to be included in a relevant decision, they must be verified. As a result, verification mandates have been added to the Reliability Requirement of BARS/MERSC.

An often-misunderstood issue is the role of the editor of a scientific journal. The editor is obligated to apply legal, moral, and ethical standards to a submitted manuscript and can accept or reject it based on these criteria.

5.3 Regulatory Science Ethics

The scientific community, including medical researchers, has established ethical standards for its members. In addition to these general requirements, there are specific ethical regulations in the field of regulatory science that apply to both those who prepare

documents for regulatory decisions and those who describe the scientific methods used in creating these documents (Moghissi, et al., 2015). Society benefits if editors of scientific journals comply with the same rules, thereby avoiding the inclusion of ideology, financial interests, or any other nonscientific issues in their publications.

Key elements of the Ethical Rules of BARS/MERSC are:

1. **Truthfulness:** This rule is universal regardless of ethnicity, religious beliefs, or cultural backgrounds of the stakeholder community. One of the key rules of this element is: *In communicating scientific information, the scientific community or an individual scientist must not exaggerate or minimize beneficial or adverse effects of an agent, a situation, a condition, or any other relevant issue.* In rare cases, individuals or organizations believe that it is in the interest of a compelling cause to be less than truthful.
2. **Communicability:** This element requires that relevant scientific issues be translated into language that is understandable to the affected communities. The Jeffersonian Principle provides the process to implement this rule.
3. **Transparency:** The use of predictive science in regulatory processes involves different levels of uncertainty. To uphold transparency, it is necessary to provide the affected community, and ideally the

public, with all the relevant information about the assumptions, judgments, inclusion of default data, and any other factors that contributed to the conclusion.

6. Regulatory Science Transparency Including Communication

William Ruckelshaus, the founding administrator of the EPA who returned later to re-position the agency, was instrumental in making transparency a key element of the regulatory process. Ruckelshaus (1983) popularized a now two-centuries-old observation and admonition by Thomas Jefferson (in his letter to a Mr. Jarvis, September 28, 1820):

“I know no safe depository of the ultimate power of the society but the people themselves; and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it away from them but to inform their discretion by education.”

To apply the Jeffersonian Principle and ensure clear communication, recipients of information are categorized into three groups based on their level of education and/or ability to comprehend semi-technical writing:

Group I - Scientific Specialists: This group consists of individuals with relevant scientific education and experience in the scientific area that is being considered.

Group II - Knowledgeable Non-Specialists: This group, often referred to as educated individuals, includes those with a general education as well as scientists who are not knowledgeable in the areas that are being addressed. Many governments and

industrial leaders and policy makers are included in this group.

Group III - General Public: Although this group encompasses Groups I and II, it specifically describes individuals who have either no, or insufficient general knowledge of the issue in consideration, but are capable of consuming information that is logical and that explains science in terms that can be understood.

6.1 Application of the Jeffersonian Principle

As predicted by Ruckelshaus (1983), the introduction of the Jeffersonian Principle caused disagreements between the proponents of the principle and those who claim that the public does not necessarily need to be involved in major decisions for the following reasons:

- The relevant science is beyond the ability of the recipient to comprehend.
- The public is unable to comprehend its needs.
- The release of the information would delay or eliminate the completion of a decision that would be vital to the judgment's proponents.
- The regulator claims lack of knowledge and familiarity with the relevant science or other key elements of the regulation.

Transparency is the foundation of acceptability of the scientific part of the regulatory process and requires that regulators describe any scientific

information that falls in one of the following categories in a language that is understandable by the affected community:

- Any and all assumptions
- Any and all judgments
- Application of default data
- Inclusion of Areas outside the Purview of Science
- Other information that cannot be reproduced - by an individual with sufficient and relevant knowledge - without access to relevant equipment and facilities

6.2 Opposition to Transparency

Some argue that the general public does not need to be involved in major decisions, particularly if the decision is highly complex or based on science that may be difficult for the public to comprehend. They believe that the public may not fully understand its needs, nor of the potential consequences of releasing relevant information. They also believe that sharing this information could delay or negate critical decision-making. For example, a prominent professor, Jonathan Gruber, made controversial comments (CBS, 2014) suggesting that voters are often unable to comprehend the importance of certain laws. Although he later apologized, his statement continues to be widely discussed.

