# DALHOUSIE UNIVERSITY

**Just Evidence: Opening Health Knowledge to a Parliament of Evidence**

**Janice E. Graham and Mavis Jones**

(Readers please note that this is an early draft version of a book chapter in B.H. MacDonald, S.S. Soomai, E.M. De Santo, & P.G. Wells (Eds.), *Science, Information, and Policy Interface for Effective Coastal and Ocean Management* (Ch. 14). Pp. 325-349. Boca Raton, Florida, United States: CRC Press/Taylor & Francis Group).

## Introduction

The chapters in this volume are prefaced by a common understanding that the health of our oceans matter. The collection of papers provides rich accounts dealing with how scientific information is used to build a research base and collaboratory networks to exchange, manage, signal risk, influence, and govern policy- and decision-making. For these authors, water matters in an ecological sense, in the same way that environment and air matter. Individually and collectively they constitute the "one health" we all share and should not take for granted (One Health Global Network 2015; One Health Initiative n.d.; Centers for Disease Control and Prevention 2013; Public Health Agency of Canada 2015). A one health approach disrupts arguments that reduce the environment to health, or health to environment (Burger 1990), or human behaviour to some purported set of rational acts of self-interest (e.g., *Homo economicus*). Taking into account ecosystems and social networks, for example, One Health reorients policy to accommodate both human and non-human indicators of health (Rabinowitz and Conti 2012). It opens a space to consider shared relational reciprocities in exchanging goods that are more complex than that explained by an anthropocentric rational market model (Sahlins 1972; Maurice 1999; Graham & Bassett 2006). Situated between these points of reference, between private corporatist strategies for profit, and natural (presumably, though contestably public) resources,

government regulatory policies and practices across all sectors are intended to safeguard citizens against undue harms.

In this chapter, we present a complementary perspective to the oceans theme of this volume by ethnographically engaging the circulation of scientific knowledge and evidence in a different but comparable policy decision-making environment. We will use two case studies in *health regulation* that explore: (i) national regulatory practices and policies for emerging health products, and (ii) global vaccine development and implementation platforms. These case studies and the conclusions that we draw illustrate the role(s) information plays in decision-making processes at the science-policy interface in regulatory contexts that parallels the observations and conclusions of the authors of other chapters in this book.

The determination of evidence deemed valuable along the health regulatory pipeline for emerging pharmaceuticals and biologics (including vaccines) is based on a range of explicit and tacit knowledge. Regulatory science, as in all science platforms, relies on the construction of standards, instruments, and guidelines that order certain types of evidence, exclude other types, and shape our lives (Collins and Evans 2002; Wynne 1996; Lampland and Star 2008; Bijker, Bal, and Hendriks 2009). Institutions define and determine expertise, evidence, and its interpretation; expert elites authorize what can and cannot be considered in order to balance technical, cultural, and political considerations. The policies and practices of the individuals and organizations who decide whose information counts, and what information is used, matter. But the process by which results are interpreted, and conclusions made, remains obscure. Clinical trial study protocols, for example, are designed by drug developers who are interested in producing data that will result in approval of their products. As a result, industry studies, compared to trials with any other source

of funding, are more likely to favour the sponsor's product. The biases, however, cannot always be explained by standard assessment tools (e.g., randomization or blinding) (Lundh, Sismondo, Lexchin, Busuic and Bero 2013). We know, for example, that financial conflicts of interest can sway opinion unconsciously (Kassirer 2007, Sismondo 2008). The importance of making primary data available for independent review cannot be lost on government scientific regulators. It was made most evident in 2015 with the reanalysis of GSK's paroxetine trial, showing that the antidepressant was neither safe nor effective in adolescents (LeNoury, Nardo, Healy, Jureidini, Raven, Tufanaru, Abi-Jaoude 2015; Doshi 2015).

Regulatory advice sought early by product sponsors improves marketing authorization success (Hofer et al. 2015), and has been encouraged in recent regulatory modernization policies. But, how close should relationships be between the sponsors of products and the regulator? Both health care providers and the public trust that there is no conflict of interest and that the mechanisms and instruments of the regulatory process ensure that the drugs and vaccines provide more benefit than harm. The trustworthiness of this evidence requires building a framework for accountability (O'Neill 2014). What questions should we be asking to ensure credibility, legitimacy, and public trust in health regulation?

The determination of regulatory policy, the reach of regulatory activity, and the scientific and ethical competencies of regulators are central to the debate about the nature of a just society and the relative importance of public health issues. For most people, however, regulatory processes are obscure, unclear, and even unfathomable. Citizens do not often think about the safety and effectiveness of the products they consume. They assume government regulators do that for them, until there is a crisis. While emergency preparedness occupies more and more of national state

and international multilateral agency activities, the role of good regulation is to cut crises off at the pass.

As an anthropologist of science, technology, and medicine, the first author's research (Graham) on health regulatory activities has taken me to the shores of Canada's three oceans as well as to the land-locked sub-Saharan African Sahel, where desertification and the recent drying trend from warming African waters are contributing to societal and health consequences. These range from respiratory infections irritated by the pervasive dust carrying winds, to malnutrition from the agricultural crises brought on by scare water resources (Giannini, Saravanan and Chang 2003; van Eeckhout 2015). Humans have fairly predictable ways to address crises. Facing environmental, social, economic, political, or health challenges, humans react. They respond. They move. They innovate. Incentivizing the tangible products of innovation has become a key objective of most governments and across several sectors.

Unfortunately, not all innovations improve health. Indeed, government's dual role, as both incentivizer of new health products and protector of the public health, puts them in a potential conflict of interest. Regulators fall prey to claims of regulatory capture when governments are seen to advance commercial or lobbyist's interests, while their agencies are mandated to act in the public interest (Carpenter 2013; Lexchin 2012). Showing that their products are novel, safe, and effective is the goal of the product sponsors. Ensuring these claims are true is the responsibility of our regulators. What happens in between is the correspondence at the interface of science and politics.

