REGULATORY SCIENCE

MANUAL

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PREFACE

This manual is a summary of an upcoming textbook with the working title *Introduction to Regulatory Science.* The preparation of the introductory book will take some time to complete. Meanwhile, In the absence of a textbook, it is desirable to provide students with a short document that introduces them to basic information on regulatory science, an emerging scientific discipline. The manual is also useful information to regulators, members of the regulated community, and interested scientists and engineers. This manual summarizes published information including papers published with the participation of students at Georgetown University at a regulatory science program.

The materials included in this manual are organized in three parts as follows:

Part 1 introduces the reader to regulatory science:

- Introduction
- Evolution of Regulatory Science
- Regulatory Science as a Scientific Discipline

Part 2 provides key elements of regulatory science

- Evolution of Best Available Regulatory Science
- Peer Review Process

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Part 3 identifies and briefly describes regulatory science tools

- Regulatory Science Ethics
- Jeffersonian Principle
- Implementation of Ethical Rules Principle
- The Role of Stakeholders in Regulatory Science
- Application of Mathematical Models
- Application of Voluntary Standards
- Application of Risk Analysis
- Application of Regulatory Economics

The information included in this manual are taken from many publications published in peer-reviewed journals and other peer-reviewed documents. Instead of having a large list of references, key references for each part are include in the reference list.

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INTRODUCTION

Regulatory and other policy decisions require the application of various scientific disciplines consisting of natural, social, and medical sciences including medical practice, and various engineering disciplines. In recent years the application of science in legislative, executive, and judicial branches of government has significantly increased, particularly in regulatory segment of executive branch. Regulatory science is an emerging scientific discipline that responds to scientific needs of policy makers notably regulators.

Several agencies in the United States rely on regulatory science to make sound policy decisions. In the United States, the oldest regulatory agency with interest in regulatory science was the Bureau of Chemistry, which was established in 1906 and eventually it was renamed as the "Food and Drug Administration" (FDA).

Another important event related to regulatory science in the US History was the Manhattan Project, which led to the creation of the United States Atomic Energy Commission (AEC). AEC was an agency established after World War II by U.S. Congress to control or regulate the development of atomic science and technology. President Harry S. Truman signed the McMahon/Atomic Energy Act on August 1, 1946. This shift brought the regulation of atomic energy from military to civilian hands, effective on January 1, 1947, and gave the members of the AEC ultimate control of the plants, laboratories, equipment, and individuals originally brought together during the WWII to produce the atomic bomb under the Manhattan Project. By 1974, AEC's functions were transferred to two

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new agencies: The Energy Research and Development Administration and the Nuclear Regulatory Commission. AEC's regulatory responsibilities were transferred to the newly formed U.S. Nuclear Regulatory Commission. On August 4, 1977, President Jimmy Carter signed The Department of Energy Organization Act of 1977, which created the Department of Energy.

Another agency with a broad regulatory mission is the U.S. Environmental Protection Agency (EPA) whose regulatory responsibilities cover control of air and water pollution; pesticides and other chemical agents; emission of chemical agents from manufacturing activities; waste management; and a wide range of other regulations. Other regulatory agencies include the Occupational Safety and Health Administration and Mine Safety and Health Administration. Finally, an agency that is recognized as the ecological protection agency is the US Fish and Wildlife Service. As the brief description of regulatory agencies in the US indicates there are many regulatory agencies and a significant need for scientific support to promulgate and enforce regulation.

The policy makers including regulators have struggled on how to apply science with various levels of maturity or reliability and in the absence of useful scientific data, they have used their judgement in applying science. In most cases they exaggerated a potential effect or used "conservative "or "protective' approaches in applying their decisions. As shown in Figure 1, the application of science started with the basic scientific process known as scientific method

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consisting of four steps as follows:

Step 1: An intellectual Struggle that is based upon an observation, an experiment, thought, curiosity, intuition, or other process.

Step 2: Formulation of a logical Hypothesis that predicts outcomes.

Step 3: Formulation of a Theory by Seeking Evidence to confirm the hypothesis. However, during this step not all areas of potential coverage of the theory may be tested, or for a number or reasons cannot be tested.

Step 4: Finalizing the process by establishing a fundamental scientific law, sometimes referred to as a principle that predicts all events that are within their range of applicability.

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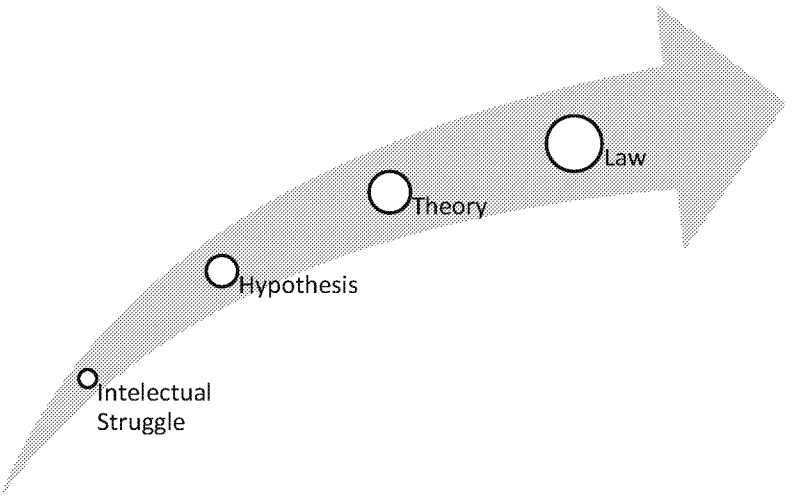

Figure 1: Evolution of basic scientific process

The application of the four-step process to technology development is shown in Figure 2

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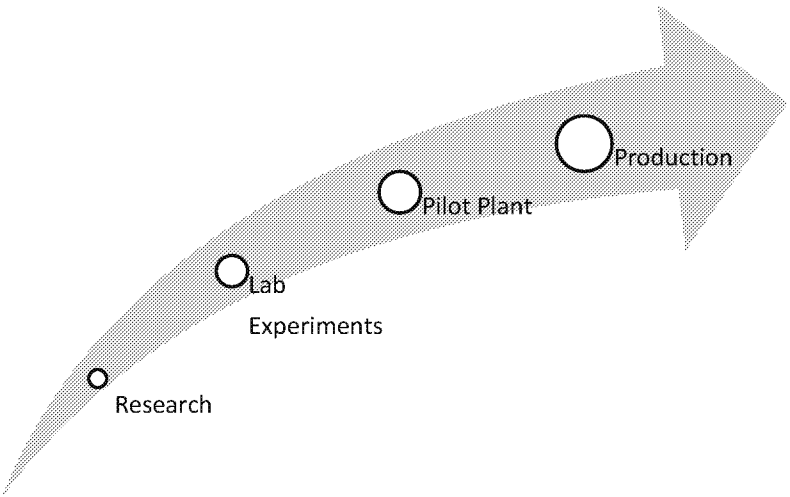

Figure 2. The four-step process in technology development

Typically, the development of a new technology starts with research. The next two steps consist of a small-scale or prototype production often referred to as pilot plant or prototype production. Typically, the level of control of various parameters decreases from laboratory experiment to pilot plant and production, where the process is inherently less controllable. Similarly, for production of items such as an airplane or a car, one or more items is produced and tested to ensure the validity of laboratory experiments. For production of drugs, testing for efficacy and safety is included in this third stage of the production process.

The four-step process is also applicable to drug development. During the drug development process, many chemical compounds

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are evaluated with the objective to identify potential candidates for a specific drug. Subsequently potential candidates are synthesized, separated form naturally occurring materials, or existing chemicals are modified, to mention a few. This step results in a reasonably pure compound that can be used in the next step.

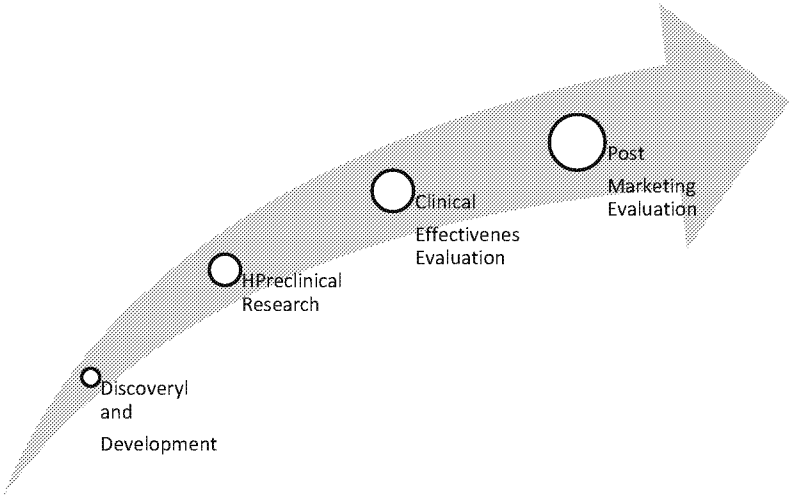

Figure 3: Drug Development Process

Preclinical Research: There are several approaches to evaluate drug candidates identified during the discovery process including evaluation of the chemical agent using relevant cell cultures known as *in vitro* studies and animal experiments known as *in-vitro* studies. The outcome of this step is identification of candidates for the next step.

