
Developing U.S. Oversight Strategies for Nanobiotechnology: Learning from Past Oversight Experiences

*Jordan Paradise, Susan M.
Wolf, Jennifer Kuzma, Aliya
Kuzhabekova, Alison W.
Tisdale, Efrosini Kokkoli, and
Gurumurthy Ramachandran*

Devising appropriate oversight for nanotechnology is a challenge. The field spans many scientific disciplines and product areas, capitalizing on the unusual properties and capabilities of material at the atomic scale. The critical feature of nanotechnology is not only the size at which manufacture occurs (~1-100 nanometers), but also the ability to control and manipulate the novel chemical, physical, and mechanical properties that emerge at this scale, including increased conductivity, optical properties, and reactivity. As nano-products enter the research and development (R&D) phase, hit the market, and enter consumer households, debate has emerged on oversight approaches. Regulators, manufacturers, and commentators are considering whether existing oversight systems are sufficient, those oversight systems need adjustment, or new oversight systems are needed.

The ultimate goal is to create or adapt oversight systems to make sure that the development of any technology and the resulting products are acceptable. Safety and effectiveness are prominent concerns. Oversight systems can distinguish between intended and unintended consequences of technology by setting boundaries or at least providing a mechanism of evaluation.

Oversight frameworks and regulatory approaches are diverse, and oversight is conducted by a range of institutions with various capabilities, cultures, and motives.¹ Regulations can articulate general guidelines or specific standards. They can regulate the result or mandate the processes by which the results are achieved. They can operate by motivating industry to share information, innovate, or change to meet

Jordan Paradise, J.D., is a Professor of Law at Seton Hall University School of Law. She previously served as the Associate Director of Research & Education at the University of Minnesota's Consortium on Law and Values in Health, Environment & the Life Sciences. **Susan M. Wolf, J.D.**, is the McKnight Presidential Professor of Law, Medicine & Public Policy; Faegre & Benson Professor of Law, and Professor of Medicine at the University of Minnesota. She chairs the University's Consortium on Law and Values in Health, Environment & the Life Sciences. **Jennifer Kuzma, Ph.D.**, is the Associate Professor and area chair of Science, Technology and Environmental Policy at the Hubert Humphrey Institute of Public Affairs at the University of Minnesota. **Aliya Kuzhabekova** is a Ph.D. candidate in Education Policy at the Hubert H. Humphrey Institute of Public Affairs at the University of Minnesota. **Alison W. Tisdale** is an M.S. candidate in Chemical Engineering and Materials Science at the University of Minnesota. **Efrosini Kokkoli, Ph.D.**, is an Assistant Professor in Chemical Engineering and Materials Science at the University of Minnesota. **Gurumurthy Ramachandran, Ph.D.**, is a Professor in the University of Minnesota's School of Public Health.

articulated targets, or they can manage industry more directly through what is often called “command and control.”² Regulatory and oversight tools include performance standards, tradable allowances, consultation between government and industry, and pre-market safety and efficacy reviews. The choice of approach can profoundly affect technological development, individual interests, and collective interests.³ Political and social considerations can also substantially affect the development and implementation of oversight approaches, as has been seen in the case of stem

five case studies in order to derive overarching lessons for nanobio oversight. In a subsequent paper, our project group will present recommendations for nanobio oversight; this paper concentrates on the prior question of what we can learn in comparing the case studies and begins to apply these lessons to nanobio.

This article uses multiple disciplines and methodologies, both qualitative and quantitative, to compare our oversight case studies. In doing so, we offer a new way to evaluate oversight and derive recommendations for future oversight approaches. Part I offers background

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cell research. In shaping oversight, it is also important to avoid stifling innovation or imposing unnecessary costs or burdens.

The oversight challenges posed by the subfield of nanotechnology known as “nanobiotechnology” (or “nanobio”) are particularly acute. Nanobiotechnology has been loosely defined as “a field that applies the nanoscale principles and techniques to understand and transform biosystems (living or non-living) and which uses biological principles and materials to create new devices and systems integrated from the nanoscale.”⁴ Nanobio refers to nano-products and nano-processes that use biological materials, that are intended to affect biological processes, or that mimic biological systems. Because nanobio sits at the intersection of engineering and biology, issues of biological efficacy (including drug efficacy), safety for individual organisms and larger biological systems, and environmental effects loom large.

In order to devise recommendations for nanobio oversight, we studied the history of oversight in five related areas: genetically engineered organisms (GEOs) in the food supply, pharmaceuticals (“drugs”), medical devices, chemicals in the workplace, and gene transfer research (commonly called “gene therapy”).⁵ Those individual case studies are presented elsewhere in this symposium.⁶ Each case study was selected because of its relevance to nanobio; these case studies focus on agencies potentially involved in nanobio oversight and consider product domains in which nanobio is potentially or already active. The successes and failures of each oversight regime offer lessons to apply in developing a sound approach to nanobio oversight. The purpose of this paper is to compare the

on the comparative studies and their interrelationship. Part II then discusses the methods used for comparative quantitative and qualitative research. Part III reports the results of our comparative analysis, using strengths and weaknesses of each oversight system to frame the discussion. Part IV provides further results by comparing correlations in each case study among evaluative criteria, asking what oversight system features seem to be related to one another. Part V then synthesizes the findings across case studies to identify key lessons learned from comparative analysis.

I. Background

A. *The State of “Nano” Science and Technologies*

Rapid developments in techniques to characterize and synthesize materials and devices at the nanoscale have led to substantial funding and progress in nanotechnology. Federal agencies, state governments, and private foundations are supporting research and development. Over 1,000 consumer products containing nanomaterials or marketed as having “nano” properties are on the market, and the number is steadily increasing.⁷

Advancements over the course of the last 100 years have paved the way for achievements at the nanoscale. In the early 1900s, x-ray diffraction techniques provided the ability to observe the geometry and shape of molecules. Electron microscopy provided further magnification power in the 1930s. The discovery of the structure of deoxyribonucleic acid (DNA) in the 1950s and the subsequent sequencing of the human genome almost 50 years later elucidated the workings of DNA, a nanoscale molecule. However, the roots of nanotechnology as a distinct technology can be traced

to 1981, when for the first time scientists were able to both visualize and manipulate matter at the atomic level. Published in that year, the first technical paper addressed the capacity of molecular engineering to manipulate molecules with atomic precision.⁸ Gerd Binnig and Heinrich Rohrer at IBM Zürich invented the scanning tunneling microscope (STM), a powerful enabling technique for viewing surfaces at the atomic level whose invention garnered the Nobel Prize in Physics in 1986.⁹ In 1985 Robert Curl, Harold Kroto, and Richard Smalley at the University of Sussex and Rice University created a new form of carbon that they named “buckminsterfullerene” (which we now call “fullerene” or “buckyballs”).¹⁰ The three scientists won the 1996 Nobel Prize in Chemistry and their work started an avalanche of research into nanoscale materials.

Over the past two decades scientists and engineers have focused on studying and controlling the composition, size, and shape of nanoparticles and nanomaterials, for use in applications as diverse as catalysis, coatings, fuel cells, sensing devices, and drug delivery. Researchers have been able to measure and manipulate materials at the nanoscale in ways never before possible, leading to nano-products with diverse uses. One example is the synthesis of dendrimer-encapsulated nanoparticles for a variety of biological applications,¹¹ including in catalysis,¹² as biological labels,¹³ and as nanomaterials that can harvest light and transfer the energy to a reaction center.¹⁴

Another important nano-product has been the carbon nanotube. Many potential applications have been proposed for carbon nanotubes, including conductive and high-strength composites, energy storage and energy conversion devices, hydrogen storage media, nanometer-sized semiconductor devices, chemical and mechanical sensors, optical elements, and probes for use in cell biology.¹⁵ Some of these applications have been translated into products, while others are still in laboratory development.

