

Principles and Guidelines for the Development of a Science-based Decision Making Process Facilitating the Implementation of the 3Rs by Governmental Regulators

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Abstract

National government establishments, including regulatory agencies, are part of national science systems, which are a subset of larger national innovation systems. The forces that have influenced the basic roles of national government establishments in five countries over the past 10 yr are reviewed on the basis of a study commissioned by Industry Canada in 1999 for the Council of Science and Technology Advisors to the Canadian government. The most significant response among countries has been found to be the financial and managerial restructuring of government science and technology establishments driven by the push toward self-financing. Trends in the roles of government science and technology in six areas are also ranked, with increasing the health and safety of the nation, providing support to industry and participating in international cooperation occupying the first three positions. Potential ramifications of these trends on the implementation of the concept of replacement, reduction, and refinement (the 3Rs) in ensuring the ethical use of animals in regulatory testing are discussed. Science advice and its role in governmental decision making is reviewed on the basis of the 1999 Report of the Council of Science and Technology Advisors, *Science Advice for Government Effectiveness*. Six principles developed for the effective use of science advice in making regulatory decision have been adapted and are proposed with accompanying guidelines as a framework for the development of a science-based decision making process to facilitate the implementation of the 3Rs by governmental regulators. The proposed series of principles and guidelines are designed to reflect the rapidly evolving and complex context for government decision making, and to remain consistent across government departments and across nations.

Key Words: globalization; harmonization; innovation; science advice; science policy

Introduction

Acceptable scientific standards and relevant ethical principles are closely interrelated. The basic condition for the successful implementation of a change in scientific practice relating to the use of animals in regula-

tory testing or research is the quality of science supporting this change as well as its understanding, recognition, and implementation by all stakeholders in a timely manner.

The fact that it took more than 10 yr for the Organisation for Economic Co-operation and Development (OECD¹) member countries to reach agreement on banning the LD₅₀ test demonstrates that more timely and effective communication is needed to share and implement best practices at the national and international level. Communication of best practices must involve not only regulators and scientists but also animal welfare organizations, the public, and decision makers as users of science.

Forces Effecting Change in the Role of National Governments as Performers in the Science and Technology Arena

A study (Hickling et al. 1999) prepared on behalf of the Council of Science and Technology Advisors (CSTA¹) to the Canadian Government examined the roles and operations of various government science and technology establishments. The manner in which five countries (Australia, Finland, the Netherlands, the United Kingdom, and the United States) adapted to a changing environment over the past 10 yr was examined. Drawing on the literature, national studies, and reports as well as interviews with officials and academics involved in science and technology (S&T¹) in each country, the study identified the major trends and forces effecting change on national S&T establishments and responses of the establishments to these changes. Factors identified below were interpreted in the context of the larger innovation system inasmuch as changes in a government's role as an S&T performer cannot be interpreted in isolation from the changes affecting other S&T performers. This point is particularly relevant to regulatory testing and animal welfare.

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¹Abbreviations used in this presentation: 3Rs, replacement, reduction, and refinement; CSTA, Council of Science and Technology Advisors; CAAT, The Johns Hopkins University Center for Alternatives to Animal Testing; EPA, Environmental Protection Agency; HPV, high production volume; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; OECD, Organisation for Economic Co-operation and Development; R&D, research and development; S&T, science and technology; SIDS, screening information data set.

Fiscal Restraint and Accountability

The end of the cold war and inflated budget deficits from the worldwide governments' role in the economy are major determinants of fiscal restraint and accountability. All governments are being pressured to spend less, spend more wisely, and clearly indicate benefits. As a result, there is a trend toward new public management of government S&T establishments.

Globalization

Intensifying international competition, increased trade and investment, and burgeoning cooperation among firms (i.e., globalization) are largely responsible for a reorientation of worldwide production. Given the close interaction between globalization and improvements in information technology, closer global interaction invariably affects the innovation systems of countries. As a result, there is increased pressure on companies to improve the efficiency of research and development (R&D¹) and shorten their R&D time horizon. This pressure is not necessarily a disadvantage from the perspective of the 3Rs. For example, it was recently acknowledged that over the 10 yr of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH¹), the harmonization of the interpretation and application of technical guidelines has dramatically reduced or obviated the need to duplicate testing carried out during the R&D phase of new medicines and therefore reduced the numbers of animals used (McCarthy 2001).