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Clinical Research and Effectiveness Evaluation: The process known as the Investigational New Drug (IND) to clinically evaluate a candidate is complex and includes multiple phases. Note that the ratio among step 1, step 2 and finally step 3 (approval of IND) is approximately 10^6 to 10^2 to 1, implying that more than a million compounds identified in step one lead to 100-1000 compounds in step two and finally one compound as an approved drug.

Post Marketing Evaluation: The FDA in the US and its counterparts in other countries typically follow how a drug performs in the market place. The primary issue related to post marketing of a drug consists of an unanticipated side (adverse) effect including higher level of adverse effect identified in the third phase of drug evaluation.

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EVOLUTION OF REGULATORY SCIENCE

There is extensive literature on the perception of many investigators on the nature of regulatory science, what makes it unique, and how to apply existing science to the regulatory process. Surprisingly, members of certain disciplines notably social sciences and law have dominated the literature dealing with regulatory science. The emergence of the term "regulatory science" occurred shortly after the formation of the Environmental Protection Agency (EPA) in 1970. Apparently that term appeared for the first time in an internal memorandum to describe how science was 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. It was argued that "science is science" regardless of its application. Meanwhile several scientific disciplines have established subdisciplines e.g. regulatory toxicology that addresses the need for a regulatory process. Meanwhile it appears the term "regulatory science" is extensively used not only in English but also in other languages including German (*regulatorische Wissenschaft*), French (*science de la réglementation*), and Spanish (ciencia reguladora).

Initially scientific needs of the regulatory process had to be addressed in various scientific fields such as toxicology, microbiology, pharmacology, chemistry, physics, biology, medicine, and several engineering disciplines. However, there were major

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problems and significant discourse within the scientific community and dissatisfaction within the regulated community on how the subject was envisioned\ . The appearance of a regulatory science discipline was—if not entirely but predominantly—in response to the desire for a more appropriate process to meet societal needs.

The first step in describing regulatory science 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. The first organization entirely dedicated to regulatory science was the Institute for Regulatory Science established in the spring of 1985 based on the desire of its founders to address the scientific needs of the regulatory process.

Definition of Regulatory Science

I: Original Definition: The founders of regulatory science struggled to define the new scientific discipline leading to the following definition:

Regulatory science constitutes the scientific foundation of policy notably regulatory decisions.

II: FDA Definition: The definition provided by the FDA addresses the mission of that agency.

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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.

III: Definition by the National Institutes of Health: This definition expands regulatory science to cover all products.

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

IV: Definition based on scientific disciplines: This definition is based on the identification of scientific disciplines such as regulatory toxicology

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

V: EPA Definition: A recent proposed rule by the EPA states:

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

VI: Simplified definition: A useful and simplified definition is:

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Regulatory science consists of a scientific segment of the regulatory process

Regulatory Science Community

There is a confusion on the structure of regulatory science community. A logical description of the regulatory science profession would have to 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. Scientists within Regulatory Organizations consisting of the staff of regulatory agencies at all levels who are involved in promulgating regulations, applying them to licensing/permitting, and enforcing them.
2. Scientists within the Regulated Community affected by regulations that are based-on or include science.
3. Members of the scientific community with interest in regulatory science who are not necessarily members of the regulatory or regulated community. This group is particularly large as many scientists including engineers are involved in addressing scientific issues with potential application to regulatory science

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Regulatory Science in Various Branches of Government

As the above definition indicates, all branches of government rely upon regulatory science as follows:

Science in Legislation: In virtually every form of government the legislative branch enacts laws that may or may not comply with the requirements of science. In the United States, the Library of Congress was established in 1800 and its research arm, the Congressional Research Service, was established in 1914 to provide Congress with the needed scientific support. In addition, both houses of Congress rely upon information gathered during hearings by inviting individuals with relevant scientific competency/expertise to testify. Both majority and minority leadership invite scientists to present their views on specific subjects.

Executive Branch: 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, major objective of regulatory science is evaluating virtually all areas that would impact society such as protection of human health; preservation of natural resources including the ecosystem; safety; and the economy. A major part of regulatory science consists of evaluating the status of science applicable to a specific application including the evaluation of an existing

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situation or condition, evaluating a proposed action, or prohibiting the continuation of an existing condition, to mention a few. Typically, a *scientific assessment* is prepared that covers the relevant scientific area. The appearance of the term regulatory science within the US government occurred at about 2010 when Dr. Margaret Hamburg, then the Commissioner of the FDA, initiated a program emphasizing the application of regulatory science in drug development, medical devices, and other areas within the FDA mission. Other regulatory agencies have yet to recognize regulatory science as a key scientific discipline, thus avoiding the use of the term regulatory science. However, they recognize the existence of regulatory science disciplines such as regulatory toxicology.

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 U.S., increasingly various courts must address scientific issues. Much like many other countries, the U.S. has local, regional, and federal court systems. The highest federal court in the U.S. is the Supreme Court located in Washington DC. According to

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the U.S. system, many decisions—including some in local and regional courts—reach the U.S. Supreme Court for the final decision. In recent years, various courts have attempted to address legal issues that include science.

Three Phases of Regulatory Science:

During the past several decades, many laws were enacted in the Unites States, particularly during the 1970s, addressing the societal needs of the United States. 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 U.S. occurred in three phases:

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 addressed during the 1970s or 1980s. In contrast, during the Initial Phase of the EPA's history that lasted more than a decade, administrators used a process that has been identified by several terms, including Best Available Information, Best Available Technical Information, or simply Available Information. 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 some EPA managers, was relevant and credible. For example, to be

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protective of the health and environmental effects of pollutants, they chose what they called the *conservative* or protective approach and thus often over-estimated, the human health and environmental effects of a pollutant. During this period, the independent peer review process was virtually unknown.

Exploratory Phase: During this phase, regulators 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 Congress required consultation with the National Academies consisting of National Academy of Sciences, National Academy of Engineering and National Academy of Medicine. At the FDA, this phase was marked by a study performed by the National Academies in 1993 on the development of processes to speed up the approval of drugs, medical devices, and the formalization of a process to withdraw drugs or limit their applications.

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 including regulatory science tools. As many regulatory decisions rely upon Partially Reproducible Evolving Science, the objective of this phase is to enhance the level of reproducibly of regulatory science.

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Application of Science During the Three Phases

As shown in Figure 4, the application of the four-step process, as described above, to the three phases of regulatory science, can be described in four steps as follows:

Step I: Scientific Assessment Based on Legal Mandates: Typically, regulatory science starts with a legal mandate consisting of a law, a judicial decision, or any other legal action that requires the inclusion of science by that relevant agency and results in the preparation of a "scientific assessment". For example, if a law mandates a standard for the establishment of a maximum concentration of an agent in the ambient air, the scientific assessment attempts to identify a threshold below which there will be no health effect. Subsequently, the threshold is used to develop the relevant standard of acceptance. Similarly, if a judicial decision requires the evaluation of a food additive, the relevant agency performs a scientific assessment on the safety of the additive. In many cases during this step, the needed science is either incomplete or non-existent. Regulators are expected to do their best to develop regulations based on the notion that occasionally it is better to have regulations that are less than perfect rather than having no regulations.

Step II: Promulgation of the Regulation: This step consists of the application of the scientific assessment to promulgate a regulation.

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The process is complex and is based on how regulations are developed including an announcement of a proposed rulemaking, publication of the proposed rule, consideration of comments received after the publication of the proposed rule, and promulgation of the final rule.

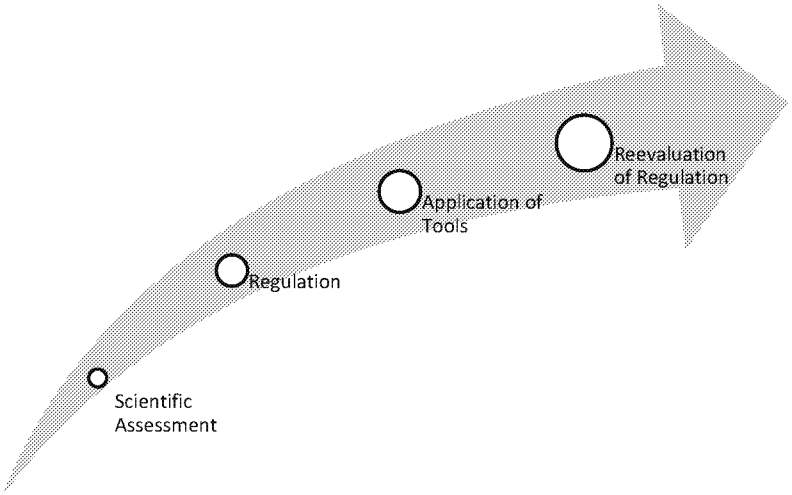

Figure 4. Regulatory Science process

Step III: Development and Application of Tools: This step provides an opportunity for the regulatory science community to impact the regulatory process. During this step, several key elements are identified, developed, and applied as follow:

1. As described in the first step, often deadlines mandate promulgation of regulations based on science that is

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uncertain, incomplete, or occasionally non-existent. During this step, the relevant segments of the scientific community reevaluate the initial scientific assessment, identify its shortcomings and attempt to improve the science so that it could be used to revise the initial scientific assessment.