Targeted delivery of therapeutics is another area of vigorous research. Liposomes, the classic drug delivery nano-vector, and more recently polymeric nano-vectors, are a promising class of nanomaterials for the delivery of therapeutics (from DNA, to small-molecule drugs, to protein therapeutics) to cancer sites and other targets.¹⁶ Like liposomes, polymeric drug delivery vectors serve to encapsulate their cargo and shield it from degradation and clearance from the body.¹⁷ The polymeric architecture allows for a range of desirable properties to be designed into the delivery vector.

B. The Role of Oversight

Despite the overwhelming promise of nanotechnology in the laboratory, acceptance of any technology for large-scale use by the public depends on proper oversight. However, development of nanobio oversight approaches — whether creation of a new nano-specific approach or clear application of an existing approach — remains at an early stage. Attention thus far has largely focused on oversight of workplace exposures, specifically occupational health issues associated with engineered nanoparticles, such as buckyballs and carbon nanotubes. Less progress has been made on developing adaptations to oversight systems for nano in food and agricultural products, drugs and devices, and gene therapy.

Development of oversight approaches for nanobio need not and should not proceed in a vacuum. The last century has seen repeated efforts to devise oversight approaches for emerging technologies. Designing appropriate oversight approaches for nanobio should be grounded in study of the strengths and weaknesses of past oversight approaches in related areas of science and technology. We should avoid oversight models that have not worked well and embrace those that have succeeded.

Early approaches to nanobio oversight, at both the national and international level, demonstrate that more work is needed. In the United States, there is no nano-specific regulation, although existing oversight systems are being applied to processes and products by federal agencies such as the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Health and Safety Administration (OSHA). EPA has implemented a voluntary reporting system for industry, although a review of that program reveals very little industry participation.¹⁸ EPA issued a 2008 notice in the *Federal Register* informing manufacturers that they must give 90 days’ notice prior to the manufacture or import of new chemical carbon nanotubes for commercial purposes, under requirements for new chemicals under the Toxic Substances Control Act (TSCA).¹⁹ At the congressional level, the House of Representatives has passed the National Nanotechnology Initiative Amendments Act of 2009.²⁰ This act mainly supports cooperative nano-research, though it also highlights the need for more data on the health and safety effects of nanotechnology.

States have been at work as well, mandating the reporting of manufacture and use of specific nanomaterials. California’s Department of Toxic Substances Control issued targeted letters in January 2009 requesting nano-specific data and worker protection methods for carbon nanotubes within one year from identified manufacturers.²¹ Massachusetts has also

started efforts to collect information on worker exposure to nanoparticles. The city of Berkeley, California requires annual reporting to the Toxics Management Division on manufactured nanoparticles.²² These reporting and tracking efforts at the state and local levels are an initial step toward gathering health and safety information in order to address what oversight approach is needed.

Internationally, there have similarly been efforts to spur reporting, though nano-specific regulation is lacking. The United Kingdom was first to implement a voluntary reporting scheme, but received minimal submissions from industry.²³ In 2004, the Royal Society and the Royal Academy of Engineering, commissioned by the British government, recommended consideration of a ban on free (not fixed in a matrix) manufactured nanoparticles in environmental applications,²⁴ although the British government has yet to act on that recommendation. Reports indicate that Canada is poised to be the first country to enact legislation regarding mandatory reporting and monitoring of nanomaterials.²⁵ The Australian government is considering nano-specific regulation following a commissioned 2008 report by Monash University scholars concluding that existing regulatory frameworks contain numerous gaps when applied to nanotechnology.²⁶ At the European Union level, the European Economic and Social Committee of the European Parliament published a 2005 opinion recommending that the European Commission introduce methods to identify nanotechnology risks and propose European guidelines by 2008.²⁷ The European Parliament has yet to deliver guidelines in response.

A variety of published reports from academics, scholarly organizations, professional organizations, and government bodies have offered assessment of the efforts so far, the usefulness of existing regulatory frameworks, what areas need further study, and what oversight options exist.²⁸ These oversight options for nanobio include creating new laws and regulations, revising existing laws and regulations, interpreting existing laws and regulations to cover nano-products, and designing non-regulatory governance approaches (e.g., voluntary industry standards). The diversity of nano-products may preclude a single approach or framework and instead require different oversight regimes for different product types. In addition, risk assessment for nanomaterials may be difficult. There is little information to date on the effects of nanotechnology, including types and routes of human exposure, dose-response relationships, kinetics and cellular interactions, fate and transport in the environment, and correlations between the properties of materials and their toxicity.

C. Developing Nanobio Oversight

Because nanobio raises significant oversight challenges, it is important to consider now what kind of oversight structures and processes would work well. This calls for evaluating both emerging approaches to oversight as well as oversight strategies used in the past for closely related technologies. We can learn from those historical case studies which approaches have worked well and which have not.

In order to ground nanobio oversight recommendations in critical study of past models, we undertook analysis of five case studies: oversight of GEOs, drugs, medical devices, chemicals in the workplace, and gene therapy. Each of these case studies appears elsewhere in this symposium. Our case studies analyze oversight approaches in a multidisciplinary and multi-modal way. We bring to bear historical, policy, legal, and ethical perspectives, analyzing these oversight experiences both quantitatively and qualitatively. Our goal is to provide a rich set of resources to inform development of nanobio oversight approaches and, more broadly, to provide new tools for analysis of science and technology oversight.

In order to see how our five oversight case studies fit together, they can be compared by substance (target technology, key oversight body, and related nano-products or processes), by stage (oversight of research, manufacturing, or commercial use), and by oversight system characteristics (including voluntary vs. mandatory, government vs. industry, and multi-agency vs. single agency).

COMPARING SUBSTANCE

These five case studies cross several federal agencies, technological areas, and products. Oversight of GEOs in the food supply uses a pre-existing regulatory framework that was originally promulgated under laws intended for non-biotech products (traditional food crops and microorganisms); application to GEOs reflects the view that GEOs are not fundamentally different from other organisms.²⁹ Three core federal agencies are instructed to regulate products of biotechnology including GEOs through the Coordinated Framework for the Regulation of Biotechnology: the EPA using TSCA and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); the FDA using the Federal Food Drug and Cosmetic Act (FDCA); and the U.S. Department of Agriculture (USDA) using the Federal Plant Pest Act (FPPA).³⁰ Relevant nano-products include organisms modified by nanotechnology, nanoparticles for agrichemical delivery (e.g., Syngenta PrimoMaxx), and nanofood products (e.g., Canola Active cooking oil). Very few of these products

are on the market, but many more are in research and development.³¹

When pharmaceuticals are the target of oversight, the key oversight body is the FDA under the FFDCA. FDA regulation has developed over the last century to include manufacturing controls for quality purposes, labeling controls for safety, and a premarket approval process to determine safety and efficacy with a risk/benefit approach.³² The related nanotechnology products are nano-drugs and nano drug delivery systems. Using its established oversight paths, the FDA has approved human drug products such as Abraxane and Doxil anticancer drugs, Rapamune immunosuppressant to prevent organ rejection in renal transplant patients, Epaxal Hepatitis A vaccine, and Estasorb topical estrogen therapy for treatment of hot flashes.³³