Technical Change

Technical change, especially in information technology sectors, is having a profound impact on the science system not only in terms of structure but also of productivity. Given its reciprocity with globalization, the effects of change in information technology on the structural organization of science have been similar, namely, increased collaborations made possible by computer networks. Through sharing data, scientists can focus on their research irrespective of their location, which encourages interdisciplinary research to flourish. This new level of cooperation has given sustenance to the concept of the virtual laboratory and its potential to catalyze the development and validation of new and refined methods for regulatory testing. Advances in computer technology have also significantly pushed the boundaries of understanding through the rapid processing of data required in the simulation of molecular reactions, an additional tool to reduce and refine the use of animals in regulatory testing.

Accompanying this increase in understanding has been a decrease in time horizons for creating new knowledge. Scientific productivity has also benefited from advances in

computers and related software, allowing the performance of more science-related activities with less equipment and money. Not surprisingly, all of these technical changes in scientific instruments have led to a burgeoning of scientific knowledge. The current move toward electronic publishing accompanying this increase in knowledge will further accelerate the communication of results while broadening access to knowledge through information networks. The result should be faster transfer of scientific information on regulatory testing and replacement, reduction, and refinement (the 3Rs¹) between government regulators and those who are regulated, thereby supporting faster harmonization of the new and refined methods between countries.

Personnel

An aging scientific workforce, combined with declining interest in some fields of science and excess of personnel in areas that suffered government cutbacks, is directly related to the future availability of well-trained researchers. This topic is being actively discussed, especially in smaller countries (e.g., Finland, Australia, and the Netherlands). In general, most countries have undergone a decline in the number of researchers employed in government S&T establishments.

International Trends in the Roles of National S&T Departments and Agencies

The most common trend among countries has been the financial and managerial restructuring of government S&T establishments driven by the push toward self-financing. Countries have reorientated their institutes to act as service providers to industry, government agencies, and local communities. Accompanying such adaptations have been efforts to focus the research of these establishments with mission statements that tie into national priorities.

In addition to their conventional role in providing a system of standards and regulations, national S&T departments and agencies have responsibility for the following roles, listed here in the generally accepted decreasing order of priority: (1) ensuring the health and safety of the nation, (2) providing for the defense of the nation, (3) conducting applied research, (4) supporting basic science and the acquisition of knowledge, (5) providing support to industry and promoting regional economic development, and (6) coordinating and participating in international cooperation.

In Table 1, the international trends in the roles of government S&T departments and agencies are summarized. The roles are ranked according to decreasing strength of activity observed across the six nations studied. As can be seen, while health and defense remain first and second priorities, respectively, in relation to the general accepted order provided above, international cooperation is being assigned

Table 1 Trends in the roles of governmental science and technology^a

Role	Canada	Australia	Finland	Netherlands	United Kingdom	United States
Ensuring the health and safety of the nation						
Providing support to industry and promoting regional economic development						
Coordinating and participating in international cooperation						
Supporting basic science and the acquisition of knowledge						
Conducting applied research						
Providing for the defense of the nation						

Key—strength of the governmental roles

Strongly decreasing Strongly increasing

Weakly decreasing Weakly increasing

Strong but static Weak but static

^aAdapted from *The Roles of the Federal Government in Performing Science and Technology: An International Perspective*, Canadian Council of Science and Technology Advisors Secretariat, April 1999. Ottawa, Canada: CSTA.

increasing importance and is placed in the third level of priority. In fact, all of the countries view international cooperation as very important, and Australia and Finland are actively working to increase that cooperation. However, this increase in cooperation is set in the context of increasing international competition. The United States, in particular, is struggling with recognition of the importance of international cooperation on the one hand and rising protectionism and concerns about foreign access to research results on the other hand. In relation to regulatory testing and the 3Rs, it is important that government from all countries continue to adapt in an effort to “achieve an open and productive science system, where scientists worldwide can exchange research results” (OECD 1998).