2. On more than one occasion new tools are developed during this step or existing tools are improved to make them more useful. A classic example is risk assessment as it was used both at the FDA and EPA. Prior to the report prepared by the National Research Council in 1983, there was confusion between risk assessment, a scientific process, risk management, and the application of risk assessment to manage the risk. There were also several other major shortcomings on how risk assessment was used. The clear distinction between risk assessment and risk management reduced numerous problems. The addition of risk communication in 1984 by Ruckelshaus provided additional improvements in this major regulatory science tool.
3. The shortcomings of scientific assessment in Step I provide an opportunity to perform basic and applied research by providing new data, new knowledge, and numerous other relevant scientific results to improve the foundation of the scientific assessment. In effect, during this step a revised and improved scientific assessment is developed.

Step IV: Re-evaluation of the Regulations: The availability of a new and improved scientific assessment provides the regulators with the opportunity to revise the original regulation and an opportunity

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to correct errors made in the initial decision. An example of this step is Vioxx an anti-inflammatory drug that was approved by the FDA in 1999 and withdrawn in 2004 because it had caused heart attacks in 88,000 individuals, resulting in the death of 38,000 patients.

Science for Policy

Regulatory agencies and other organizations have used science during their decision process. Currently, except for FDA, these agencies and organizations use other terms such as science for policy, or do not use the term regulatory Science. However, there is wide recognition that science is used in regulatory and other policy decisions. For example, a recent (2018) a search at the website of the National Academy Press for "regulatory science" resulted in numerous reports. Although reports dealing with the FDA mission dominates, there are also reports on ecosystems, engineering in environmental regulation, transuranic waste, science at the EPA, biotechnology, and many other topics that are outside of the mission of the FDA.

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REGULATORY SCIENCE AS A SCIENTIFIC DISCIPLINE

There are those who claim that there is nothing unique about regulatory science as applied version of various scientific disciplines are routinely used in the regulatory process. The argument is that there is no commonality among various scientific disciplines used in the regulatory process and regulatory science is, in fact, a compilation of many disciplines and thus it does not qualify as a scientific discipline.

What is being overlooked is the unique nature of regulatory science particularly certain tools that are used by the applied version of virtually all scientific disciplines used in regulatory science. Based on the claims identified above, one can ask if chemistry is a scientific discipline. There are many disciplines included in chemistry including analytical chemistry, biochemistry, environmental chemistry, electrochemistry, combustion chemistry, food chemistry, Forensic chemistry, inorganic chemistry, medicinal chemistry, nuclear chemistry, organic chemistry, physical chemistry, and chemical engineering—to mention a few.

Another view is that regulatory science inherently includes uncertainties and thus does not qualify as a science. What is 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 advancement of scientific knowledge.

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Consideration of scientific uncertainty is not limited to regulatory science. Weather reports on adverse conditions are typically associated with various levels of uncertainty. Predictions on the direction and severity of hurricanes such as Irene and Sandy changed over the course of those events. If one accepts arguments about regulatory science as described in this chapter, a legitimate question would be: Is meteorology a scientific discipline?

There is an unambiguous need to apply practices common in scientific disciplines to regulatory science. Elements of the development of the regulatory science discipline are as follows:

Regulatory Science Education

Thanks to the initiatives of the FDA, several universities provide regulatory science education covering areas within the mission of FDA. Other regulatory agencies have yet to recognize regulatory science as a segment of their mission much less the need for educating regulatory scientists covering their regulatory mission.

Regulatory Science Research

For obvious reasons, there is a lack of recognition for the need for relevant research. Examples or areas of interest are:

- Assessment of the level of maturity of science used in the regulatory process.

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- How does one translate science used in regulatory process in a language that is understandable to the affected community?
- How to avoid inclusion of ideology and other non-scientific issues in scientific assessments used in the regulatory process?
- Finally, one of the most important areas of research is to initiate studies in various traditional scientific disciplines that address regulatory science needs

Regulatory Science Communication

The first step in regulatory science education is to convince individuals involved in relevant activities that they are indeed regulatory scientists. Although most scientific societies have recognized the need for communicating the results of their findings, including those with direct or indirect applicability to regulatory science, there are a limited number of mechanisms to communicate with members of the regulatory science community. The following initiatives are likely to enhance communication:

- Initiation of journals devoted to regulatory science disciplines
- Conferences, workshops, and related activities.
- A website devoted to regulatory science
- Educational programs to train scientists

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Introducing the Uniqueness of Regulatory Science to the Relevant Community

A key step in regulatory science education and communication is to introduce the unique nature of regulatory science to practitioners of various basic scientific disciplines, medical science, various engineering including technology disciplines, emphasizing that regulatory science uses scientific knowledge with variable levels of maturity. For example, an investigator who has invented a technology would greatly benefit from understanding the regulatory science process if the technology has the potential to be used in activities that would require the development of regulations or policies or compliance with them. Regulatory science thinking provides a reasonable pathway to the decision process.

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EVOLUTION OF BEST AVAILABLE REGULATORY SCIENCE

The development of system in response to the need of regulators and other policy decision makers was the result of extensive efforts to systematically evaluate several key scientific issues. The evolution of Best Available Regulatory Science (BARS) and Metrics for Evaluation of Regulatory Science claims (MERSC) derived from BARS are traceable to several research and publications addressing the concept of Best Available Science (BAS) and Metrics for Evaluation of Scientific Claims (MESC) derived from BAS (3). The BARS/MERSC is the application of BAS/MESC to the unique nature of regulatory science discipline, requiring certain modifications and expansions of BAS/MESC.

As shown in Figure 5, the result was a structure that included fundamental principles as well as three pillars, as follows:

Principles of BARS

The updated version of principles (BAS leading to BARS) indicates that the three principles (open-mindedness, skepticism, and reproducibility) remain unchanged, while the two other principles are revised. The updated five versions of principles are as follows:

Open-mindedness Principle: This Principle implies the willingness to consider new knowledge. Every claim on a discovery; the development of a new drug; identification of a potential human health problem; or the description of an environmental risk requires the willingness to carefully evaluate the claim.

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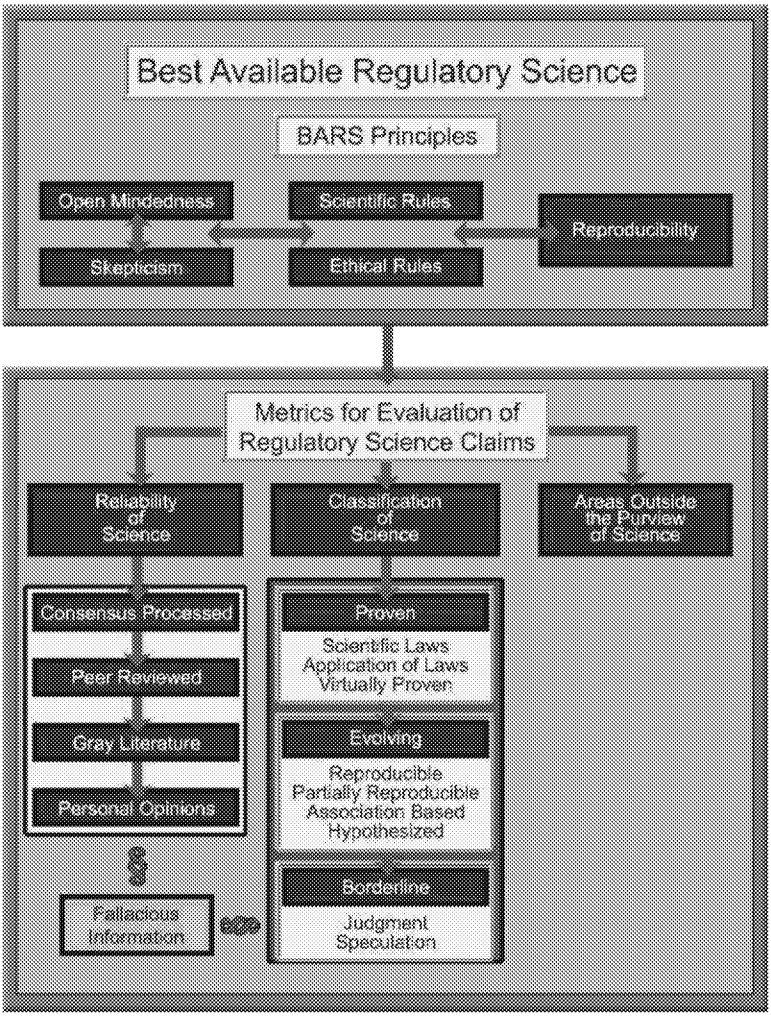

Figure 5: The structure of BARS/MERSC system

Skepticism Principle: This Principle implies that it is incumbent upon those who make a scientific claim to provide sufficient evidence supporting their claim.