**Weaving the Technical, Relational, and Political into a Parliament of Evidence-based Knowledge**

Innovation inspires; it drives humans beyond static *being* into dynamic *becoming*. It brings new solutions to old problems, new values to tired tenets, opens up new markets, needs, and desires. Human evolution maps to the creation, replacement, and communication of new ideas and artifacts. We evolve with novel technologies that simultaneously change us culturally and biologically. The anthropologists Augustín Fuentes (2013) and Tim Ingold (2013a) suggest an intertwined, woven "correspondence" between biology and social relationships that places human *beings* perpetually in the process of *becoming* human. In this view, where we are not born but become, genetics and social identities "mix and mingle with one another in that zone of interpenetration we are used to calling the 'environment'" (Ingold 2013b, 16). Relationships with one another and with other things are formational to humanity and to most material achievements. Our relational accomplishments, for these must be acknowledged as innovations too, develop, perform, inform and transform along intersecting social and technical pathways. We coalesce around new things and we make friends and enemies, colleagues, and competitors, around ideas that change us. Biology, in this view, might be seen to be more complicated than genetics, acting on our genes and composed of complex synergistic epigenetics and behavioural and symbolic inheritance systems that can radically transform us. We are continuously *becoming* human in our interactions throughout our lifespan. We become, as Fuentes has said, "what we eat, who we meet, how we use our feet, and how we perceive the world" (Fuentes 2010).

People are won over by the enthusiasm surrounding new things. While we innovate to make living better, however, our best intentions can go awry; novel products build and sustain, but they can harm and destroy too. Whether innovations are used to feed our families better, kill our

enemies, clear an oil slick, or prevent, detect, treat, and manage disease and sickness, they unfold into unknown future ecologies as expectations at first and then material accomplishments or detriments that make up our individual and collective becoming. Inevitably, the products of biosocial relations are fraught with risk and uncertainty and with benefits and harms that can surprise even their developers.

It is the task of regulators to be on guard before a product is approved and remain afterwards for the identification, assessment, communication and response to real risks in the world. The post-market world holds uncertainties that cannot be contained in the controlled clinical trials of the pre-license process. The adverse events identified in small clinical trials needed to attain a product's approval cannot foresee population effects brought on by adverse events, viral type replacement, declining immunogenicity, herd immunity, epidemics, climate change, tsunamis, droughts, crop failures, forced migrations and relocations. Cascading unknowns can upset the fine balance upon which the original regulatory decisions were based. While synthetic pharmaceuticals, protein targeted radiopharmaceuticals, vaccines, and other biologics can make us more comfortable, prevent disease, even cure us, they also disrupt.

How might it be possible to widen input into decision-making to include more diverse communities, a broad range of expertise beyond the regulatory scientists required to meet both government policies (e.g., "faster access"), and rigorous scientific critical appraisal?

Isabelle Stengers (2005) proposes a cosmopolitical future that allows for the deliberative engagement of all "constituents" who share a common goal that implicitly involves social justice and generational equity. This vision aims to benefit more than harm. If that common goal is

secured through improved health of our bodies, populations, and environments, then the avenue to that end must include full and open disclosure of all potential conflicts of interest, of all research data, including untampered clinical study reports (Doshi, Jefferson and Del Mar 2012; Jefferson, Jones, Doshi, Spencer, Onakpoya and Heneghan 2014). Different constituencies build different evidence bases and explanations for their interests, for what matters to them, and the kinds of facts they need to gather and manipulate in order to be convinced. If regulators have only partial access to data, or to only one or two sectors within a potential range of constituencies, the impartially of their decisions in applying the best of scientific rigor is left open to doubt. If knowledge and beliefs are constructed and communicated in the everyday practices of science and medicine, regulation, and markets, then tools need to be developed that open and make transparent all sources of data and study design, analytical interpretations, and regulatory decisions, to avoid the perception of conflict of interest, lack of transparency or regulatory capture. What Gluckman and Allen (2016) have referred to in Chapter 10 as "the balancing act of science in public policy", and what Sarkki and colleagues (2014) describe as "balancing credibility, relevance and legitimacy" might be developed into a decision-making framework that, drawing from the works of Bruno Latour (1993) and Isabelle Stengers (1997), would be a cosmopolitical parliament of drug evidence. Such a platform would involve open access to all data for independent analysis, and a transparent platform for engaged and reflexive deliberation and decision-making with mechanisms to prevent more powerful actors from influencing the process.

Multiple constituents would be included in openly determining the safety, effectiveness and quality of a health product. Routes to follow-up studies that are relevant to constituents post-market would be made available through a lifecyle approach that can introduce and address new information from all communities.

**Indication and Intellectual Property Creep**

Clinicians often prescribe drugs developed originally for one medical indication, for instance a biologic for non-Hodgkins lymphoma, for a different condition, such as, treating sufferers of rheumatoid arthritis. This introduces uncertain considerations surrounding safety and effectiveness. Does the product qualify as new? Can it then be privileged for extended patent protection? A synthetic drug said to be moderately effective for the treatment of people with Alzheimer's disease is prescribed for the "worried well" for mild memory loss (Graham 2008). Is there a problem with that? Health technologies are commonly prescribed for conditions other than their original intention. Often on the fly; no record of experimentation or clinical trials. Weapons were transformed into surrogate limbs when Afghani amputees adapted used missile casings for prosthetics. Lifesaving therapies can turn into killers when off-label indication creep unknowingly captures those at-risk. Before its withdrawal in 2004, the COX-2 non-steroidal anti-inflammatory drug Rofecoxib was approved and aggressively marketed. Notoriously, Merck withheld evidence of increased risk for heart attacks and strokes for over five years, resulting in an estimated 88,000 to 140,000 deaths (Graham et al. 2005; Bhattacharya 2005). Both the withholding of data for safety and efficacy and its exceptionally aggressive marketing contributed to the large number of deaths through misinformation and therapeutic creep (Wright et al. 2001; Therapeutics Initiatives 2001, 2001-2002, 2004). Similarly, the recombinant glycoprotein hormone, erythropoietin, useful in cancer care treatment, can also cause lethal thrombotic complications (Hébert, Paul, and Stanbrook 2007). Therapeutic or indication creep commonly comes from information seeded by industry to clinical scientists conducting late Phase III and Phase IV post-marketing studies. It is enabled by prescribing clinicians (Fugh-Berman and

Melnick 2008; Djulbegovic and Paul 2011; Kesselheim, Meloo and Studdert 2011; Riggs and Ubel 2015).