When medical devices are the oversight target, the FDA again plays the key oversight role. FDA regulation of medical devices has evolved since the 1930s in response to rapid technological advances. The 1976 Medical Device Amendments to the FFDCA created a regulatory scheme based on risk classifications affording different levels of scrutiny.³⁴ The FDA has struggled to clarify its oversight approach to products combining drugs, medical devices, and biologics, and Congress recently created an Office of Combination Prod-

ucts at the FDA. Devices involving nano and within the FDA's purview include nano-coatings on medical devices and nano-sensors in the body. Medical device nano-products that have already entered the market include Vitoss bone graft substitute, TiMesh tissue reinforcement and hernia repair, EnSeal™ tissue sealing and hemostatis system for laparoscopic and open surgery, and the CellTracks Analyzer II in vitro diagnostic device.³⁵

The Oversight of chemicals in the workplace falls largely to OSHA. Oversight of workers' exposure to chemicals in the workplace has its roots in early workplace exposure guidelines proposed in the 1940s by the American Conference of Governmental Industrial Hygienists (ACGIH).³⁶ Government oversight has been grounded primarily in three federal laws: the Mine Safety and Health Act of 1969,³⁷ Occupational Safety and Health Act (OSHAct) of 1970,³⁸ and TSCA.³⁹ OSHA has taken the lead, with research assistance from the National Institute of Occupational Safety and Health (NIOSH). Relevant nano-products are nanoparticles and nanomaterials in the workplace, including the scientific laboratory, such as nano-titania, ceramic nanofibers such as silicon carbide and zirconium carbide, and a wide variety of fullerenes, quantum dots, nano-wires, and carbon nanotubes.

Figure 1

Total Product Life Cycle (TPLC) Emphasis of Each Oversight System

This chart maps the 5 oversight case studies onto those stages in the total product life cycle (TPLC) for which that oversight model provides most insight. These TPLC stages are taken from the TPLC model created by the FDA's Center for Device and Radiological Health. See D.W. Feigel, "Total Product Life Cycle," available at <www.fda.gov/cdrh/strategic/presentations/tplc.ppt>. The circle illustrates the primary foci of the oversight system(s) for each case study.

Oversight Case Study	Total Product Life Cycle									
	Laboratory Development									
Gene Therapy	X	X	X	X						
Drugs			X	X	X	X	X	X		
Medical Devices		X	X	X	X	X	X	X		
Chemicals in Workplace					X	X		X		
GEOs in Food Supply	X	X	X	X	X	X	X	X		

Figure 2

Comparison of Characteristics of Oversight Systems

Oversight System	(V)oluntary v. (M)andatory	(G)overnment v. (I)ndustry	(M)ulti-agency v. (S)ingle agency	(S)tate v. (F)ederal	(I)mmEDIATE entry into market v. (P)re-market notification v. Product (A)pproval
Gene Therapy	M	G	M	F	A
(New) Drugs	M	G	S	F	A
Medical Devices	M	G	S	F	P + A
Chemicals in Workplace	V	G + I	S	S + F	I + A
GEOs in Food Supply	V + M	G + I	M	F*	I + P + A

* Note that although some states have passed specific laws to deal with GEOs, product approval is federal.

Oversight of gene transfer research (or “gene therapy”) first evolved in the 1970s-1980s. This oversight regime exemplifies oversight of research, as no approved products have yet come to market. Oversight of gene therapy has involved two main bodies: (1) the National Institutes of Health’s (NIH) Recombinant DNA Advisory Committee (RAC) under the supervision of the Office of Biotechnology Activities (OBA), and (2) the FDA, in particular its Center for Biologics Evaluation and Research (CBER). Nanotechnology in gene therapy offers new means of non-viral gene transfer. Relevant nano-products include a variety of technologies currently in R&D phases, including nanoparticle vectors for targeted gene delivery of tumor-suppressing proteins, nanoparticle-nucleic acid complexes for *in vivo* gene delivery, organically modified silica nanoparticles that bind to plasmid DNA and express encoded proteins, and use of RNA to package and deliver therapeutic agents for gene delivery.⁴⁰

COMPARING STAGES IN THE TOTAL PRODUCT LIFE CYCLE

Another way to integrate these oversight case studies is by considering what phases of product development and deployment each oversight effort targets. Figure 1 depicts the focus of each oversight case study in rela-

tion to stages in the total product life cycle (TPLC), a concept widely used at FDA and in industry.⁴¹ This graphic depiction suggests that different oversight approaches may be relevant to different stages of nano-product development. For example, gene therapy oversight and oversight of drugs and devices may have much to offer oversight of nano research, especially human subjects research on nano-processes and products. On the other hand, once products are approved and in commercial use, oversight of GEOs in the food supply may tell us more about effective oversight options to safeguard consumers and the environment.

COMPARING CHARACTERISTICS OF OVERSIGHT SYSTEMS

A third complementary way of comparing oversight experiences is to compare key characteristics of oversight systems, including whether the system is a mandatory or voluntary system, whether the oversight is chiefly performed by government or industry, whether oversight involves a single agency or multiple agencies, whether the oversight system operates primarily at the state or federal level, and what type of approval is required (whether immediate entry of the product into the market is allowed without oversight, pre-mar-

ket notification is required, or full product approval is needed). Figure 2 depicts comparisons of characteristics among our five case studies in chart form. No two systems are identical when compared this way, although the oversight systems for gene therapy, new drugs, and medical devices have the most in common when depicted this way. The GEOs oversight system is the most complex of the five systems; this is a result of the multi-agency cooperation for these products and the scope of applications.

II. Methods for Quantitative and Qualitative Comparison

We used a range of quantitative and qualitative strategies to compare the five case studies. The case studies vary among themselves in methodology and approach; each case study's methodology is described in that study elsewhere in this symposium.⁴²

This section is organized into three parts. The first provides a quantitative analysis, describing the purpose and results of the data and calculations. The second section provides a qualitative analysis for a more integrative investigation of the five case studies that combines our data with the literature and other resources. The final section discusses the methodological limitations of this study.

A. Quantitative Analysis

In order to evaluate these oversight systems quantitatively, we performed expert elicitation using a survey tailored for each case study.⁴³ A generic expert elicitation survey instrument is available in Appendix A. The expert elicitation surveys for each case study are referenced in the individual case studies in this symposium. Surveys were designed to collect the opinions of targeted experts on the success of the oversight system in question, as judged using a list of 28 criteria generated through a methodology published elsewhere,⁴⁴ based on asking experts what are the most important features of oversight systems and consulting the relevant literature. The 28 criteria are listed on Figure 3. There are 7 criteria that address development of the oversight system (D1-7), 15 that address attributes of the system (A8-22), 1 that addresses change in the system over time (E23), and 5 that address outcomes of the system (O24-28). Each case study in this symposium discusses these criteria at length.

We incorporated the 28 criteria into a survey that was used, with slight adaptation, to ask experts to evaluate one of the five oversight systems. The survey asked each expert to evaluate an oversight system by assigning a number for each oversight criterion; our survey instrument offered descriptive phrases to help the expert translate the scale provided. The response

scale was divided into five ranges: 0-20 (improbable, probably not, unlikely, near impossibility), 21-40 (less than an even chance), 41-60 (even chance), 61-80 (probable, likely, I believe), and 81-100 (near certainty, virtually certain, highly likely). However, the survey instrument also told respondents that "you do not have to refer to these phrases at all, and can enter your scores directly based on your own interpretation of the criteria."