Scientific Rules Principle: One of the most important subjects in MERSC is compliance with the Scientific Rules Principle. As regulatory science includes the application of virtually all scientific disciplines that are used in the regulatory process, it is crucial that relevant methods, processes, and techniques are appropriately used. Furthermore, scientific laws apply not only to a specific discipline but to all scientific disciplines. For example, all scientific disciplines use specific computational methods and apply the rules of statistics in sampling, analysis, and reporting their results.

Ethical Rules Principle: One of the reasons for controversies associated with regulatory science is the lack of recognition by the regulators that the science used in the regulatory process must be translated into a language that can be comprehended by the regulated and other affected communities and ideally by the public. [TS1]Both national and international agreements developed by scientific, medical, engineering, and other organizations have promoted global acceptance of scientific ethics. In contrast, there appears to be a lack of recognition for the ethical requirements of regulatory science such as truthfulness, communicability, and transparency.

There a global acceptance of scientific ethics resulting from national and international agreements such as those developed by medical,

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chemical, and engineering organizations. In contrast, there appears to be a lack of recognition of ethical requirements of regulatory science notably truthfulness, communicability, and transparency.

Reproducibility Principle: The ultimate proof of the validity of a scientific claim is to be reproducible by those who have the necessary competency and the needed equipment and facilities. This principle separates undisputed areas of science from those that include assumptions, interpretations, and in some cases, the inclusion of ideological and societal objectives in a scientific assertion.

MERSC Pillar: Areas Outside the Purview of Science

There is overwhelming evidence that the inclusion of societal objectives including ideology, and political views in the scientific process would jeopardize the objectivity and consequently the acceptability of scientific information. The primary objective of regulatory science is to provide policy makers with reliable information, including its level of maturity.

One of the most often violated requirements of regulatory science is the inclusion of ideology, beliefs, faith, societal, political, or any other non-scientific objective in scientific assessments. The scientific foundation of a policy should be identical if it is performed in the U.S., Russia, China, Saudi Arabia, Brazil or any other country. The process would include the description of the level of reliability and the identification of the level of maturity of the science, both

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being reasonably objective. In contrast, the policies derived from science can be significantly different in countries identified above.

In a famous speech given by William Ruckelshaus at the National Academy of Sciences on the relationship between science and the societal issues, he stated: "... all scientists should make it clear when they are speaking as scientists— ex cathedra—and when they are recommending policy they believe should flow from scientific information." and "What we need to hear more from scientists is science." Obviously, Ruckelshaus appears to support this principle

MERSC Pillar: Classification of Regulatory Science Claims

One of the primary reasons for the uniqueness of regulatory science is the need to consider the level of maturity of a regulatory science claim. Surely one would have more confidence in a claim that is based on a scientific law as compared to a judgment of a scientist or a scientific group. It is well established that science evolves and that new discoveries, advancement of scientific knowledge, and numerous technologies result from the evolution of science. Therefore, it is necessary to classify scientific claims in terms of its level of maturity and its reproducibility.

Proven Science: This group of regulatory science claims consist of scientific laws—sometimes called scientific principles—and their applications. The cornerstone of this group is compliance with the Reproducibility Principle, implying that any investigator who has the necessary skills and the proper equipment can reproduce it. Therefore, a

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scientific claim included in this group does not require assumptions or any other conditions for its validity. This group not only uses scientific laws but also applies scientific laws that exclude assumptions.

Evolving Regulatory Science: The overwhelming scientific advances in virtually all disciplines are Evolving Science. Virtually all regulatory science materials are included in this group.

Reproducible: Reliable scientific claim that is not completely understood constitutes the core of this class based on two attributes:

1. It must comply with the Reproducibility Principle, implying it is clearly and unambiguously reproducible by those with appropriate skills and equipment.
2. It may not violate the Universal Rules Principle.

Advancements in virtually all branches of science including physics, chemistry, biology, and many other scientific disciplines are based on the desire of investigators to develop knowledge into scientific law.

Partially Reproducible: In previous publications, this class was referred to as Rationalized Science, or Extrapolated Science. The key characteristic of this class is that the scientific foundation of a claim placed in this class is derived from Proven Science or Reproducible Evolving Science. Typically, it uses assumptions, extrapolations, default data, and other processes in deriving its

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results and conclusions. Note that a scientific claim in this class does not meet the Reproducibility Principle. An investigator who is trying to reproduce a scientific fact must not only have proper skills and the necessary equipment but must also accept the asserted scientific foundation; assumptions; choice of mathematical processes; default data; and numerous other prerequisites. Regulatory science relies heavily upon this class. A hereto unrecognized subject is the fraction of reliance upon Proven or Reproducible Evolving Science. Consequently, for the sake of simplicity, scientific claim in this class can be subdivided into mostly reproducible, somewhat reproducible, and slightly reproducible evolving science.

Association-Based: Sometimes called correlation or observation studies, this class is not based on Proven Science or Reproducible Evolving Science. Instead, often an investigator attempts to correlate an effect to a cause. Consequently, the level of reproducibility of information in this class ranges from unknown to reasonable. One of the primary goals of this class is to eventually elevate it to Reproducible Evolving Science. A large part of evidence-based medicine falls into this class. A hereto neglected and unrecognized area of this class consists of economic predictions. Often economists are asked to predict an event such as growth rate of a segment or the entire gross national product. These predictions are based on previous

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events that do not necessarily imply their reproducibility in the future.

Hypothesized: This class consists of an organized response to an observation, an idea, or any other initiating thought process. In many respects, this class is analogous to hypothesis in the classical scientific process. Experience shows that although many great scientific discoveries started with this class; still, there is also a long list of claims that have proven to be either wrong or not worth pursuing.

Borderline Regulatory Science: As the title implies, this group does not qualify as science as described in the sections devoted to Proven or Evolving Science. We have identified two classes in this group as follow:

Judgment: On occasion, decisions must be made without having the needed prerequisites including basic principles, the necessary data, and other scientific requirements. The methodology for expert judgment is reasonably well developed and consists of asking several presumably knowledgeable individuals to give answers to specific questions and to statistically assess the results. Note that information in this class is often an educated guess.

Speculation: This class consists of claims that cannot meet standards described in any of the above classes. It is often based

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on the intuition of an individual who wants to stimulate a discussion or initiate a research project.

MERSC Pillar: Assessment of the Reliability of Regulatory Science Claims

One of the key issues in managing regulatory science is the reliability of scientific claims. How can a regulator; a judge; a member of a legislative body; a reporter; or anyone else judge the validity of a claim? The substantial increases in regulations dealing with energy, drugs, food, health, environment, and other areas has caused a demand that scientific foundation of regulations be evaluated to ensure that ideology; accommodation of special interests; or the arbitrary decision of the regulators does not influence the decision process. The desire for assessing the reliability of scientific information is not limited to regulations. Legislative actions, judicial decisions, and numerous policies dealing with subjects such as national security require an assessment of reliability of their scientific foundation. The reliability of regulatory scientific claims can be categorized as follows:

Personal Opinions: The expression of views by individuals regardless of their training, experience, and social agenda, is included in this group. In a free society, every individual has the right to state an opinion. This freedom of expression is also applicable to expressing views ranging from Proven Science to Fallacious Information.

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Are the reputation and scientific standing of an individual the determining factors in accepting a claim? As we will see later in this chapter the acceptability of a personal opinion is impacted by the reputation of the claimant. This process known as Matthew Effect influences how the media and the scientific community react to a scientific claim. Intuitively one is inclined to accept a claim by an accomplished and renowned scientist. However, history is full of events when highly qualified scientists are proven to be wrong.

Personal opinions are seldom, if ever, acceptable as the foundation of reliable science. Society is entitled to convincing evidence that a scientific claim is valid. Unfortunately, the standard process of the public media is reliance upon this category in its reporting of scientific issues.

Gray Literature: This category consists of written information prepared by government agencies, advocacy groups, and others that has not been subjected to an independent peer review. Often Gray Literature is an organized and written form of personal opinion. Experience shows that the scientific quality of this category is unknown and ranges from various classes of Evolving Science to Fallacious Information. This is the favorite category of many government agencies, advocacy groups, and individuals who want to promote an idea.

Peer-Reviewed: The value of peer review and similar processes in assessing the validity of scientific assertions has been known for at least two centuries, and there is a voluminous amount of literature describing the peer review process.

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Consensus-Processed: This category consists of the result of a process used to resolve scientific disputes, particularly those in contested areas of science. This process is particularly useful in regulatory science as in most cases scientific claims are at best Partially Reproducible Evolving Science and often includes assumptions, judgments, default data, and related areas. Due to the similarity of consensus-processed and peer review, both are described in the following section.

Fallacious Information

Historically, those who feel strong about a subject have attempted to present information claiming to be science with the objective to promote their societal goals. This class of information is often called "pseudo-science", "junk science", or "politically-processed science". As expected, information in this class, cannot pass independent peer review, the key process for the determination acceptability of a scientific claim. There are those who justify the dissemination of fallacious Information on the basis that it is necessary to exaggerate a problem to move the population to accomplish a noble goal. What is being overlooked is that such an approach is unethical and has the potential of causing long-term damage.