Misinformation seeded by other groups, motivated politically, religiously, or maliciously, takes on a different sort of threat. Often grounded in local logics, anxieties and rumours continue to derail vaccine campaigns (Leach and Fairhead 2007). Clinical researchers and public health vaccine campaigns have begun to pay attention to the fact that ignoring local understandings and explanations is at an immunization campaign's peril (Ghinai et al. 2013; Larson 2014).

How does the knowledge of scientists, health providers, policy makers, and citizens—whether that information sits as data in scientific repositories or in citizens' collective thought and actions—get equitably configured into evidence databases? Logical systems, no matter whose logic, are not immutable (Longino 2002). Sometimes new studies bring to light old (folk) remedies. Local knowledge that may have been dismissed by experts as anecdotal, or folklore, or gossip, reappears later with scientific recognition and potential market value (Canadian Broadcasting Corporation 2015). The intellectual property rights for new medicines can be fought over in highly contested legal fields and are unlikely to provide the same gains to the original creators as they do for larger, more powerful industry interests (Hayden 2003).

Considerable public and private efforts are pu into incentivizing and supporting the development of new technologies to address the matrix of multidimensional factors that contribute to and threaten the one health we all share. Indeed, incentivizing the development of global health technologies has become the goal of a growing cadre of billionaire philanthropists. Their foundations advance the principles and ideologies that brought them their wealth in the first place

and provide them with the resources to set the research agendas of their hearts' desires, ranging from agricultural and health technologies to ocean sciences (*New York Times*, March 15, 2014). Philanthrocapitalists, rather than public agencies and independent experts, have increasingly directed strategic planning for global health and environment. Much of the money put forth in the strategies advanced by philanthrocapitalist groups is directed from public funds, commonly in the guise of public-private initiatives (Mazzucato 2011; Light 2009; Lezaun and Montgomery 2015). By the time the private sector becomes "technically" involved (political involvement is integral to the philanthropic strategic plan), there are few risks for an already advanced product. The return on the (private) investment at the end stage of development has been assured by the public coffers. The Ebola vaccines developed by the Public Health Agency of Canada and the National Institutes of Health in the US, now referred respectively as the Merck and GSK Ebola vaccines, are exemplary cases in point.

**Moving to a Solution: Some Questions First**

So far, the dual role of governments and the relational reality of cozy regulatory-industry activities has been discussed, which put forth a rhetoric of fireguards between industry and regulator, but nonetheless include opportunities for bilateral meetings to introduce new evidence to persuade a hesitating regulator. What would prevent trial design and research evidence from being gamed by industry? What if evidence of therapeutic improvement had to be agreed upon by an independent body of evaluators representing diverse backgrounds, rather than fast tracked through a regulatory pipeline increasingly compromised by a government advocating and creating policies for industry partnerships, commodity fetishism, and corporate drivers (Graham 2001)? How might the independence of evaluators be as integral as industry imposed regulatory time limits? What would evidence of value-added health improvements look like in a setting

where the push for newer drugs faster that are not always better could be reset (Graham and Nuttall 2013)?

Central to this inquiry would be the development of techniques to demand that new health technologies contribute significantly to value-added health improvement (not all new therapies work better). In liberal democracies, it is important to find out how the actors and practices that command techno-scientific authority sometimes hold sway, and sometimes do not, in matters of decision-making, governance, and the determination of what matters. It is worthwhile to unpack the disproportionate roles and interests different actors have in determining what information matters, where it comes from, who it is passed to, who *gives* and who *receives* knowledge, training, and treatment, and whose metrics are used to measure and declare the success of interventions. Information flows in many directions, and decision-making is often more political than scientific (Bishop and Lexchin 2013; Burchett et al. 2012). Brian Wynne has argued that we should be critically engaged in "the enrollment of science in global economic and political forms" (Weiner 2011). To that end, we might consider systematically unpacking the circulation of expertise (and interests) that contributes to the approval of health products. At issue, in the governing of the public's health is whether it is possible to gather a panel of truly independent evidence-based evaluators together whose expertise in research design, methodological rigour, and clinical experience is not compromised by some form of conflict of interest. Central to the work of several science and technology studies scholars has been an examination of the information that scientific and political actors use to build evidence. In addition, the degree to which authorities listen to and involve diverse communities in building the knowledge base, then reach decisions using those data, and the role of scientific advice in democracies generally have been ongoing questions (Bijker, Bal, and Hendriks 2009).

We shall briefly present two case studies on how the information from the best-made science can be diverted by practices that prevent knowledge from being fully realized in the world. We will conclude the chapter with a prolegomenon of what we might do to resolve this problem. Our recommendations will emphasize a close parallel to issues that confound decision making at the science-policy interface described in other chapters in this volume.

### 14.4.1 Case 1: International Regulatory Practices and Policies for Emerging Health Products: Efficacy and Safety

Beginning in 2001, Graham became engaged in several years of participant–observation in a regulatory platform (the Canadian federal department Health Canada). This research was pursued in order to describe the regulatory actors and their tasks, map the regulatory territory of scientific evidence and policy decisions, and illustrate how a regulatory system adapts in response to contingency and rapidly emerging scientific and policy changes. This study followed the step-by step process of product submission and regulatory review as teams of research scientists, biologists, medical officers, and technicians, equipped with state-of-the-art technologies and instrumentation, evaluated clinical science trial data and inspected manufacturing sites. Scientists, clinical evaluators, and policy advisors reviewed regulatory submissions, sampled consistency, conducted extensive chemistry and manufacture confirmatory tests, reanalyzed data, and checked back with the sponsors for missing data or for any queries they might have had about the submitted evidence. Decision-making frameworks were established by the various parties, but decisions to submit, re-submit, or finally withdraw an application were in the hands of the sponsor. Inevitably, the actors on both sides of the product decision must balance legislated

deadlines with partial data, and weigh individual and public health safety against public and industry desires.