Experts were identified based on several factors including their contributions to the scientific literature, membership on advisory boards and/or editorial committees of key journals, and status within their respective communities. The total number of expert responses received varied among the case studies. The GEOs survey had 17 responses (33% response rate), devices had 14 (45% response rate), drugs had 15 (48% response rate), workplace chemicals had 20 (74% response rate), and gene therapy had 5 (19% response rate). The respondents were classified into one of four categories based on their self-reported institutional affiliation: industry, academic, non-governmental organization (NGO)/non-profit organization, and government.

Data analysis was performed and reported independently for each case study (see the separate articles in this Symposium).⁴⁵ While case study methodologies varied,⁴⁶ some common analyses were carried out. First, each case study research group calculated the mean expert rating for each criterion. These mean ratings were then sorted into three ranges (0-39, 40-60, and 61-100), which are depicted in Figure 3 by an unshaded circle, a half-shaded circle, or a full shaded circle, respectively. We also determined the level of agreement among expert ratings on each criterion by classifying the responses based on how spread out the experts were in their rankings. For example, a high level (H) of agreement was found where most expert responses for a particular criterion fell into one range; a low level (L) of agreement was found where experts were across the boards on their ratings; and a neutral level (N) of agreement was found where experts did not lump into one range and were also not spread across the ranges on their rating. (See Figure 3.) Due to the small sample size for gene therapy, we included the data from the five experts on Figure 3, but shaded it to indicate that it is not included in the quantitative analyses across case studies.

To construct an influence diagram depicting the relationship among criteria, we also calculated the Pearson correlation coefficient (r) between each pair of criteria for each of the case studies except the gene therapy study. This numerical score can be interpreted as follows: if the correlation coefficient between two

Figure 3

Quantitative Assessment of Oversight Systems' Strengths Based on Mean Ranges

The strengths of each of the oversight systems on various criteria are assessed by identifying the range within which the mean score by experts for each criterion falls and the level of expert agreement in rating the criterion. The ranges are presented by circles. A full-shaded circle ● indicates means from 61 to 100. A half-shaded circle ◐ indicates means from 40 to 60. An unshaded circle ○ indicates means from 0 to 39. Levels of agreement among experts are indicated with parenthesized letters (L), (N), (H), indicating low, neutral, or high level of agreement among experts respectively. The shaded area indicates data from the case study with a small number of responses.

Criteria	GEOs		Drugs		Devices		Workplace Chemicals		Gene Therapy			
	Mean	Range (level)	Mean	Range (level)	Mean	Range (level)	Mean	Range (level)	Mean NIH	Range NIH (level)	Mean FDA	Range FDA (level)
Development												
D1. Impetus	52	◐(L)	34	○(H)	36	○(N)	26	○(H)	68	●(L)	56	○(L)
D2. Clarity of technological subject matter	69	●(H)	71	●(H)	53	◐(L)	50	◐(L)	80	●(H)	63	●(L)
D3. Legal grounding	39	○(N)	63	●(N)	52	◐(N)	63	●(L)	54	◐(M)	74	●(M)
D4. Public input	46	○(L)	68	●(N)	61	●(L)	43	◐(H)	69	●(M)	50	◐(M)
D5. Transparency	34	○(H)	60	◐(H)	64	●(L)	44	◐(N)	61	●(M)	50	◐(L)
D6. Financial resources	38	○(N)	48	◐(L)	38	○(L)	30	○(N)	65	●(L)	60	◐(L)
D7. Empirical basis	45	◐(L)	66	●(N)	58	◐(L)	55	◐(N)	78	●(H)	71	●(M)
Attributes												
A8. Legal grounding	45	◐(L)	65	●(N)	55	◐(L)	64	●(L)	58	◐(M)	65	●(L)
A9. Data requirements & stringency	53	◐(L)	83	●(H)	65	●(N)	37	○(N)	86	●(H)	90	●(H)
A10. Post-market monitoring	27	○(H)	57	◐(N)	45	◐(N)	25	○(H)	82	●(H)	91	●(H)
A11. Treatment of uncertainty	43	◐(L)	62	●(N)	54	◐(N)	41	◐(N)	72	●(L)	68	●(L)
A12. Empirical basis	57	◐(L)	83	●(H)	67	●(H)	58	◐(N)	88	●(H)	90	●(H)
A13. Compliance and enforcement	47	◐(L)	74	●(H)	66	●(N)	39	○(N)	63	●(L)	80	●(M)
A14. Incentives	53	◐(L)	68	●(N)	62	●(N)	33	○(N)	74	●(H)	78	●(H)
A15. Treatment of intellectual property	37	○(N)	55	◐(N)	58	◐(H)	45	◐(N)	80	●(H)	55	◐(L)
A16. Institutional structure*	77	●(H)	53	◐(L)	53	◐(L)	–	–	75	●(M)	58	◐(L)
A17. Flexibility	62	●(H)	50	◐(L)	51	◐(L)	31	○(N)	60	◐(M)	63	●(L)
A18. Capacity	37	○(H)	42	◐(N)	41	◐(N)	24	○(H)	73	●(M)	53	◐(L)
A19. Public input	40	◐(N)	49	◐(L)	44	◐(N)	55	◐(L)	78	●(M)	58	◐(L)
A20. Transparency	41	◐(N)	48	◐(L)	48	◐(L)	39	○(N)	65	●(L)	55	◐(M)
A21. Conflict of interest	37	○(N)	52	◐(L)	57	◐(L)	51	◐(L)	80	●(H)	65	●(M)
A22. Informed consent	26	○(H)	67	●(N)	58	◐(L)	32	○(N)	81	●(H)	73	●(M)
Extent of change												
E23. Extent of change*	47	◐(L)	72	●(H)	52	◐(L)	–	–	74	●(M)	58	◐(L)
Outcomes												
O24. Public confidence	54	◐(N)	49	◐(H)	43	◐(N)	41	◐(L)	61	●	52	◐(M)
O25. Research & innovation	55	◐(N)	52	◐(H)	48	◐(H)	52	◐(N)	48	◐(M)	51	◐(M)
O26. Health & safety	61	●(N)	73	●(H)	64	●(L)	43	◐(L)	84	●(M)	83	●(M)
O27. Distributional health impacts	58	◐(L)	64	●(N)	62	●(L)	–	–	66	●(L)	68	●(M)
O28. Environmental impacts	61	●(N)	48	●(H)	50	◐(H)	41	◐(L)	73	●(M)	75	●(M)

*Note that for these two criteria, ranges do not indicate strength or weakness of a system. High expert rating on the criterion of institutional structure means that the oversight system has a complex structure rather than it is strong. Similarly, neutral expert rating on the criterion of the extent of change does not indicate whether the change was good or bad.

criteria is $r^2=0.50$, this means that 50% of the variation in one of the criteria is related to variation in the other.⁴⁷ A cutoff of $r=0.7$ (or equivalently, $r^2=0.49$) was chosen as a minimum for determining significant correlations. Findings from the four case studies with more respondents (GEOs, drugs, medical devices, and chemicals in the workplace) were then compared to determine which significant correlations were common among these four cases and an influence diagram was constructed (see Figure 4). These results are discussed in Section IV.