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PEER REVIEW PROCESS

Independent peer review is a significant part of reliability pillar of BARS/MERSC, and a key element of regulatory science. There are multiple types of peer review ranging from asking an individual to review a document to participating in a peer-review panel with the objective to reach consensus. The elements of the process are as follows:

1. An individual is asked to perform peer review or join a panel to perform the peer review. The individual must be qualified and independent, implying that the individual has no conflict of interest.
2. The individual or the panel is provided with review criteria consisting of questions requiring responses.
3. Ideally, an oversight committee oversees the entire process.

Qualification of Peer Reviewers

The selection of a reviewer must be based on the totality of that individual's qualifications. Key elements of qualifications of the reviewer are:

1. **Education:** The reviewer should have a minimum of a B.S. degree in the relevant scientific discipline. In most cases a reviewer has advance degrees.
2. **Professional Experience:** Because of rapid scientific

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advancements, often relevant professional experience is as important or more important than earned degrees. Consequently, significant experience in the area that is being reviewed or assessed is necessary.

3. **Peer Recognition:** Election to office of a professional society; serving on committees of scholarly organizations; relevant awards; and similar activities are considered a demonstration of peer recognition.
4. **Contribution to the Profession:** The individual's contribution to professional advancement may be demonstrated by publications, particularly those in peer-reviewed journals. In addition, patents and similar activities are also considered.

Conflict of Interest

One of the most complex and contested issues in peer review is the independency of the reviewers, collectively called "conflict of interest." The ideal member of the peer review panel is an individual who is intimately familiar with the subject and yet has no monetary interest in it. Despite this apparent difficulty, the scientific community has successfully performed peer reviews without having a real or an apparent conflict of interest. As stated above, the guiding principle for conflict of interest in peer reviews is as follows:

Those who have a stake in the outcome of the review may not act

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as a reviewer or participant in the selection of the reviewers.

To insure the independency of panel members, they are required to sign a statement indicating a lack of personal or financial interest in the outcome of peer review.

Peer Review Criteria

The recommendations of a reviewer or a review panel are responses to specific questions called review criteria, charge of the panel, review questions, or lines of inquiry. There are many other organizations seeking peer review. However, key groups seeking peer review can be categorized as follows

1. Scientific journals are by far the largest users of peer review. Typically, they choose multiple reviewers and seek their advice on the publication of submitted manuscripts.
2. As the submitted requests for funding far exceed available funds, Funding agencies use peer review to seek peer review to select projects to be funded
3. Regulatory agencies seek peer review of scientific assessment documents

Experience has shown that sponsoring agencies and organizations would benefit from the availability of general guidelines for selection of project-specific review criteria. The following criteria

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guide to the sponsoring organizations for preparation of project specific review criteria:

1. Scientific validity is by far the most important aspect of any project. It consists of compliance with established scientific principles and relevant standards as expressed by Scientific Rules Principle of BARS/ MERSC. The scientific validity criterion is applicable to scientific journals, funding process as well as regulatory science documents.
2. Scientific Originality implies that the information is new and provides additions to the body of knowledge. It is particularly applicable to submissions to scientific journals and funding organizations.
3. Scientific Creativity is recognized to be more difficult to identify s compered to scientific validity and originality by attempting to identify new pathways; entirely new approaches to address a problem; or numerous other approaches that may lead to a scientific breakthrough. This criterium applies primarily to funding projects but is also desirable for journal publications
4. Relevancy applies to all three groups seeking peer review implying that the information that is being peer reviewed be relevant to their mission or respond to their needs.
5. Qualifications of the Personnel and Availability of Facilities are applicable to funding agencies.

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6. Finally, certain criteria address submission, legal and ethical requirements that are applicable to certain projects

Shortcomings of Peer review process

In recent years many published papers have been retracted. Meanwhile several organizations have been established to identify papers that have been retracted and the causes of retraction. Probably the best-known organization is *Retraction Watch* that almost daily provides relevant information. A study in progress at Georgetown University has identified several potential causes of retraction of papers as follows:

1. The claim of the authors is undetectable during correctly performed peer review
2. Errors by the editor consisting of intellectual, political, and other biases of the editor
3. Inadequate peer- review process resulting from poor selection of qualified peer reviewers, inadequate selection of review criteria, or lack of attention by the editor to the process including interaction with the authors
4. Business interests of the journal because the journal needs funds typically provided by the open-access journal
5. Errors by the authors including republication, plagiarism, violation of ethical requirements, or other potential Errors
6. The journal needs papers to meet publication schedule

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A reasonable review of shortcomings of peer review, as currently practiced would be too extensive to be included in this manual, I stead two significant examples are described

Wakefield Effect: An "Early Report" published in *Lancet* by Andrew J. Wakefield et al claimed that normal children may develop autism after having been vaccinated with a measles, mumps, and rubella vaccine. Wakefield et al. conceded that, "We did not prove an association between measles, mumps and rubella vaccine and the syndromes described." Although the paper by Wakefield et al was eventually retracted, it was used by individuals, organizations and certain public media dedicated to a specific ideology to oppose childhood vaccinations, thus causing significant adverse health consequences. Obviously, the peer review process used by a well-established and prominent biomedical journal was not functioning. How could a properly performed peer review did results in the publication of a paper that could not establish an association between the MMR vaccination and autism? Obviously *Lancet* had other motivations.

Nuclear Fusion: Probably a most famous example of shortcomings of peer review is a claim by Fleischmann and Pons (1989) of having achieved fusion of deuterium (an isotope of hydrogen) atoms at slightly above room temperature otherwise known as cold fusion. The peer review did not and could not find a reason for rejecting the paper as the authors provided the details of their experiment.

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How could peer review identify the result of an experiment that is well -managed? The only possible solution was an attempt to reproduce the claims of the authors. Given the enormous consequences of the study, quickly several investigators attempted to reproduce the claim and found it to be wrong.

Matthew Effect: introduced by Morton based on a statement in Bible "For all those who have, more will be given, and they will have in abundance; but from those who have nothing, even what they have will be taken away." It is true that peer recognition has been and continues to be one of the key criteria for assessing the qualifications of an author, an investigator, or an individual considered to be a peer. However, will an identical paper submitted by a Nobel laureate and a young and unknown investigator be treated the same? The "Mathew Effect" is particularly severe if personal opinions or gray literature is considered during the scientific assessment

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REGULATORY SCIENCE ETHICS

Much like other emerging scientific disciplines regulatory science has shown significant advancement. During the evolution of the new scientific discipline it became necessary to make a distinction between its elements and its tools. As described in this manual Best Available Regulatory Science (BARS) and Metrics for Evaluation of Regulatory Science Claims (MERSC) evolved as a key element of regulatory science. Another key element of regulatory science is independent peer review by providing the reliability of a scientific claims. The next step in the evolution process was the identification of regulatory science tools. 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. Many individuals and organizations attempted to explain a scientific issue in a manner that promoted their societal objectives. There were many other problems in the application of a scientific discipline with variable level of uncertainty.

The inadvertent or sometimes purposely exaggerated presentation of specific scientific subject was and continues to be a key issue in regulatory science. Such an action is likely to damage the cause rather than helping it. Another key problem was and continues to be communicating scientific issues to the three groups involved in the regulatory process. The education, training and experience of

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members of the regulator, regulated and relevant scientific communities covers many disciplines ranging from physical and biological sciences; engineering disciplines; and medicine, to social sciences and law.

Numerous problems including those identified above led to the development of regulatory science ethics. This key tool follows the existing ethical requirements of various scientific including medical ethics. A review of existing medical and other scientific ethics is beyond the scope of this Manual. As reviewed by Moghissi et al the misdeeds of Nazi regime led to Nuremberg trials which in turn became the foundation of international including the most recent World Medical Association Declaration of Helsinki. Although medical ethics have dominated many other professions have also developed relevant ethics.

Instead of addressing regulatory science ethics in this section, relevant ethics consideration ise included in discussions of various regulatory science tools

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JEFFERSONIAN COMMUNICATION PRINCIPLE

A key tool of regulatory science is traceable to Thomas Jefferson, the third president of the Unites States. There is a widespread perception among a segment of policy makers that the public is incapable of comprehending the unique structure of regulatory science. The proponents of such a view need to consider the following principle expressed more than two centuries ago. The Jeffersonian communication principle is derived from a frequently quoted statement by Thomas Jefferson:

> *If we think the people are not enlightened enough to exercise control with a wholesome discretion, the remedy is not to take it from them but to inform their discretion by education.*

The statement by Jefferson can be converted to a language applicate to regulatory science as follows:

> *If the regulators and other policy-makers believe that the affected community is incapable to comprehend regulatory science, the remedy is not to ignore them but to translate science including its uncertainties in a language that is understandable not only to the affected community but also to the public at large*

Opposition to Jeffersonian Communication Principle There are those who, for several reasons, believe that the public does not need to be involved in major decisions particularly if the decision is too complex, or is based on science beyond the ability of the public

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to comprehend. Thus, to proponents of this concept, the public cannot comprehend its needs. This group believes that the release of relevant information would cause avoidable harm. The release of the information would delay or negate the completion of a decision that to the judgment of proponents of the decision would be vital. Jonathan Gruber, a well-known and highly accomplished Professor claimed that the voters are too "stupid" to recognize the significance of a law. Although he apologized for having made the statement the claim remains in the public domain. The Opponents to Jeffersonian Principle includes the following groups:

Claiming Ignorance: Individuals representing this group consist of certain regulators and other policy makers who claim that they are unfamiliar with the relevant science or are unqualified to describe the scientific aspects of the regulation. As described in several places in this manual, in virtually every case, regulatory science can be reasonably translated in a language that is understandable to a knowledgeable non-specialist.