Beginning in the early 2000s, the Health Products and Food Branch (HPFB) of Health Canada established a series of initiatives to "ensure that Canadians have faster access to the safe drugs they need" (Government of Canada 2002). Focusing originally on smart regulation (Graham 2005), HPFB moved to a more acceptable language of a "lifecycle approach" as part of the regulatory modernization at Health Canada (Health Canada 2015). In keeping with government policy, Health Canada developed policies and instruments to open up access to new drugs. While regulatory work up to 2004 had mostly concentrated on the assessment of pre-market pharmaceuticals and biological therapies, i.e., isolated from natural sources such as living cells or tissues, for market approval, the lifecycle approach was intended to manage the approval of drugs for market placement more quickly, through a progressive licensing strategy. Although a post-market approval authority to follow the products in their application was part of the scheme, health advocates were concerned that funding and enforcement would lag behind approval, compromising the safety of Canadians prescribed by these early licensed products (Graham and Nuttall 2013). Internationally, there has been wide adoption of regulatory modernization across all government sectors such that the parallels in how this development has been carried out among these sectors, for example, health and environment, will become apparent to the reader. As in all such processes, intricate convergences of human and non-human environments and technological and cultural ecologies have occurred.

Clinical trial evidence that is not open or transparent harms everyone (Muir Gray 2012). Graham was fortunate to have been a student at McMaster University in Hamilton, Canada in the early

‘80s, when the innovators of what became known as evidence-based medicine (EBM) were tutors in the graduate clinical epidemiology and biostatistics course and were testing their systematic review methodologies. She learned to analyse the clinical trial evidence by critical appraisal of the methodological designs, data, and interpretations of medical studies. Graham believed, as acolytes do, in the potential of evidence-based approaches to open up and make transparent clinical study data so that critical appraisal could be carried out by anyone curious enough to care about the results. How disillusioning, then, to watch the sleight of hand as these evidence based standards for the scientific stewardship of clinical trials research were undermined by interests other than science and by consensus panels and expert advisory committees which sometimes exercised authority without attending necessarily to the evidence. Things are not always as they appear (Gilbert 2009). The keepers of best practice in health care miss the integrative thinking needed for health systems (or, for that matter, coastal zone management).

David Sackett et al. (1996) described EBM as the integration of “individual clinical expertise and the best external evidence.” A problem occurs, however, when the best evidence is limited. The gold standard of the blinded randomized controlled trial (RCT) is ideal in theory, but has corroded in practice. The costs of conducting sound EBM trials have restricted it largely to private firms, who control the data in and the analysis out. Field biologists as well as economists know how difficult it is to control for external conditions in the laboratory, let alone the natural world. If externalities can be controlled, taking account of every known contingency, the unknowns will still rule the day. This is why slow cautious longitudinal research in natural conditions is invaluable, if nothing more than to remind us of the damage wrecked by Frankenstein’s hubris.

Items missed in the data collection in an RCT cannot always be accounted for afterwards. The best studies for the best external evidence do not necessarily see the light of day. Expensive to conduct, most randomized controlled trials are industry sponsored, whose objective is to produce evidence that will see their products approved for market. The sponsors were most often the pharmaceutical industry hoping to make profits. So, many types of drugs that are already past patent protection, simple products like aspirin, for example, have been largely neglected in clinical trials while the hope and money have been placed on much more profitable, because they are patentable, *innovative* new drug products. Only about half of all RCT studies are ever published, and negative studies, that is, research that shows no improvement of treatment in comparison to the control group, are seldom published at all (Maund et al. 2014; Scherer, Langenberg, and von Elm 2007; Chan et al. 2004). Why? Because interested sponsors fund trials, and often industry backed researchers carry out the research. You are not likely to sell a car if you tell someone it is a lemon. Therefore, we mainly see partial and "interested" information directed at selling a drug as a commercial commodity rather than therapies and services for the public good.

The randomized controlled trial is a standard that misses an important component, *clinical meaningfulness*, advanced by Alvan Feinstein (1987) in response to statistical dominance in medicine, though not without critique (Hobart 2007). In the 1990s, as a naïve postdoctoral fellow, Graham thought that "meaningfulness" would provide an avenue to tie patient and caregiver experiences into a truly integrated approach to evidence for treatment outcomes for clinical trials. She developed a qualitative methodology that would take into account everyday symptoms of decline and improvement from patient's, caregiver's and doctor's points of view. To her mind, this approach would provide a valuable humanistic and personal component for ascertaining the

effectiveness of potential treatments. She thought that this symbolic local ecological knowledge (as an anthropologist, local knowledge matters) (Geertz 1983), could augment the materialist statistical significance of clinical trial studies (Graham 2008). Unfortunately, and predictably (as time taught me healthy skepticism), the manufacturer who sponsored our study selected only the positive results from our database and ignored the not so positive cases in order to make its argument for inclusion of the drug into provincial formularies.

Quick to catch on that personal testimonials matter more than statistics, industry carefully selected the particular data from our study to sell their product. The company cherry-picked the best evidence to tell a different story. A profit-incentivized pharmaceutical company captured my method, but only used the positive accounts to promote the drug. If the stories of decline had been included, the minimal effectiveness of the drug would have been shown. Furthermore, by placing that drug in the provincial formularies, its costs were charged to the public health care system. Several years later, Graham witnessed the last province to resist allowing that drug into its formulary, based on the paucity of evidence, fold under political pressure from an aggressive campaign of "expert" clinical-researchers, namely, the same folks who had conducted the industry's studies, as well as assembled industry-funded patient groups.