6.3 Science Versus Policy

One of the three pillars of MERSC is Outside the Area of Science. The essence of this pillar is the maxim that societal objectives, ideology, political vision,

religious belief, and similar worldviews or beliefs should remain independent of regulatory science. This pillar of MERSC is traceable to former EPA Administrator William Ruckelshaus who made a distinction between when an individual is speaking as a scientist or as a citizen [A summary of various views held by Ruckelshaus can be found in Moghissi et al.,2012]. According to Ruckelshaus (1983), “...all scientists must make it clear when they are speaking as scientists—*ex cathedra*—and when they are recommending policy...it should flow from scientific information... What we need to hear more of from scientists is science.” Ruckelshaus emphasized that citizen scientists are entitled to their political opinions as is anyone else in society, but they should not think that their opinion is somehow more worthy than the political opinion of any other citizen because they are scientists.

The number of regulations influenced by societal objectives is debatable and potentially increasing. Decision makers often prioritize public acceptance of decisions, leading to a reliance on societal considerations. However, the implementation of the Jeffersonian Principle would greatly benefit decision makers by avoiding the concealment of truth as a solution.

An equally complicated issue is the composition of science panels that advise regulatory agencies. These panels often consist of nonscientists or individuals without specialized knowledge. Rather than

providing policy options, which should be the responsibility of policy makers, these panels should focus on presenting the current state of scientific knowledge. If regulators require advice on incorporating science into specific regulatory processes, a separate panel should be established.

6.3 Mathematical Models

Mathematical models play a crucial role in regulatory science. With advancements in mathematics and the rise of powerful computers, modelers can greatly improve their methods and findings. These models are commonly used in regulatory and policy decisions to determine the potential impacts of proposed policy actions. In simple terms, a mathematical model involves identifying important parameters, establishing relationships between them, and using this information to create equations that address specific regulatory concerns. The reliability of mathematical models ranges from *Evolving Science to Borderline Science*. The development of models consists of multiple steps:

- Step 1: Identifying parameters.
- Step 2: Developing a mathematical equation, often using assumptions.
- Step 3: Verifying the model, ideally via multiple methods.
- Step 4: Reiterating the process as required.

Some of the most valuable models are weather predictions which, while not always accurate, provide a reasonable level of

confidence for many societal decisions (e.g., whether to launch a rocket). These models have served the global community well by attempting to predict adverse weather conditions.

6.4 Cost-Benefit Analysis

Cost-benefit analysis is frequently used in the regulatory process. Historically, regulatory scientists have been hesitant to utilize this approach due to the challenges associated with determining the costs and economic benefits of proposed regulatory actions (Arrow, 1996). However, President Reagan (1981) acknowledged the importance of cost-benefit analysis and made it mandatory for certain actions. Despite the uncertainties involved, it can be argued that an analysis that acknowledges and considers uncertainties is preferable to one that lacks pertinent information. The EPA recently published a proposal (EPA, 2020) that offers guidance on conducting economic analysis that is relevant to regulatory decision-making.

6.5 Stakeholder Participation

Stakeholder participation is widely recognized as a crucial aspect of the regulatory process. However, there is a persistent lack of clarity regarding the definition of a stakeholder. Currently, stakeholders are predominantly influential individuals who belong to advocacy organizations. Nevertheless, it is important to acknowledge that true stakeholders are the individuals directly affected by a proposed decision.

7. Application of Evolving Science in Policy: Focus on Regulatory Decisions

The principle of regulatory science emphasizes the exclusion of non-scientific factors from the decision-making process, such as policy, ideology, politics, religion, or any other nonscientific issue. However, current practices often incorporate nonscientific elements into regulatory decisions.

Scientists play a key role in evaluating scientific evidence and applying it to policy, including regulatory decision making. Regulatory agencies rely on multiple panels and committees to review scientific information, which is then used to inform policy decisions. Organizations like the National Academies of Sciences Engineering and Medicine (NASEM) also evaluate relevant information and make recommendations.

8. Conclusions

Recognition of regulatory science as a legitimate discipline with a recognized identity is becoming a reality, as outlined in this paper. Regulatory science applies specific scientific disciplines to regulatory and policy decisions. Through the evolution of BARS/MERSC, processes and tools have been developed to apply regulatory science effectively. These include independent peer review, assessment of mathematical models, cost-benefit analysis, stakeholder participation, and regulatory science ethics.

One of the fundamental principles of regulatory science is the requirement to maintain reasonable and transparent separation between science and policy, as implored by Ruckelshaus. Regulatory agencies should adhere to ethical requirements that emphasize transparency. This means providing the affected community and the public with the assumptions, judgments, and decisions that inform regulatory actions. Regulatory agencies should actively consider relevant societal issues in decision-making processes, but a clear and transparent distinction should be made between societal ambition (as desiderata) and policy alternatives (resulting in government regulations and public actions) so that all stakeholders remain optimally informed and engaged. It is imperative that all relevant information be communicated to the public in language that is easily understood by all.

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