The Desire to Achieve a Goal: There are individuals, advocacy organizations, government agencies, and others who consider achieving a societal goal to be important enough to maintain secrecy and avoid informing the affected community on the scientific details of a societal decision.

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Lack of Freedom: This group considers the inclusion of the people including the affected individuals and groups to be unnecessary. According to the philosophical foundation of this group, most people are "stupid" to understand the science and its application. Therefore, transparency is a wasted effort.

Categorization of Affected Community

The language used in communication regulatory science must consider the needs of affected community. Therefore, the communication of regulatory science claims must be translated in a language that is understandable to three groups as follows:

1. The first group consists of Individuals who are specialists in the relevant scientific discipline. This group includes members of various disciplines that are used in regulatory science

2. The second group consists of knowledgeable non-specialists. This group consists of individuals who have sufficient knowledge to understand a scientific issue and can communicate with individuals with insufficient understating of the science. Most policy makers, members of various scientific disciplines, and many others are included in this group.

3. The third group consists of individuals who are neither specialists nor knowledgeable non-specialists.

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Ideally regulatory science must be written in a language that is understandable to all three groups. However, the second group is of significance as regulators and other decision makers are likely to fall in this group. In addition, key segments of the regulated community and various scientific disciplines are also likely to be knowledgeable non-specialist. Therefore, regulatory science must be written in a language that is understandable to this group. For example, many regulatory science documents include mathematical equations that are not necessarily understandable to knowledgeable non-specialists. In most cases, the content of mathematical equations can be described in an understandable language for non-mathematicians.

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IMPLEMENTATION OF ETHICAL RULES PRINCIPLE

The development of regulatory science ethics is traceable to the Ethical Rules Principle of BARS. The following information excludes a description of scientific ethics as there is already an extensive literature covering scientific ethics. There have been extensive national and international agreements such as those developed by medical, chemical, and engineering organizations. Instead this section emphasizes regulatory science ethics.

Truthfulness and Communicability

Truthfulness is universally accepted regardless of the ethnicity, religious belief, or cultural background. On occasion, individuals or organizations claim that it is in the interest of a good cause to be less than truthful. Those that modify science must recognize that is unethical to be less than truthful regardless of the reason to do so. The relevant regulatory science ethics is as follows

In communicating scientific information, the scientific community or an individual scientist may not exaggerate or minimize beneficial or adverse effects of an agent, a situation, a condition, or any other relevant issue

The communicability element of Ethical Rules Principle may as well be called implementation of Jeffersonian Principle. The relevant regulatory science ethics is as follows:

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The regulatory science communication must be in a language that is understandable to the affected community

Regulatory Science Transparency

Science used in regulatory decisions is largely predictive in nature and often regulatory decisions are made based on insufficient scientific knowledge. Specifically, regulatory decisions are based on regulatory science ranging from Partially Reproducible, Association-Based, Hypothesized Evolving or Borderline Science to Judgment and Speculation included in Borderline Science. Therefore, regulations include assumptions, judgments, inclusion of default data, and speculation. As described under Regulatory science truthfulness, BARS/MERSC provides guidance on how to address the need for transparency implying that the regulators must provide to the affected community various elements of their scientific decisions.

Regulatory science transparency may not be confused with the requirements of national security. On occasion, it may be necessary not to provide the scientific details of a subject to the public as it may create apprehension or even cause damage to that public.

Virtually every scientific discipline used in regulatory science is impacted by regulatory science transparency. The example of regulatory toxicology may be used to demonstrate the point.

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One of the most studied carcinogens is Ionizing Radiation. There have been many animals, as well as epidemiological studies including Hiroshima and Nagasaki atomic bomb survivors, radium dial painters, workers at facilities of Atomic Energy Commission, and others. Based on these studies, the (US) National Academies (consisting of National Academy of Sciences, National Academy of Engineering, and National Academy of Medicine) recommended the application of linear, non-threshold (LNT) model to assess risks of exposure to ionizing radiation in the regulatory process. The National Academies recognized the lack of scientific evidence and to be protective suggested that cancer may be caused by exposure to ionizing radiation linearly from levels that have been observed to zero levels. The LNT assumption has caused significant regulatory impact. In contrast the French equivalent of the National Academies came to the opposite conclusion suggesting that there is a threshold for cancer causation. The French appear to have accepted the principles established by Paracelsus, the father of toxicology that "the dose makes the poison" The French Academies explicitly relied upon numerous evidences contradicting the LNT mode. For example, in several cities around the world with naturally occurring radiation there have no more cancer in the population than other cities with much less exposure. In addition, there is evidence called "hormesis" indicating that exposures to ionizing radiation cause low level positive health effects.

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Meanwhile the Health Physics Society, one of the primary professional societies dealing with radiation protection came to similar conclusions provided by the French Academies

The two relevant ethical rules address two issues. The first issue deal with scientific assumptions:

Those who make a scientific claim including a claim addressing a regulatory science issue must provide their assumptions, judgments, and similar parts to the affected community in a language that is understandable to a knowledgeable non-specialist.

The second and equally significant ethical rule the inclusion of areas outside the purview of science

A scientific claim, particularly a regulatory science claim, may not include societal objectives, ideology, or any other issue that is outside the Purview of Science.

Consequently, the decision of National Academies to be protective in recommending LNT is outside the purview of science.

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THE ROLE OF STAKEHOLDERS IN REGULATORY SCIENCE

Stakeholder participation is an important tool of regulatory science. Regulatory agencies claim to involve stakeholders in their decision process, but in many cases, only advocacy groups and their members constitute the only group involved in the decision process. There two key issues in stakeholder participations process.

- Who is a stakeholder?
- How to contact the true stakeholders?

Historically the word stakeholder came into use in the early 1700s combining the words "stake," meaning to mark land with stakes or pointed sticks, and "hold," as in keeping, tending, or watching over. A recent search for the definition of stakeholders led to the following

Stakeholders are individuals or representatives from organization or interest groups that have an interest in the agencies' work or policies

According to this definition a stakeholder is anyone who wants to be involved in a decision or an action. Before the subject of stakeholder participation is discussed, it is helpful to address the difference between public and stakeholder participation. The public is typically defined as "people as a whole" implying that the entire population constitutes the public.

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As currently practiced, despite numerous efforts to use a systematic process, stakeholder participation is dominated by advocacy organizations. Surely one should recognize that if a factory is next to the Georgetown University its operation may impact the people who live near the University more than individuals who live in Alaska, California, Texts, or Florida, regardless of their belief, political view, or ideology. The stakeholders can be categorized into three groups.

1. Decision Makers and Directly Impacted Stakeholders

Decision Makers: This group consists of managers of the agency proposing new regulations, corporate executives who are proposing an action, or any other decision maker. As the initiators of the proposed action, the decision makers have a clear stake in the outcome of the process. Because of their affiliation with agencies or companies involved in the process, these individuals are easily identified and easy to engage in ongoing communication throughout the process.

Directly Impacted Stakeholders: This group consists of individuals or organizations that may be directly impacted by a proposed action. The impact includes the following:

- Adverse health effects
- Adverse financial effects
- Loss of jobs
- Exposure to noise, foul smells, and other elements

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Experience shows that members of this group of stakeholders are reluctant to participate in the decision process as they are often unwilling to devote time to study a subject or participate in a stakeholder meeting unless they perceive a significant impact on their daily lives. Love, one of the initiators of stakeholder participation process, recommends that an *affirmative outreach* approach is necessary to ensure their participation.

2. Facilitators and indirectly impacted stakeholders

Facilitators: This group consists of the individuals or organizations that are responsible for implementing the actions of the decision makers. This group might include employees of a regulatory agency, a company, or other individuals that have a key role in facilitating the process. Members of this group can be readily identified.

Indirectly Impacted Stakeholders: This group consists of those who directly or indirectly represent the interest of decision makers, or directly impacted stakeholders. They include relevant elected officials at the federal, state, and local levels or other individuals and organizations whose constituents consist of decision makers or directly impacted stakeholders.

The identification and notification of this group of stakeholders is not difficult as they are normally associated with a known institution. Elected officials expend a significant effort to become

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known within their constituency and thus are readily identifiable. Once identified, these stakeholders are notified by phone, in writing, or via electronic communication.

3. Generally concerned stakeholders

This group includes individuals who, based on their personal philosophies, beliefs, or ideologies, are interested in or concerned about the action under consideration. As practiced today, this group consisting of advocacy organizations constitute the majority and most influential stakeholders. In addition, this group also includes a small fraction of the public that is concerned over the process that is used to manage a proposed action.