Industry pays for the research, the researchers, and the evidence that most advances their interests. Personal testimonials from select actors trumped the minimal evidence for therapeutic improvement. Profits (in a country where natural resource extraction often overrides the best evidence of declining supplies and catastrophic environmental consequences) do not always have public health among their interests. The use of scientific evidence and the regulators who protect

good science need governance. The independence of science and education of policy analysts to recognize its importance warrant continuing attention.

In case this account seems a testimonial in itself, it is not uncommon. The *British Medical Journal's* "open data campaign" defended key Cochrane reviewers who demanded to see company protected data in order to assess the efficacy of the influenza antiviral Tamiflu (oseltamivir) medication sufficiently. Reviewers from the internationally recognized Cochrane Collaboration, who conduct systemic reviews of primary research in health care and health policy using evidence-based approaches, were denied access to clinical study reports held by the manufacturer, Roche (Doshi, Jefferson, and Del Mar 2012). These reviews address important questions such as: "Does treatment X work better than Y and will it do more good than harm?" Through "sophisticated marketing rather than verifiable evidence," countries around the world stockpiled Tamiflu, costing billions of dollars, by purchasers who believed that Tamiflu would suppress the threat of pandemic H1N1 influenza. There was no reliable evidence to confirm this position. Regulators failed to appraise the full data; they failed the public trust.

### 14.4.2 Case 2: Global Vaccine Development and Implementation Platforms. Equity. Developing Vaccines for the Global South

In 2001, the Gates Foundation provided seed funding to develop a new *Meningococcal serogroup A* conjugate vaccine, *MenAfriVac*™ for endemic and repeated epidemics of *Meningitis A* in sub-Saharan Africa. The vaccine had to be affordable, selling for around 50¢ a dose. While a Meningitis C vaccine was developed within months during an outbreak in the United Kingdom in the 1990s that killed 1000 people, in Africa during the same period, some 700,000 people were affected by Group A *Neisseria meningococcus*, the most prevalent meningitis strain in sub-

Saharan Africa. *Meningococcal serogroup A* infection claimed 100,000 lives and left 600,000 others with life-long morbidity. The vaccine promised to save hundreds of thousands of people devastated by periodic meningitis outbreaks. Other meningitis vaccines existed, but patents make them unaffordable and no manufacturer was interested in developing a vaccine with limited potential for large profit. Fueled by a feasibility study of existing intellectual property, a multilateral partnership under the umbrella of the World Health Organization / Program in Appropriate Technologies (PATH), the Meningitis Vaccine Project arranged for the technology transfer, clinical trials, regulatory approval, and implementation of *MenAfriVac* (LaForce, Konde, Viviani, and Préziosi 2007; LaForce and Okwo-Bele 2011; LaForce, Ravenscroft, Djingarey, and Viviani 2009). The vaccine worked and Meningitis A has been controlled in vaccinated populations. But, while hundreds of millions of dollars spent to build capacity for disease and safety monitoring, surveillance, and training was directed to the epidemiological centre in the nation's capital, little knowledge filtered into (or out of) the communities (Graham, Borda-Rodrigeuz, Huzair, and Zinck 2012; Mounier-Jack et al. 2014). When *Meningitis W-135* and *X* and *Streptococcus pneumonia* meningitis popped up in epidemic clusters, the year after the campaign, just as Graham's Burkinabé colleagues told her would happen four years earlier, people who thought they had been immunized against meningitis were infected. The capacity and knowledge for a single disease targeted vertical vaccination program was not integrated, it did not filter down to real people or local health care workers. Worse still, local knowledge, scientific, medical, and lay, was not engaged. The monovalent vaccine, rather than a quadrivalent to protect against the other meningitis subtypes, was slated to be adopted into the routine immunization program. In a country that spends only $9/day/capita on health services, fees are still charged for hospital and clinic visits, illiteracy is around 26%, and child mortality remains one of the highest in world. Despite strengthened surveillance, mass campaigns, such as the *Men A* introduction

remain missed opportunities to strengthen health systems because they lack "integration with other health systems" (Mounier-Jack et al. 2009; Sanou et al. 2009). Vertical global health programs, even successful ones, miss, or strategically ignore, the everyday reality and significant local knowledge (McGoey 2012a, 2012b, 2014).

**14.5 Integrating Knowledge from All Levels in a Parliament of Evidence**

Within the social studies of science, risk regulation regimes are characterized as dominated by a technocratic approach, and as neglecting publicly located, socially situated epistemological standpoints, i.e., the real world. Several nations have taken this critique on board through regulatory modernization, where strategic efforts are being directed to open up, enable scrutiny, and solicit input into decision-making from a broad range of citizens. We have suggested that the evidence base for risk regulation could benefit from accommodating more ways of knowing (Graham and Jones 2010; Jones and Graham 2009). We have argued that it is not only "lay" public knowledge, but also "expert" scientific understanding that are neglected in modern risk regulation regimes. A symmetrical approach to evidence-based risk regulation is needed which draws from ethnographic studies, the literature in risk, regulatory science, and science and technology studies. Drawing from the work of Bruno Latour and Isablle Stengers, this framework can be developed as a parliament of evidence for decision-making.

Policies might be created that solicit, even promote, wide public dialogue that could generate broad information exchanges across public platforms (i.e., those outside official science-based regulatory offices) as evidence that could be included in evidence-based decision-making. These policies could encourage citizens with specialized knowledge to contribute to regulatory decision-making. Amongst Canada's regulatory comparators—the United Kingdom, the United

States, France, and Australia—public input is generally sought in cases where the government seeks policy direction or approval for decisions. However, few mechanisms exist to consider public input in a similar manner to scientific evidence.