B. Qualitative Analysis

In addition to quantitative data analysis, we performed a qualitative evaluation integrating expert elicitation results, interviews with experts (in the GEOs case), existing literature and law, including regulations. Given the variation in expert sample sizes across case studies, the combination of quantitative and qualitative analyses provides a more complete picture across all five oversight systems. Each case study with quantitative findings from a higher number of respondents (GEOs, drugs, devices, and chemicals in

the workplace) also reported the qualitative strengths and weaknesses of the oversight systems with respect to each of the 28 criteria. To derive these qualitative findings, we interpreted the mean expert rating for each criterion to indicate that this oversight feature was a strong, neutral, or weak aspect of the oversight system. We based this interpretation not only on the expert elicitation data described above, but also on information gathered from the literature and (in the GEOs case study) from phone interviews with 11 of the 17 GEO experts surveyed. Qualitative findings from the gene therapy case study relied on integrating the expert rating scores in the survey responses with consultation of the relevant literature and law, including regulations.

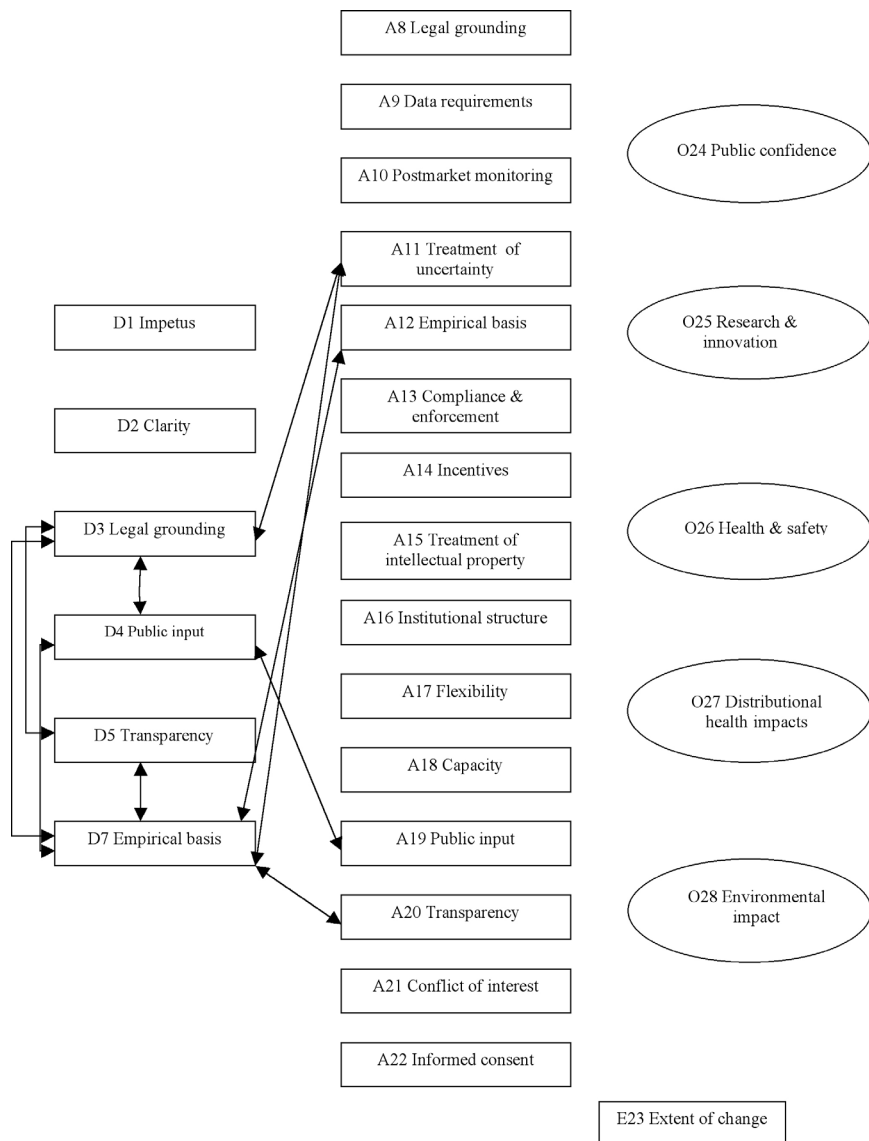
C. Limitations

This paper integrates multiple case studies with diverse characteristics. Study limitations derive from varying sample sizes among the case studies, the selection process for experts, and ambiguity in interpreting the meaning of scores assigned by experts. First, the number of expert respondents for each case study ranged from 5-20. This variation is due to multiple factors, including the number

Figure 4

Influence Diagram

This diagram shows correlations between criteria across four cases (GEOs, drugs, devices, workplace chemicals).



of experts identified for a particular oversight system and the willingness of experts contacted for a given case study to respond and participate in expert elicitation, a methodology more familiar to experts in some disciplines than in others. Even in the case studies with the largest number of respondents, the sample size is still fairly small, although other studies in the literature using expert elicitation report similar sample sizes.⁴⁸ However, in the case of gene therapy the sample size was small enough to limit our use of quantitative analysis. Thus this paper attempts to draw broad conclusions that apply to all five case studies without having identical data input from all of them.

Second, experts were chosen non-randomly by project investigators, introducing potential selection bias. There is also an uneven distribution of affiliation of respondents. (See Figure 5.) The disproportionate number of experts who listed themselves as academics, compared to the very limited number of government, NGO/non-profit, and industry respondents, makes comparisons by expert affiliation difficult.

Third, there is ambiguity in the scores assigned by the experts. For example, a score of 50 could mean that the expert feels neither one way nor the other, or that the expert is unsure about their answer. This distinction is important, but the answer cannot be gleaned from analysis of the data.

III. Comparative Analysis Using Strengths and Weaknesses

We sought to compare the relative strengths and weaknesses of the oversight systems we analyzed by interpreting the quantitative findings, as well as combining quantitative and qualitative findings. In using quantitative data to evaluate strengths and weak-

nesses of oversight systems we are defining the terms “strength” and “weakness” broadly. The survey instruments were drafted to provide a range of responses from 0 to 100. At the low end of this range (0), we chose descriptors that were generally less favorable (e.g., weak, not at all, low), while those at the high end of the range (100) were described as generally favorable (e.g., strong, extensive, high). In framing the responses in this manner, we attempted to create a spectrum from less favorable to more favorable, or in other words, from weakness to strength in the oversight system. However, the rating scales for some criteria do not lend themselves to this weakness-strength interpretation; each case study addressed each criterion individually.

Given the varying methodologies employed by the case studies and sample sizes of experts responding to the survey instruments, it is not feasible to draw definitive conclusions looking comparatively across the quantitative findings of these case studies. The case studies on GEOs, drugs, medical devices, and workplace chemicals employed similar methodologies for reporting expert elicitation data and had a similar number of experts. On the other hand, the gene therapy case study relied less on expert elicitation and more on qualitative examination of the oversight system as described in the literature and elsewhere. For these reasons, in utilizing quantitative data, we will primarily discuss only the four case studies with 14 or more experts, although all five case studies are represented in Figure 3.

This section will first focus on quantitative findings, comparing mainly among four case studies: GEOs in the food supply, drugs, devices, and workplace chemicals. (See Figure 3.) Second, the section will examine findings qualitatively, integrating the data with expert elicitation results, existing literature and law, including regulations. (See Figure 6.)