Stakeholder Participation Management

The categorization of stakeholders in various groups, the process for reaching them, and their participation in the decision process implies that an action is predictable. Activities that are either unpredictable or their impact extraordinarily large such as prevention and mitigation of terrorist actions, large-scale natural disasters, and acts of war would require a significant modification of the process. One of the most important issues of concern to the stakeholders is the timing of their involvement. Many stakeholders complain that decisions are made, and the stakeholder participation is mere "window dressing" to justify the decision. Many stakeholders have a deep-seated mistrust of agencies responsible for public and stakeholder participation. Similarly,

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there are those who believe that as-long-as stakeholders are given the opportunity to "vent their anger," it is not necessary to consider their concerns when making decisions.

Numerous issues of concern to stakeholders include regulatory science. In many cases, the concerns of stakeholders, notably directly impacted stakeholders, are expressed with trepidation because often they have insufficient scientific competency to appreciate the intricacies of the issues that impact them. However, these fears can be substantially reduced or eliminated if the information provided to stakeholders addresses the issues of their concern in a manner that is clear, concise, and easy to understand. Examples of activities that would particularly benefit from stakeholder participation are:

- Various stages of development of Environmental Impact Statements
- Licensing a project with significant environmental and public health impact
- Approval of a drug with significant public heath impact
- Evaluation of safety of drinking water in a reasonably large area.
- Independent peer review of a significant project

Finally, it is imperative to recognize the unique nature of each stakeholder group, how members of reach group can be reached, their unique importance and contribution, and the benefit of

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stakeholder participation. Just listening to stakeholders is not enough; their comments must be seriously considered.

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APPLICATION OF MATHEMATICAL MODELS

Predictive mathematical models have provided a great service to humanity by predicting various events with various levels of accuracy. Probably the most important service provided by mathematical models is predicting weather for specific areas ranging from hurricanes to pleasant weather. Experience shows that the predictions of the severity and the timing of an event improve the closer the events takes place.

There is a wide-spread misunderstanding between mathematical equations that describe scientific laws and related activities and predictive models. Equations that describe Proven Science including scientific laws are not models but accurately describe the relationship between two or more parameters. One of the most significant scientific equations is Einstein's law:

$$E= m.C^2$$

Where E is energy, m is mass, and C the speed of light. This equation is the foundation of nuclear power, and the atomic bomb. A simple example of an equations describing reproducible activities is

$$D= S.t$$

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Where D is the distance, S is the speed, and t in time indicating that a distance that needs to be traveled (e.g. 100 km or 100 miles) is determined by the speed (e.g. 50 km or 50 miles per hour) and the time (two hours). The above equation is not a mathematical model but a computation following scientific principles.

In contrast, mathematical models consist of mathematical equations that attempt to establish a relationship among several parameters with variable level of reproducibility. The BARS/MERSC system provides a definition and identifies various categories of predictive mathematical models as follows:

A mathematical model consists of identification of key relevant parameters, establishment of interaction between and among them, and using the resulting information to develop a mathematical equation that responds to regulatory needs

Primary Predictive Models: Although the foundation of many models, particularly those that address contested areas of science, is *Proven* or *Reproducible Evolving Science*, they also use assumptions, judgments, and other tools to develop or apply the model. Therefore, their predictions include inherent uncertainties. Consequently, Primary Predictive Models are entirely Partially Reproducible Evolving Science.

Secondary Models: These models use primary models as their foundation. The predictive ability of these models is significantly

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lower than those of Primary Models. These models are likely to fall at best into *Scientific Judgment.*

Tertiary and Lower Models: These models use secondary models as their foundation. The predictive ability of these models is at best *Speculation.*

Identification of Various Categories of Predictive Models: Despite significant shortcomings of mathematical models, many policy decisions including regulations dealing with environment, safety, transportation, human health, ecology, budgets, and economics are based on predictive models. Assessment of mathematical models used in regulatory science requires consideration of certain specific and distinct areas. Modelers recognize qualitative, semi-quantitative, and quantitative models. There are also deterministic and probabilistic models. Mathematical predictive models provide an outstanding tool to initiate the understanding of potential understanding of an event. It is critical to appreciate that mathematical models include uncertainties. Therefore, they may not include societal objectives, ideology or any other non-scientific issue. Ideally, a mathematical model needs to be verified before it is used in policy including regulatory process. Unfortunately, often the regulators must decide. Occasionally mathematical modelers equate a mathematical model with Proven Science or Reproducible Evolving Science disregarding the inherent uncertainties associated

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with models. Therefore, the Ethical Rules Principle of BARS/MERSC requires that the decision makers follow BARS

Relevant Ethics

A scientific issue is settled only if anyone with the necessary scientific skills, required equipment, and facilities can reproduce it

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VOLUNTARY STANDARDS

Voluntary standards attempt to standardize various systems, operations and activities developed by private organizations covering virtually every aspect of human activities. They provide requirements, specification, consistency, and characteristics to ensure that materials, products, processes, and services are fit for their purpose. Typically, they are generally developed by private organizations notably Professional societies who intend to advance their professional goals. They are also developed by trade associations with the objective to promote their industry's products.

For several reasons government agencies in the United States and most other countries avoid developing standards. The Federal government has recognized that due to the needed exceedingly large number of standards it is impractical for the government to develop them. The *National Technology Transfer Act* mandates that voluntary consensus standards be the preferred types of standards for Federal government to use unless they violate laws. Numerous government rules and guides provide a process on how to use voluntary standards

Recognizing the need for internationally accepted standards the International Standardization Organization (ISO) consisting of representatives of standard-setting organizations of various countries was established to coordinate and approve standards developed by various national organizations.

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In the United States American National Standards Institute (ANSI) is the national organization that provides approval of voluntary standards developed by various standardization organizations to be provided to ISO for international approval. Consequently, the ANSI approval is the prerequisite for approval of any standards by the ISO

Metrology

One of the key voluntary standards used in virtually all areas is metrology consisting of measurement science. In the Unites States between 1830 and 1901 there was an *Office of Weights and Measures* within the Department of Treasury and then was transferred to the Department of Commerce and renamed *National Bureau of Standards.* Finally, in 1988 it was renamed to National Institute for Standards and Technology (NIST). The goal of NIST is to advance measurement science, standards, and technology.

In contrast to almost all countries, United State currently uses two measurement systems simultaneously. The primary system in known by several names and originating in the English system. The second system is known as *International System of Units* (SI). Due to uncertainties in the English system, in 1893 the US adopted standards for length and mass and units such as inch, foot, pound, quart and other units that were defined in terms of meter and kilogram

In 1875 the US along with 17 other nations signed the *Treaty of the Meter* that established *Bureau International des Poids et Mesures* (BIPM) in France. Ever since there-have been many efforts to adopt

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the SI system. For example, in 1968 Congress authorized a three-year study to evaluate the desirability of converting the US system to SI and most members favored the conversion. In 175 Congress passed The *Metric Conversion of 1975* establishing a *Metric Board.*

As stated above currently both English and SI systems are used in the US. A key and confusing situation exists in medicine. US Regulations (41CFR 101-29-101) require that federal agencies use "metric system of measurements in Federal product descriptions". In the US, normally the SI system is used as well as and many other products that are intended to export such as wine.

Fahrenheit

Currently the Unites States is the only major country that uses Fahrenheit as a unit for temperature. The unit was developed by Daniel Fahrenheit in Danzig at that time a city within Prussian Confederation. In 1724, Fahrenheit used a mixture of water and several other molecules as the foundation for establishing a temperature scale. He also developed a thermometer using mercury as a key agent. For obvious reasons the temperature was named after its developer, Fahrenheit.

Water covers more than 2/3 of the surface of the earth. Water constitutes more than 60% of human body weight. Weather is largely impacted by water vapor and water droplets. Water is also the primary component of cooking. Given the significance of water it is understandable that not only original Fahrenheit, but also Celsius temperature measurements are based on water. However, the difference between Fahrenheit and Celsius

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is how the degrees are organized. Why is the freezing point of water is 32^0 in Fahrenheit and not a different number? The same applies to boiling point (212 ^{o}). In contrast in the International System (SI) water freezes at 0^0 C and evaporates at 100^0 C. Both evaluation of weather conditions and cooking would greatly benefit from the application of the SI

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RISK ANALYSIS

The scientific, engineering, and medical communities are concerned over the potential risk associated with their activities Despite its relatively long history there continues to be a confusion on the terminology of risk analysis .

One of the most significant events in the history of risk analysis was a comprehensive multi-volume report prepared by Norman Rasmussen on probabilistic risk as applied to nuclear power plants. That report originally commissioned by the then AEC was completed after the AEC was divided into two including the Nuclear Regulatory Commission. The formation of the EPA risk assessment became an important part of regulatory process. Due to the confusion between two key elements of risk analysis, eventually, it became necessary to seek the advice of National Academies on the distinction between risk assessment and risk management. Finally, a statement by the America Association of Engineering Societies provided a reasonable terminology as shown in Figure 6

Risk Assessment is the scientific process that attempts to provide a quantitative relationship between an event such as exposure to an agent and an effect. Risk Management attempts to apply the result of the risk assessment to a policy decision such as promulgating a regulation. The objective of risk communication is to communicate risk assessment and how it was used in risk management to the

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affected community and the public. The three- step process (assessment, management and communication) is risk analysis.