International efforts to consider other types of citizen evidence are part of regulatory modernization. It keeps pace with political neighbours in terms of policy, economy, and science and technology, using such harmonizing tools as Memoranda of Understanding, trade agreements, accords, and other means of operating at a supra-state level. To the extent that it resembles the late twentieth-century project of modernity, regulatory modernization authorizes scientific knowledge to be the principal informant for evidence-based decision-making, characterizing the mutually-dependent features of innovation and economic growth as essential "goods." In this configuration, modernization prioritizes narrowly construed definitions of expert rationality over open, democratized forms of decision-making.

Yet, openness and democratization feature centrally in governments' expressed vision of regulatory modernization. Where unresolved uncertainties about risk proliferate, regulators operate in conditions where international trends lean towards public participation in technology governance. This is particularly true of regulatory systems designed to protect citizens from high-profile risks when lives are at stake such as those connected with therapeutic health. When regulatory failure results in compromised health or death among members of the public, trust in the regulatory system is compromised. This is an important implication of modernization: it works to reduce not only technological risks, but also political ones**.** States not actively engaging citizens risk being characterized as out-of-touch at best, "illegitimate," at worst. Structuring-in public participation is a symbol of good governance, of the state's capacity for the social

distribution of expertise. The challenge of the modern regulator is to create a system capable of pre-empting the critique that this democratic version of regulatory modernization is merely rhetorical, a way to enhance the legitimacy of the regulatory regime while devolving responsibility for detecting and assuming risks onto members of the public, in the name of citizenship.

Although modernization lends itself as a topic for science studies researchers interested in the transition from knowledge to practice, much scholarship in this area suffers from an incomplete understanding of the requirements of on-the-ground regulatory practice. Regulators, industry, expert advisors, and citizens are all regulatory actors engaged in risk governance. On a daily basis, these actors encounter elements of their environment that both constrain and enable transformation. They engage in practices that help them make sense of their environment; considering their differing epistemological positions, often these practices lead to contests over meaning and significance.

The determination of evidence is a prominent site of contest in risk regulation. Different actors may entertain different perceptions of what is and is not appropriate evidence for regulatory decision-making. Growing public awareness of the role of industry in shaping scientific evidence, from the tobacco lobby to clinical trials and global warming means that few debate that politics can affect the production and dissemination of scientific research (Oreskes and Conway 2010).

In a "changing paradigm of risk," regulators attempt to address the tension between *perceived* (culturally constructed) and *objective* (identified through expert measurement) risk (Doern and Reed 2000, 10). But the ideal of regulatory objectivity is performed differently in political

cultures (Jasanoff 2011). The distinction between *objective* and *perceived* risk, while analytically useful, is loaded with inequity when perceptions and experiences that count for some are not taken into account by others. This distinction reproduces objectivity as an achievable criterion for evidence assessment. It neglects the significance of values, power and culture within scientific decision-making, as well as the widespread acknowledgement of conflicts of interest and bias buried in evidence based, and in particular, industry-sponsored studies. This critique of objectivity familiar to science studies scholars is gaining ground in scientific communities, forced to acknowledge how evidence has been compromised through conflicts of interest, and indeed, how even the term "sound science" could be appropriated and used by the tobacco lobby. With the recognition that technologies developed to create science are equally fallible to human foibles (biases and conflicts of interest), the need for alternative paths and mechanisms to assess evidence for risk regulation has emerged.

The approach we proposed would enable qualitatively different kinds of evidence to be assessed, evaluated, and judged to be "valid" via distinct, identifiable, and transparent techniques. We considered how to arrive at a modernized regulatory framework that accounts for both the need to assess risk objectively through measures of safety and efficacy, *and* the need to include local understandings and experiences as relevant, valid contributions to the evidence base. The policy features of *accountability* (accepting responsibility for the consequences of decisions), *openness* (willingness to consider input from public sources), *transparency* (making available study data and information about decisions), and *flexibility* (recognizing that a "one size fits all" approach to regulatory decisions is not always appropriate) figure centrally. While the inclusion of "timeliness" is a clear address to the ubiquitous industry and patient-group complaints of the slowness of regulatory decision-making, the "open" form of modernization proposed

presents a gentler, more democratic, pluralist version in contrast to the innovation-friendly, technocratic form of modernization. This *symmetrical* framework proposed for transforming evidence-based risk regulation would expand on international trends for transparency and accountability, rather than endorse drivers for economic innovation alone.

### 14.6 Modernization, Risks, and Regulatory Science

Objective and perceived risk remain in hierarchical tension: the consequence of state reliance on (scientific) evidence-based decision-making to the exclusion of pragmatic citizen knowledge. Regulators have first, excluded important information based on local ways of knowing and social context; second, they have risked fostering public cynicism by maintaining a hold on access to proprietary data thereby denying independent review despite high profile exposures of gross misrepresentations and misjudgments in scientific advice; and third, they have neglected the role of values in shaping scientific knowledge. As a result, science and technology policy tends to suffer high levels of critical attention (and, therefore, politicization) as publics and scientists alike query what exactly is going on in these closed regulatory circles. The response to political pressure often taken by official decision-makers is to "give the people what they want": open up the system to accountable practices, set up mechanisms for participation, and enhance goodwill (and legitimacy) by demonstrating a commitment to meeting public demands.

However, the adoption of such measures without critical reflection and a carefully thought out methodology and vision is unlikely to accomplish what it sets out to do. Moreover, such an approach risks eroding the legitimacy already held by state expert systems, as well as compromising the credibility of the regime by investing time and taxes in consultations and similar activities that may result in very little visible change in the trajectory of decisions. The

National Institute for Health and Clinical (changed to "Care" in 2012) Excellence (NICE) is an example of an agency that works hard to incorporate best science with a deliberative process of citizen engagement. Despite its attempts, it is constantly under assault by industry and patient lobbyists whenever it arrives at recommendations (Graham 2008).