A. Using Quantitative Findings to Determine Strengths of the Systems

The expert elicitation yielded data on what the experts perceived as the strengths and weaknesses of each oversight system. Figure 3 depicts the mean of expert responses to the survey by criterion in each of the five case studies, as well as the level of agreement. As discussed in Part II, we have described a mean score in the range of 61-100 as a “strength of the system,” represented in Figure 3 by a blackened circle. A mean score in the range

Figure 5

Expert Affiliations

	Number of experts			
	Industry	NGOs	Academia	Government
GEOs	3	2	9	3*
Drugs	2	3	9	1
Devices	2	2	9	1
Workplace Chemicals	7	0	7	6
Gene Therapy	2	0	3	0**

* One expert associated with a think tank in the GEOs case was classified as a government representative for the purposes of this table because of his/her prior governmental role.

** Several experts in the gene therapy case study had current or past governmental experience as well, serving on the RAC.

of 0-39 is described as a “weakness of the system,” represented with an empty circle. A mean score in the range of 40-60 is described as “neutral,” represented with a half-blackened circle. The level of agreement of the experts is indicated by a letter in parentheses following the mean score (L=low agreement, N=neutral, H=high agreement). Part II.A. above has detailed how the level of agreement was determined. Figure 5 provides the expert affiliations for each case study.

For comparative purposes, we focus on the mean score of each criterion across the four case studies with at least 14 experts. (See Figure 3 for description of each criterion linked to the letter and number code.) Looking across those four case studies, the top three strengths for GEOs oversight were institutional structure of the oversight system (criterion A16, mean score 77), clarity of technological subject matter in development of the oversight system (D2, mean 69), and flexibility of the oversight system (A17, mean 62).

Figure 6

Qualitative Assessment of Oversight Systems’ Strengths Based on the Results of Expert Elicitation, Interviews, and Literature Review

The strengths of each oversight system on various criteria were assessed by comparing the results of quantitative assessment of strengths (based on mean rating scores by experts and level of expert agreement in rating) with the results of interviews (for GEOS) and literature review. The qualitative results are summarized using black, white, and half-black/half-white squares. A black square ■ indicates that the system was strong on that criterion based on qualitative assessment. A white square □ indicates that the system was weak. A half-black/half-white square ◐ indicates that the system was neither strong nor weak.

Criteria	GEOs	Drugs	Devices	Workplace Chemicals	Gene Therapy
Development					
D1. Impetus	◐	□	□	□	◐
D2. Clarity of technical subject matter	■	■	◐	◐	■
D3. Legal grounding	□	◐	◐	◐	◐
D4. Public input	□	◐	■	◐	◐
D5. Transparency	□	◐	■	◐	□
D6. Financial resources	□	□	□	□	□
D7. Empirical basis	◐	◐	◐	◐	■
Attributes					
A8. Legal basis	◐	◐	◐	◐	◐
A9. Data requirements	◐	□	■	□	■
A10. Postmarket monitoring	□	◐	□	□	◐
A11. Treatment of uncertainty	◐	◐	◐	◐	◐
A12. Empirical basis	◐	■	■	◐	■
A13. Compliance	◐	■	■	□	■
A14. Incentives	◐	◐	■	□	■
A15. Intellectual property	□	◐	◐	◐	◐
A16. Institutional structure	■	◐	◐	-	□
A17. Flexibility	■	□	◐	□	◐
A18. Capacity	□	□	□	□	□
A19. Public input	□	□	□	◐	□
A20. Transparency	□	□	◐	□	□
A21. Conflict	□	◐	◐	◐	■
A22. Informed consent	□	◐	◐	□	■
Extent of change					
E23. Extent of change	◐	◐	◐	-	□
Outcomes					
O24. Public confidence	◐	□	□	◐	□
O25. Research & innovation	◐	◐	◐	◐	□
O26. Health & safety	◐	□	■	◐	◐
O27. Distributional health impacts	◐	◐	◐	-	◐
O28. Environmental impact	◐	□	◐	◐	■

For oversight of drugs, the top three strengths were data requirements and stringency of the system (A9, mean 83), empirical basis of the system (A12, mean 83), and compliance and enforcement mechanisms of the system (A13, mean 74). For oversight of devices, the top three were empirical basis of the system (A12, mean 67), compliance and enforcement mechanisms of the system (A13, mean 66), and data requirements and stringency of the system (A9, mean 65). For oversight of workplace chemicals, there were only two criteria ranked in the “strength” range: legal grounding in development of the oversight system (D3, mean 63) and legal grounding of the system as an attribute (A8, mean 64).

The core conclusion to draw from these quantitative results is that experts found different strengths in the oversight systems for GEOs, chemicals in the workplace, and drugs and devices. “Strengths” for drugs and devices were very similar and indeed overlapping. This may reflect the fact that both drugs and devices are overseen by the FDA, while other agencies take the lead on GEOs and workplace chemicals. Yet the roster of strengths across all four case studies is telling — clarity of technological subject matter, flexibility in oversight, data requirements, and an empirical basis for oversight, as well as compliance and enforcement mechanisms. This begins to suggest what our experts valued in oversight systems germane to nanobiotechnology.

Of course, interpreting agreement or disagreement among experts depends on the make-up of our experts group. Figure 5 shows the affiliations of the experts we surveyed. It categorizes the experts for each case study into four categories as self-reported by the experts: industry, NGOs, academic, and government. Academia is the most highly represented category. Clearly, different results could have emerged if we had chosen a different mix of experts. Nonetheless, expert agreement in our analysis provides a helpful window into the strengths and weaknesses of these oversight system and helps identify avenues for further research.

B. Using Qualitative Findings to Determine Strengths of the Systems

A qualitative assessment of strengths and weakness is depicted in Figure 6. We determined the strengths and weaknesses of each system by subjectively combining the quantitative data (based on mean score for each criterion) with the results of literature review, legal analysis, and interviews with experts (for the GEOs case study). Details of the qualitative process and methods are described in each individual case study.⁴⁹

There were no strengths crossing all five oversight systems, but a number of criteria that ranked as

weaknesses or neutral across all five. All case studies ranked the following criteria as weaknesses: financial resources in development of the oversight system (D6) and capacity of the system (A18). This suggests that garnering adequate resources and assembling adequate capacity are problems across many oversight systems. All five case studies ranked as neutral the legal basis of the system (A8) and the treatment of uncertainty in the system (A11). This may suggest that none of the five case studies analyzed exemplifies an oversight system with strong grounding in underlying law and a strong approach to empirical uncertainty.

The following criteria were ranked across 3 or 4 out of 5 case studies as weak: impetus for development of the system (D1), post-market review (A10), public input to the system (A19), transparency of the system (A20), and public confidence (O24). This suggests common problems that oversight systems face. The following criteria were ranked across 3 or 4 out of 5 case studies as neutral: clarity of science and technological subject matter in development of the system (D2), legal grounding in development of the system (D3), public input in development of the system (D4), empirical basis for development of the system (D7), treatment of intellectual property in the system (A15), treatment of conflict of interest in the system (A21), extent of change in the system (E23), effect on research and innovation (O25), effect on health and safety (O26), distributional health effects as an outcome of the system (O27), and environmental effects as an outcome of the system (O28). This is a long list, 11 out of 28 criteria total. As our list of 28 criteria was originally developed through a mix of expert elicitation and literature review, asking what are the important characteristics of an oversight system,⁵⁰ it is remarkable that most of the oversight systems analyzed failed to show strength on these criteria

IV. Comparing Correlations among Criteria across Case Studies

A key goal of our work was to develop ideas about what features of oversight systems are associated with outcomes that most people would consider positive, such as beneficial health and environmental impacts, equitable distribution of health benefits, high public confidence, and promotion of research and innovation. In order to probe relationships among oversight system development, attribute, and outcome criteria, we generated correlation coefficients in pair-wise combinations for all possible combinations of criteria in the four cases with sufficient survey response rates (GEOs, drugs, devices, and chemicals in the workplace). We then identified all correlation coefficients in pair-wise combinations of criteria that were sig-

nificant at a p-value < 0.05 across all four cases. The resulting pair-wise combinations generated an influence diagram (Figure 4). The arrows in the diagram represent hypothesized associations among criteria in the oversight systems.