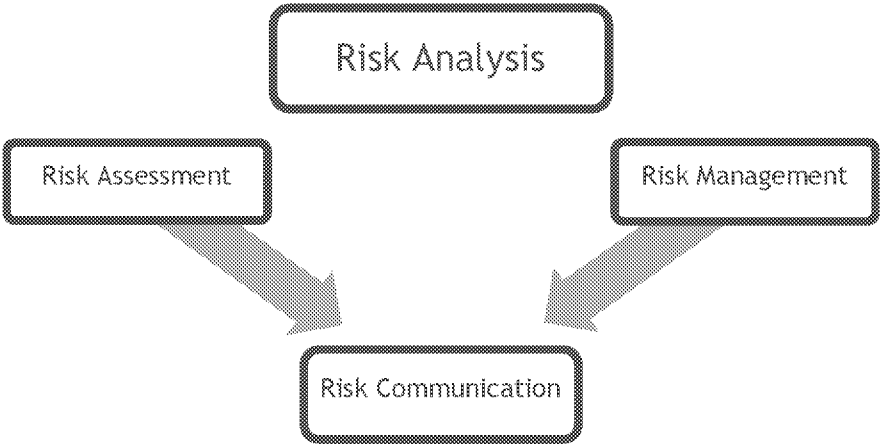

Figure 6. The structure of risk analysis

For obvious reasons the scientific community must perform risk assessment. In contrast, risk management is the responsibility of regulators and other policy makers. Following the Jeffersonian Principle, the scientific community is also responsible for translating risk assessment materials in a language that is understandable to knowledgeable non-specialists and the affected community.

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Risk Assessment Process

There are three key forms of risk assessment. For obvious reasons human health risk assessment dominates the process to be followed by ecological risk assessment. Both human health and ecological risk assessment rely upon deterministic mathematical processes. In recent years certain risk assessors, at least partially attempt to apply probabilistic methods in their assessment process. In contrast based on its application, probabilistic risk assessment relies heavily upon probabilistic mathematical models. The probabilistic risk assessment must predict an evet such as breakdown of a devise, a pipe, a wall, or many other situations to compute its consequence.

A detailed description of the three forms of risk assessment would be too complex to be included in this manual. However, there are several elements that are common to all three processes as follows:

Hazard Identification: The first task of a risk assessor is to identify a potential hazard without attempting to quantify the impacts of the hazard. Examples of hazard identification are:

- Human injury and/or fatalities because of an accident.
- Breakdown of a bridge because of wear and tear.
- Induction of cancer resulting from exposure to a carcinogen.
- Human injury or fatality as a result fire.

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Source Assessment: The next step consists of evaluation of events that may lead to an exposure using methods such as Fault Tree Analysis, Event Tree Analysis, or evaluation of routine operations. The process consists of three parts:

1. Identification of unit operations, their components, and subcomponents.
2. Assessment of the probability of failure of each unit operation and its components based on experience, knowledge of the process, or assumption.
3. Evaluation of the nature and quantity of resulting releases, or "source terms" for each unit operation and its components.

Exposure Assessment: This step attempts to characterize sources by identifying emission rates, or source terms to the recipient of an agent. Exposure Assessment for the three primary users of risk process deviate somewhat. However, the most comprehensive process deals with human health. The transport and transformation of a toxicant in environmental media is evaluated and either measured or using models, is predicted. Note that an agent released into the air may be transported but also transformed; it may be deposited into the soil or waters via rain; it may enter the food chain directly via vegetation or indirectly through milk, meat, fish, etc.

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For human-health risk assessment, computation of exposure to hazardous condition incudes:

1. The magnitude of exposure (e.g. concentration)
2. The frequency of exposure
3. The duration of exposure
4. The routes of exposure: air, water, and food
5. The routes of intake consisting of ingestion, inhalation, or skin absorption
6. The size of the population.

Note that the same process as identified for health risk assessment, with some modifications can be used for ecological risk assessment.

Effects Assessment: The effects-assessment process requires the establishment of a relationship between exposure and an adverse effect. For human-health risk assessment the endpoints may be accidental death or injury; morbidity, and mortality caused by exposure to toxic agents. Ideally, exposure (dose) response relationship should be based on epidemiological or animal data. Note that specific models are used to convert data resulting from animal experiments to human equivalent data thus supplementing epidemiological data

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Risk Characterization: Ideally this final step in risk assessment should include the following Potential adverse effects:

1. Affected population
2. Unique populations
3. Uncertainties of risk
4. Estimate of most likely risk and its statistical limits
5. Site-specific requirements

The true risk characterization must be responsive to the needs of risk managers without compromising science. currently, there is disagreement among three groups on the inclusion of societal objectives (conservatism) in risk assessment process:

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COST BENEFIT ANALYSIS

This tool is based on the notion that a proposed action, requires computation of their economic consequences. Included in this tool are cost-benefit analysis, risk-benefit analysis, and related activities

Currently, the process of cost-benefit analysis and related processes are being reevaluated by proposed rulemaking of the EPA. As the final rule is likely to significantly change the current processes, this section will be written once the final rule is published.

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KEY REFERENCES

Part 1: Introduction

Food and Drug Administration. The promise of regulatory science FDA 2010 www.fda.gov/scienceResearch/specialtopics/RegulatoryScience/ucm2282002.htm

Food and Drug Administration: FDA and NIH announce collaborative initiative for fast-track innovation to the public. www.fda.gov/Newsroom/Pressannouncements/2010/ucm201706.htm

Moghissi AA, Straja SR, Love BR, McBride, DK, and Stough RR. Innovation in Regulatory Science: Evolution of a new scientific discipline. *Technology and Innovation*.16; 155-1165: 2014.

Moghissi AA, McBride DK, and Amin M. Regulatory Sciences: Description of the discipline, education, and ethics. *Japan Ministry of Science and Technology*: 2012

National Institutes of Health. Regulatory Science http://commonfund.nih.gov/regulatory science. Accessed January 2018.

ED_002546_00000008-00078

Part 2 Key Elements of Regulatory Science

Merton RK. The Matthew Effect in science. *Science* 159; 56-63: 1968

Moghissi AA, Calderone RA, McBride DK, Jaeger L. Innovation in Regulatory Science: Metrics for Evaluation of Regulatory Science Claims based on Best Available Regulatory Science. *Journal of Regulatory Science*. 5; 50-59: 2017

Moghissi AA, Keim M, McBride DK, and Swetnam MS. Wakefield Effect. *Synesis* 4; 15-23: 2013

Moghissi AA, Love BR, Straja SR. Peer Review and Scientific Assessment: A Handbook for Funding Organizations, Regulatory Agencies, and Editors. Alexandria VA, Institute for Regulatory Science: 2013; Available from Amazon.com

Ruckelshaus WD. Science risk and public policy. *Science*. 221; 1926-1028: 1983

Wakefield et al. Ileal-lymphoid hyperphasia, and pervasive developmental disorder in children. *Lancet* 351; 637-641: 1998

ED_002546_00000008-00079

Part 3 regulatory Science tools

American Association of Engineering Societies. Risk Analysis: The Process and its Application. A Statement of the engineer's public policy council of AAES February 13, 1996.

American National Standards Institute. Overview of the U.S. Standardization System. www.standardsportal.org/usa_en/stndards_system.aspx Accessed November 2017

Environmental Protection Agency. Environmental modeling reports from the Science Advisory Board. www.epa.gov/measurements/environmental-modeling-reports-science-advisory-borad Accessed November 2017

Environmental Protection Agency. Human Health Risk Assessment www.epa.gov/risk/human-health-risk assessment; accessed Mai 2018

Heinz, S. *Mathematical modeling*. New York: Springer. (2011)

Love, BR, Straja, SR, Streeter, JR, Jones, SD, and Moghissi, AA. Stakeholder Participation: A New Process and Its Application to Environmental Decisions. *Technology* 11(2): 61-74: 2008.

Moghissi AA, Gurudas NA, Pei S, McBride DK, and Swetnam MS. Scientific ethics: Emphasizing regulatory science requirements. *Technology and Innovation* 17; 61-73: 2015

ED_002546_00000008-00080

Moghissi AA, Calderone AA, Azam A, Nowak T, Sheppard S, McBride DK, and Jaeger L. Regulating Ionizing Radiation Based on Metrics for Evaluation of Regulatory Science Claims. *Dose Response*. 16; 1-6; 2018

National Research Council. Risk assessment in the Federal Government: Managing the Process. Washington, DC. National Academy Press 1983

Nuclear Regulatory Commission. Reactor Safety Study (also known as Rasmussen Report). Wash 1400. Washington DC, Nuclear Regulatory Commission, (October) 1975

ED_002546_00000008-00081