Regulators are placed in a dilemma. If they retain their reliance on extant expert systems to produce the evidence for decision-making, they risk further destabilization from public demands associated with growing distrust in science. If they bow to demands for greater public participation, they risk eroding the existing strengths of their system, i.e., efficiency of systematic evaluation and risk assessment in the vast majority of reviews. The problem facing risk regulation regimes engaged in modernization is how to find an acceptable medium that does not compromise safety and efficacy along that spectrum of choices.

To that end, symmetrical regulation would require accountability through constructivist realism (*not* accountability through objectivity alone); openness (*not* just transparency); and reflexivity (*not* flexibility).

**A Symmetrical Approach: Constructivist Accountability, Openness and Reflexivity**

**i) Accountability through Both Independent Scientific Assessment and Constructivist Realism**

Objectivity (along with value-neutrality) is a defendable aspiration of expert systems of scientific advice supporting regulatory frameworks; its intent of application of rigourous science and methods is a necessary aim. The independence (value neutrality) in which objectivity claims are associated are, however, widely critiqued. The consequence is that the legitimacy of scientific

knowledge as the primary authority for policy advice is questioned along with the legitimacy of the policy decision. In the cause of symmetrical regulation, constructivist realist knowledge might be adopted to address this legitimacy gap, thereby acknowledging partial perspectives, social contexts, and shaped standpoints.

How would a constructivist realist accountability look in practice? Consider, for example, the accumulation of physical and social facts, call them symptoms, which mark a neuro-social degenerative condition such as Alzheimer's disease. The decision as to which particular constellation of symptoms and signs one calls upon to understand this illness depends on whether one is a clinician or a family member. Political, social, and physical-pathology are flexible factors affecting diagnosis (Graham and Ritchie 2006). Building both clinical and social outcomes and regulatory mechanisms to accommodate these varying data sources involves necessarily both constructivist *and* positivist analyses. In a similar way, regulators and indeed, the clinical-research community could apply their awareness of interpretive relativism to their regulatory outcomes. They could push for more rigorous clinical trial design and methodologies, including the independent analysis of research data and results in order to detect methodological and interpretive bias. Consultation with independent (non-sponsor) clinical researchers could be used to balance the data and interpretation provided by sponsor-supplied researchers. Legislation to control more comprehensively the premature marketing and hyping of new products could be enforced.

**ii) Openness, Not Just Transparency**

Transparency is about provision of detailed information through one-way communication. It can be seen, however, as a photo-op for deliberative democracy in a political climate of gag orders, as

a way of overloading pressure groups seeking information on opaque policy processes. Transparency devolves responsibility onto citizens without giving them real opportunities to contribute to decisions. Openness, on the other hand, is two-way, where information flows in multiple directions through engaged exchange and discussion.

How might openness look in practice? The inclusion of a broader range of constituents on official bodies would gain ground as a trust-building measure. Bringing different perspectives to the same table is one way to support the co-production of a symmetrical evidence base.

**iii) Reflexivity for a Symmetrical Evidence Base**

Finally, the third feature of a symmetrical evidence approach is reflexivity, *not* flexibility. Flexibility is a feature of "smart" risk regulation regimes, critiqued elsewhere (Graham 2005). Reflexivity, instead, recognizes and builds a dialogue between conflicting systems of knowledge (e.g., experts, and experienced and concerned citizens). Conflicting expert advice leaves decision-makers with the task of determining which expert advice to follow.

Reflexivity recognizes that not all types of evidence are assessed in the same way. Standardization is an essential part of the process. The dilemma of regulation is that standardization—seen as a way to ensure both fairness and rigour—often accomplishes just the opposite. Regulators need to be prepared to enact flexibility, not through a predetermined kit of approaches from which they can draw "the perfect tool," but rather, by assessing each case according to the best way to deal with its particularities.

Reflexivity requires vigilance by regulators regarding methods and outcome. If regulatory scientists discuss a "risky" (uncertain, potentially unsafe) product together, they should be able to identify common questions and approaches to answer them. This process should not be a systematic wearing down of evaluators' queries by industry-sponsored scientific teams. Regulators need to define what outcomes are appropriate, and sponsors must provide those outcomes. The decision on acceptable outcomes should not be a negotiated benchmark between sponsor and regulator, but a carefully determined outcome from several expert (independent and non-conflicted) sources.

**Conclusion**

The three features described here—accountability through constructivist realism, openness and reflexivity—are not necessarily new in the recommendations sections of scholarly critiques of risk regulation regimes. They can be seen to overlap to features that Sarkki, Niemela, Tinch, van den Hove, Watt and Young (2014) refer to as "trade-offs" between credibility, relevance and legitimacy in what Gluckman and Allen (this volume) call the "the balancing act of science in public policy". In Canada, accountability, openness and reflexivity have been actively employed in regulatory policy-making and practice. In low income and emerging countries, as we have seen, local knowledge (even scientific and clinical knowledge) may provide only minimal input in targeted disease initiatives. It is in the regimes themselves where the way these features are operationalized will have an impact on not only the power of the evidence base, but also the effectiveness of the regulatory regime as a whole. Worldwide, policy makers have turned their attention to post-approval regulatory activities, emphasized as a more holistic, real world "lifecycle" approach in regulatory renewal frameworks. How regulators will reinforce the integrity of pre-market assessment in a post-market environment remains to be seen in practice.

Whether subsuming commercial technical drivers of innovation and economics under principles of timeliness can satisfy all the actors, scientific and other citizens alike, calling for accountability, openness, and reflexivity, also remains a question. Perhaps especially in the growing global health economies.

A symmetrical approach to regulatory decision-making that provides mechanisms to hear and assess different types of evidence, multiple epistemologies, would begin to address the decline in trust of regulatory decisions brought about by highly publicized product withdrawals and exacerbated by the close relationship between regulator and industry, and by the preponderance of industry sponsored evidence. It would preempt the need for reanalysis by independent reviewers that result in findings of unsafe and ineffective therapies. A symmetrical approach would bridge rigorous scientific evaluation and public input, providing the best evidence from all available sources to be discussed and contested by a diverse range of actors towards the goal of arriving at a common agreement. The question, paraphrasing Latour (2003, 4), should not be whether the conclusion has been constructed, for of course it has been, but whether it is based on an accountable, open and reflexive process that can "differentiate good and bad construction" in order to arrive at the optimal decision to approve or reject a new health product.