International Cooperation for More Effective National Science Advice

In its report *Science Advice for Government Effectiveness* (CSTA 1999), the CSTA to the Canadian Government defined science advice as “a value-added guidance deriving from scientific theories, data, findings and conclusions provided to inform policy and regulatory decision making.” Typically, governments use science advice in relation to decisions involving risk assessments that arouse public concerns about their health, safety, and long-term well-being, or decisions capitalizing on opportunities afforded by advancement in S&T.

The context for government decision making is highly complex and in constant evolution. Policies and decisions should take into account the diverse physical and social considerations at the national level. Increased access to information fuels heightened public interest in science-based issues. There is greater public scepticism of science-government-industry interactions. There is also greater emphasis on active public involvement in decision making in all countries.

The following three outcomes of an effective science advice process also apply to science advice for regulatory testing and the 3Rs: (1) government representatives are confident that a rigorous and objective assessment was made; (2) the public and parliamentarians are confident that the science advice is credible and used in the best interest of the citizens; and (3) each nation has enhanced ability to influence international solutions to global problems.

Principles and Guidelines for Effective Science Advice on the 3Rs in Regulatory Testing

On the basis of the CSTA report, the following six principles with associated guidelines have been formulated as a proposed framework to assist regulators, scientists, animal welfare organizations, the public and decision makers in implementing science advice on the 3Rs in relation to regulatory testing: (1) early identification, (2) inclusiveness, (3)

sound science and science advice, (4) uncertainty and risk, (5) openness, and (6) review. The proposed framework capitalizes on common goals. It can be used by governmental regulators from any country, irrespective of cultural differences and size, as a tool to progress toward the development of a science-based decision making process facilitating the implementation of the 3Rs in regulatory testing and harmonization between countries.

International science advice on regulatory testing issues must fulfill the following basic requirements to achieve effectiveness: (1) It must reflect the evolving context for government decision making, and (2) it must remain consistent across governmental departments and nations. The following principles and associated guidelines are intended to assist regulators and scientists, as well as animal welfare organizations, the public, and decision makers as users of animal-based science in implementing science advice on the 3Rs in relation with regulatory testing. Such science advice may be necessary when considering new testing methods that offer animal welfare advantages, or when animal care and use requirements are being considered that may directly impact testing procedures.

Principle 1: Early Identification

Departments should anticipate, as early as possible, those issues for which science advice will be required. Interdisciplinary, interdepartmental, and international cooperation should be in place to identify, frame, and address the 3Rs as a horizontal issue.

Guidelines

- Decision makers should cast a wide net through internal/external/international consulting to assist in the identification of issues.
- Departments should support and encourage their science and policy staffs to establish linkages with each other and with external and internal sources. For example, links should be established between those responsible for overseeing animal use and those responsible for describing the needs (e.g., regulatory agencies for environmental health and therapeutic products).

Principle 2: Inclusiveness

Advice should be drawn from a variety of scientific sources and from experts in many disciplines to capture the full diversity of scientific schools of thought and opinion. Inclusiveness aids in achieving sound science advice by reducing the impact of conflicts of interest or biases that exist among advisors. For example, it may be useful to develop a central knowledge base for nonproprietary information and historical data for both chemical and pharmaceutical testing.

Guidelines

- Decision makers should balance the multiple viewpoints received
- Departments should be open to both solicited and unsolicited advice from external sources.

Principle 3: Sound Science and Science Advice

Due diligence procedures for assuring quality and reliability, including scientific peer-review, should be built into the science advisory process.

Guidelines

- All advisory processes should be subject to due diligence.
- Decision makers must ensure there are sufficient resources to support policy research and analysis to underpin the science advice process.
- Selection of advisors should include at least some experts from other, not necessarily scientific, disciplines and be rotated regularly with replacements chosen to preserve balance of representation. A good example of this process is the peer review of validated methods implemented by the US Interagency Coordinating Committee on the Validation of Alternative Methods, with subsequent recommendations to regulatory agencies.

Principle 4: Uncertainty and Risk

In addition to hazards, uncertainty may include potential benefits or opportunities that should not be ignored. The goal of risk management combines scientifically sound, cost-effective, integrated actions that reduce risks while taking into account social, cultural, ethical, political, and legal considerations.