We found two types of associations: (1) those within a group of criteria (development, attributes, or outcomes) and (2) those between development and attributes criteria. We found no associations between attributes or development criteria and oversight outcomes. In other words, expert assessment of the development criteria and attributes of the oversight system was not significantly correlated with expert assessment of the outcomes across all four cases. One interpretation of this result is that in each of the oversight systems, different criteria are associated with the same desirable outcomes and there is not a simple answer as to which of the criteria should be emphasized to make any oversight system successful. Another interpretation is that the development criteria and attributes of the oversight system that our experts *subjectively* identified as most important,⁵¹ are not necessarily *objectively* associated with the most desirable outcomes. This explanation, however, is less likely since pair-wise correlations between development criteria and attributes were observed in individual cases. It is more likely that there is no one single recipe that worked for all oversight systems.

All correlations of types 1 and 2 were positive, meaning that the criteria that were correlated moved in the same direction — if one criterion went up so did the other, and if the former went down so did the other. The development criterion that showed the greatest number of relationships to other criteria across the four cases was empirical basis during development (D7). It was found to be related to public input (D4), transparency (D5), and financial resources (D6) during development. In addition, it was found to be associated with treatment of uncertainty (A11), empirical basis as an attribute of the system (A12), and oversight system transparency (A20). These relationships generate a number of potential areas for exploration in future research. For example, these relationships suggest that the extent of use of scientific evidence in decision making about the system is associated with the following: (1) the degree of public input during development; (2) the overall transparency of the process of development of the oversight system; (3) the availability of financial resources during development; (4) the transparency of the oversight system itself; (5) the extent of use of scientific evidence in the oversight process; and (6) the ability of the system to treat uncertainty.

These are relationships identified by the expert elicitation that need to be tested by future research. They do not imply that greater empirical basis during development *causes* greater public input, transparency, financial support during development, and later, as well as better ability of the system to treat uncertainty. It is also possible that greater financial resources during development stimulate a better empirical basis or that greater public involvement or transparency has this effect. In other words, our findings suggest that some relationship exists between the two criteria identified, rather than showing the direction of the relationship. Determining the direction requires future research. A further word of caution is that the relationships we are discussing are between experts' subjective ratings of characteristics of the oversight systems, rather than between assessments based on objective measurements.

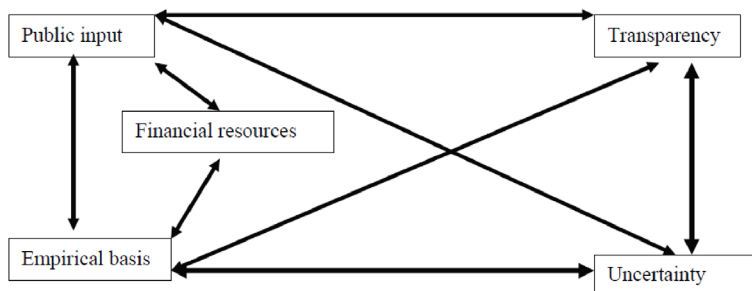
Another development criterion that showed correlation with a number of oversight system criteria across four cases was public input during development (D4). This criterion was found to be related to transparency (D5), financial resources (D6), and empirical basis (D7) during development, as well as to treatment of uncertainty as an attribute of the system (A11). The degree of public input during development of an oversight system is thus associated with (1) the extent of transparency of the oversight system during development, (2) the level of financial support of the system during development, and (3) the ability of the system to treat uncertainty.

Transparency during development was also related to public input during development (D4) and as an attribute of the system later (A19), treatment of uncertainty (A11), and empirical basis (D7). We also found a correlation between treatment of uncertainty (A11) and public input (A19). The extent of transparency during development of an oversight system is thus associated with (1) the ability of the system to treat uncertainty; (2) the extent of public input throughout the life of the system; and (3) the ability of the system to treat uncertainty.

Figure 7 depicts the five characteristics of an oversight system that were correlated across the four case studies with enough expert respondents to perform the calculation. We cannot be sure which of the five characteristics are causes and which of them are effects. However, we can hypothesize that if we want a system to have any of these five characteristics, we may increase the likelihood by having all other characteristics in place. As an example, if we want to increase the capacity of an oversight system to treat uncertainty, we would invest more financial resources, stimulate pub-

Figure 7

Common Correlations among Criteria across Four Case Studies (GEOs, Drugs, Devices, Workplace Chemicals)



lic input, increase transparency, and strive for greater reliance on empirical data in decision making.

V. Lessons Learned

We compared qualitative and quantitative data across the case studies to derive lessons for oversight of emerging technologies and products generally and for nanobiotechnology and its products specifically. Each case study presented its own lessons that may more closely apply to certain products of nanotechnology. For example, lessons from oversight of GEOs in food and agriculture could be specific to oversight of GEOs using nanoparticles or nanopesticides, as GEOs are regulated as pesticides under FIFRA. Similarly, lessons from drugs oversight could be specific to oversight of pharmaceutical nanoformulations. Lessons from the individual case studies are discussed in the individual case studies in this symposium.⁵² Below we discuss the general lessons that cut across case studies.

A. Post-Market Monitoring: Toward Life-Cycle Approaches to Oversight

Currently, few laws require monitoring and data collection after initial product approval for market or clinical release. Across all of the case studies, a common lesson emerged: post-market monitoring is an important feature of oversight. No oversight system, no matter how perfectly designed and executed, can anticipate all downstream consequences from product release, use, and diffusion. Only in multiple settings and over time can products or therapies truly be shown to be safe to human health and the environment and to promote overall societal well-being. Thus, post-market monitoring is important. Unfortunately, most statutes do not emphasize or require data collection and analysis after market approval of new technological products. Exceptions are re-registration and adverse event reporting requirements under FIFRA⁵³ and adverse event reporting for drugs and devices

under the FFDCA.⁵⁴ Recent statutory amendments to FFDCA have increased post-market surveillance.⁵⁵ The FDA has authority to recall products, although the agency relies largely on voluntary market removal by manufacturers.

This lesson relates to a relatively new idea in the area of oversight: life-cycle oversight. Several groups are beginning to push for regulations and statutes that consider products from their beginning or synthesis from raw materials, through their use, to their end as recycled materials or waste.⁵⁶ Currently technological products are overseen by multiple agencies and

laws throughout their life cycle, and there seems to be little coordination among the stages of oversight. With nanotechnology, as oversight policies are emerging, there are opportunities to design creative mechanisms for life-cycle regulation to avoid gaps and redundancies in ensuring health and environmental safety for all product stages.

B. Coordination among Multiple Agencies

If life-cycle approaches to oversight are to work, there will need to be better mechanisms and policies for inter-agency coordination in oversight. Several of the case studies suggest that problems arise when more than one department, agency, or office has responsibility for the same product. The GEOs and gene therapy oversight stories show the difficulties that can arise from lack of communication among relevant agencies. In those cases, lack of communication led to gaps in acquiring safety data and may have contributed in gene therapy to human injury and death. In oversight of drugs and devices, the communication gaps occur in one agency, the FDA, but among multiple centers. For nano-drugs and devices, given their convergent nature, multiple FDA centers are likely to be involved in oversight.

Multiple bodies involved in oversight can have the advantage of evaluating a product from different perspectives. For example, EPA oversees GEOs from an environmental protection perspective, whereas the USDA oversees GEOs from an agricultural protection perspective. Both perspectives are important. They can also serve as a check on each other; if one agency spots a problem, the question will naturally arise whether the other sees a problem as well. Thus, the lesson is not to avoid multiple bodies in overseeing a class of products, but rather to provide clear mechanisms and structure for effective inter-agency communication and coordination. These will be especially important in overseeing new technologies, such as nanobiotech-

nologies, that stretch the jurisdictional boundaries and expertise of existing oversight bodies.

C. Public Input into Oversight

There have recently been calls for more public engagement in discussion, deliberation, and decision making about emerging technological products.⁵⁷ In our analysis described above, public input was correlated with several other criteria — transparency, financial resources, uncertainty, and empirical basis — across all four quantitatively assessed oversight models (Figure 7). Public input could play a pivotal role in enhancing many features of oversight. Greater public say in decision making might lead to increased support for regulation at the political level and thus lead to greater financial resources for oversight from Congress. Similarly, enhanced financial resources could better ensure rigorous data collection for product review and approval. For now, these are hypotheses that need to be tested. However, they suggest that criteria previously seen as “legitimacy-based” (i.e., increase public confidence and trust) are correlated with criteria that are thought to be more “science-based” (e.g., empirical basis and treatment of uncertainty). As our thinking about the role of public input in oversight matures and some systems begin to incorporate mechanisms for greater input (that is, beyond notice and request for comments in the *Federal Register*), it will be important to evaluate whether oversight systems that incorporate such mechanisms have greater success in implementing other features of quality oversight and lead to better outcomes. We have an opportunity to test this hypothesis in the design of nanotechnology oversight.

One barrier to enhancing public input is the tension between transparency and the need to protect intellectual property rights (IPR). In each oversight system, especially those addressing emerging technologies (e.g., gene therapy, drugs, devices, and GEOs), information about products to be overseen may not be available to those outside the laboratories involved, industry, and the regulatory agencies due to confidential business information and the need to recoup investment through the IPR system. This is a large and significant barrier that will require creative and careful thinking for public input in oversight to be mainstreamed. The concept of trading zones⁵⁸ should be considered to create spaces where information exchange and transparent dialogue takes place.

D. Preparedness for Novel and Complex Situations

A lesson that emerged from several of the case studies is that oversight systems should anticipate and adapt to new technological products as they emerge.

This lesson runs deeper than our initial definition of the criterion “flexibility” and is better seen as “preparedness for novelty.” With increased novelty comes a higher level of uncertainty, as exhibited by historical experiences with GEOs and gene therapy. Nano-products now in the market pipeline will not be the same as those in the pipeline in even a few years. All of the case studies illustrate the need for oversight systems to have the capacity to respond to changes in technology. Even the relatively proactive oversight system for GEOs established in the mid 1980s has not sufficed for today’s genetically engineered (GE) products such as GE mammals and insects. And in oversight of workplace chemicals, the regulatory system has not had the capacity to change safety standards from mass-based to surface-area-based standards to address ultrafine particles and nanoparticles as these classes of particles have grown in the marketplace.

Part of the dilemma is that statutes and laws, even regulations, are difficult to change once promulgated. Decades can pass before revisions are enacted. Regulation of emerging products is often not at the top of the political priority list. Financial crises, wars, and other social goals take precedence, with regulatory reform slipping to the bottom in all but the best of times. Therefore, we suggest that oversight systems need to be designed at the outset to include mechanisms of adaptation to technological advance. Even when advances cannot be accurately predicted, mechanisms can be created to recognize and respond to change.

E. Capacity and Financial Resources

Acting on the above lessons requires resources. Each case study revealed a shortcoming in the amount of resources, whether financial, infrastructure-based, or expertise. Capacity could be defined as an agglomeration of these capabilities. Capacity and resources are essential to reaching the goals of life-cycle oversight, inclusion of public input, coordination, and preparedness. In the case study of chemicals in the workplace, the lack of capacity was most prominent, and this oversight system was rated poorly by the experts. OSHA has been notoriously understaffed and underfinanced.⁵⁹

As previously discussed, capacity depends on the political will to devote time, energy, and resources to appropriate oversight. In nanotechnology policy circles, there is a call to increase resources for oversight, particularly at OSHA, the Consumer Products Safety Commission (CPSC), EPA, and FDA.⁶⁰ However, this call is coming in a period of budgetary crisis at the state and federal levels. It remains to be seen whether oversight for emerging technologies will garner attention and funding from Congress.

F. Clear Goals of Oversight

Another lesson that emerged from several case studies is the need for clarity in the goals of oversight systems. The goals of oversight can include protecting health and the environment, promoting public confidence, being fair and transparent, and promoting research and innovation. Research and innovation are important to society. In the oversight systems we evaluated, we were unable to draw clear conclusions on whether strengthening oversight leads to a reduction or increase in research and innovation in the related industry. The relationship is likely to depend on the class of products, structure of the industry, and the point in time of oversight.

In many of our case studies, we saw confusion about the goals of the regulatory agencies involved. For GEOs, the USDA's goals are to protect and promote agriculture, whereas EPA's are to protect the environment. Which takes precedence for GEOs oversight? For gene therapy, the NIH oversight body has emphasized protection of human subjects in research and discussion of significant and novel ethical issues posed by gene therapy protocols, whereas the FDA has focused on assessment of safety and efficacy. Statutes and regulation can help to clarify goals, but when multiple agencies or units are involved, there needs to be greater attention to coordination.

The FDA's own mission statement has the dual goals of protecting health and safety and promoting research and innovation.⁶¹ Yet, if these two goals sometimes conflict, what takes precedence? If the primary goal were to promote research and innovation and a secondary one were to maximize safety of products, oversight would look very different than if the goals were reversed. For each class of nano-product, goals of oversight should be clear. When multiple agencies regulate a product, goals should be agreed upon as part of coordination.

Our five case studies thus suggest that nanobio oversight should strive for life-cycle oversight, public input, adequate oversight resources, coordination, preparedness for technological change over time, and clear goals. We are hopeful, but not naïve about the attainment of these goals for nanobio oversight. There will be significant challenges and opportunities in implementing these lessons for nanobio as well as other emerging technologies.

Conclusion

This article pioneers a new approach to generating recommendations for how to structure oversight of an emerging technology. By identifying historical oversight experiences that are germane to the oversight of a new technology, researchers and policy makers can

look backward to see what has succeeded and what has failed. They can also assess what characteristics of an oversight system seem to group together. This article models both quantitative and qualitative approaches to assessing oversight. Integrating these evaluative strategies offers the most powerful approach to learning the lessons of past oversight experiences. As the volume of nanotechnology R&D expands, and the importance of nanobiotechnology grows in biomedicine, agriculture, and a host of other domains, the need for sound oversight strategies has become urgent. We should learn the lessons of 20th century oversight of science and technology, as we advance in the 21st century.

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