Guideline

- Science advisors and decision makers should communicate to the public and stakeholders the degree and nature of scientific uncertainty and the risk management approach used in reaching decisions. For example, the call for “a nontoxic environment,” or the assertion that “we must assure the public that chemicals are safe,” is wholly unrealistic (Balls 2002, this issue).

Principle 5: Openness

Democratic governments are expected to use decision making processes that are transparent and open to stakeholders. There should be consultation with stakeholder groups and

public disclosure to ensure that public values are considered in formulating policies.

Guidelines

- Decision makers should provide early warning of significant policy and regulatory initiatives to key interest groups, other governments, or international organizations, as appropriate.
- Departments should allow scientists freedom to pursue a broad base of inquiry and undertake widespread and thoughtful discussions.
- Departments should make every effort to support and encourage scientists to publish their research findings and conclusions in external peer-reviewed publications.

For example, at the OECD Existing Chemicals Task Force meeting March 1999, the Environmental Protection Agency (EPA¹) announced a change in requirements for testing high production volume (HPV¹) chemicals. Originally in 1998, Vice-President Gore had announced a cooperative agreement between the US Environmental Defense Fund, the EPA, and the Chemical Manufacturers Association (now known as the American Chemistry Council) to test approximately 2800 chemicals produced or imported in volumes of more than 1 million pounds/year—the HPV Challenge Program. The testing was to be carried out using the screening information data set (SIDS¹) requirements as recommended by the OECD (Green et al. 2001). A subsequent meeting of industrial, governmental, and academic scientists that was convened by The Johns Hopkins University Center for Alternatives to Animal Testing (CAAT¹) examined the status of alternative methods for SIDS endpoints. The meeting and subsequent follow-up, termed the CAAT TestSmart-HPV, succeeded in making recommendations, which EPA subsequently acted on and should result in a reduction of more than 70% of the originally projected 1.2 million animals to be used to provide complete data for the targeted 2800 chemicals.

Principle 6: Review

The review principle includes two elements: (1) subsequent review of science-based decisions to determine whether recent advances in knowledge affect the science and science advice used to inform the decisions, and (2) evaluation of the decision making process.

Guidelines

- Policy decisions should be reviewed to determine whether recent advances in knowledge affect the science and science advice used to inform the decision. The period for the review will depend on the state of the science.
- Departments should capture best practices that emerge

from advisory process and incorporate them into their guidelines to use for scientific advice in the future. For example, the OECD member countries reviewed and updated the three alternative test guidelines on acute oral toxicity testing, enabling the deletion of the classical LD₅₀ test guideline 401. In addition, the EPA periodically updates its testing guidelines to reflect current science.

Conclusion

The forces that have brought change to government S&T establishments over the past decade are numerous and interrelated not only to each other but also to the responses they have provoked. For example, the calls for fiscal restraint were partly a necessary reaction to prolonged recessions and to the shifting of scientific priorities after the end of the Cold War. The budget cuts that ensued, which were in response to the current politico-economic environment, became a force of change to the entire organizational structure of the science system.

In its report *Science Advice for Government Effectiveness* (CSTA 1999), the CSTA to the Canadian Government recognizes the intimate relation between effective science advice and government's effectiveness, particularly in the actual complex context for government decision making. Among the positive outcomes of an effective science advice process described in the report, the resulting enhanced ability of each nation to influence international solutions to global problems also applies to regulatory testing and the 3Rs.

Given such complexity, the major forces identified in this review—fiscal restraint and accountability, globalization, technical change, and personnel—are but a sample of the forces affecting the science system. They nonetheless categorize the major factors that directly influence government-performed S&T, including regulatory testing. Fiscal restraint is useful in identifying efficient mechanisms. In the context of regulatory testing and animal welfare, the topic of these Proceedings, fiscal restraint encourages the development of strategies based on in vitro screening, for example, rather than the demand for costly and unnecessary animal tests.

Trends in the six roles of governmental S&T, ranked by decreasing international intensity for each role, positioned international cooperation next only to health and industrial support. However, the study revealed that the United States was struggling with the recognition of the importance of international collaboration. In relation to regulatory testing and the 3Rs, it is important that governments from all countries continue to adapt in an effort to achieve an open and productive science system.

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