In a symmetrical approach to regulation, scientists, policy makers and all citizens have the opportunity to modestly witness, as Donna Haraway (1997) calls it, the interpenetration of capitalism and technoscience. We have seen where clinical research, health technology assessment and global health initiatives do not follow citizen driven models of horizontal alliances in the type of deep democratic manner involving longitudinal community engagement and input considered, for example, by Arjun Appadurai (2001). Nor do they adhere to the plea for

slower science proposed by Isabelle Stengers, where "we slow down, that we don't consider ourselves authorized to believe we possess the meaning of what we know" (Stengers 2005, 2). Instead, we witness the power of financial and corporate elites to control interests and to "favour the 'project' model, in which short-term logics of investment, accounting, reporting and assessment are regarded as vital" (Appadurai 2001, 30). At stake are precautionary consideration, democratic engagement, and sustainable health delivery systems. In the years leading up to the implementation of the Meningitis A vaccine, African scientists and clinicians recognized and expressed to me an array of concerns surrounding the meningitis vaccine project, including a fear of new outbreaks of Streptococcus pneumonia, *Men W 135 and Men X*. Their knowledge, though overlapping with the Meningitis Vaccine Project's scientists and clinicians and policy workers, was deeper in contextualized understanding of the landscape of diseases and the availability of resources to address them.

A symmetrical approach to decision-making would provide mechanisms and a platform to hear, assess and incorporate diverse methodologies and understandings. A Latourian parliament of things would bring science and politics together to address the decline in trust of regulatory decisions exacerbated by anti-vaccine groups, highly publicized product withdrawals, and by the the preponderance of industry sponsored evidence and regulatory capture.

The principles of accountability through constructivism, openness (two-way information exchange between engaged actors) and reflexivity (where all types of evidence are not assessed in the same way) could provide a space whereby citizens, scientists, regulators, and the private sector could each express a common value that would filter into their engagement. In line with post-normal approaches to wicked issues, extending the expertise on which decisions are based

offers a path to respect the political commitments that are at stake (for "stakeholders"). Such innovations would be a force for social and environmental change (Turnpenny et al. 2011) – rather than for individual interests and desires. Through accountable, open and reflexive science with public deliberation, we could see our innovations working towards a common future where human becomings are socially, ethically and ecologically transcendent. In a parliament of evidence, power elites alone would not drive decision-making (Wynne 1996); vulnerable groups could be heard and conflicts of interest addressed. In a parliament of evidence, the cost of not attending to our water, our environment, our health would matter more than financial profit (Stern 2006).

**Acknowledgments**

This work was supported by the Canadian institutes of Health Research grant OGH-111401, Articulating standards: Translating the practices of standardizing health technologies.

**References**

Appadurai, A. 2001. "Deep Democracy: Urban Governmentality and the Horizon of Politics." *Environment & Urbanization* 13 (2): 23-44.

Bhattacharya, S. 2005. "Up to 140,000 Heart Attacks Linked to Vioxx." *New Scientist* January 25. https://www.newscientist.com/article/dn6918-up-to-140000-heart-attacks-linked-to-vioxx.

Bijker, W. E., R. Bal, and R. Hendriks. 2009. *The Paradox of Scientific Authority: the Role of Scientific Advice in Democracies.* Cambridge, Massachusetts: The MIT Press.

Bishop, D., and J. Lexchin. 2013. "Politics and Its Intersection with Coverage with Evidence Development: A Qualitative Analysis of Expert Interviews." *BMC Health Services*

*Research* 13 (88). http://www.biomedcentral.com/1472-6963/13/88.

Broad, William J. 2014. "Billionaires with Big Ideas are Privatizing American Science." *New York Times*, March 15. http://www.nytimes.com/2014/03/16/science/billionaires-with-big-ideas-are-privatizing-american-science.html

Burchett, H. E., S. Mounier-Jack, U. K. Griffiths, R. Biellik, P. Ongolo-Zogo, E. Chavez, H. Sarma, et al. 2012. "New Vaccine Adoption: Qualitative Study of National Decision-Making Processes in Seven Low-and Middle-Income Countries." *Health policy and planning* 27 (Supplement 2): ii5-ii16. doi:10.1093/heapol/czs035.

Burger, E. J. 1990. "Health as a Surrogate for the Environment." *Daedalus* 119 (4): 133-153. http://www.jstor.org/stable/20025342.

Canadian Broadcasting Corporation. 2015. "Medieval Potion Kills Antibiotic-Resistant MRSA Superbugs." *CBC News*, April 3. http://www.cbc.ca/news/technology/medieval-potion-kills-antibiotic-resistant-mrsa-superbugs-1.3020735

Carpenter, D. 2013. "Corrosive Capture? The Dueling Forces of Autonomy and Industry Influence in FDA Pharmaceutical Regulation." In *Preventing Regulatory Capture: Special Interest Influence and How to Limit It*, edited by Daniel Carpenter and David Moss, 152-172. Cambridge: Cambridge University Press.

Centers for Disease Control and Prevention. 2013. "One Health." http://www.cdc.gov/onehealth/. (Accessed September 15, 2015).

Chan, A. W., A. Hróbjartsson, M. T. Haahr, P. C. Gøtzsche, and D. G. Altman. 2004. "Empirical Evidence for the Selective Reporting of Outcomes in Randomized Trials: Comparison to Published Articles." *Journal of the American Medical Association* 291: 2457-65. doi: 10.1001/jama.291.20.2457.

Collins, H. M., and R. Evans. 2002. "The Third Wave of Science Studies." *Social Studies of*

*Science* 32 (2): 235-296. http://sss.sagepub.com/content/32/2/235.short.

Djulbegovic, B., and P. Ash. 2011. "From Efficacy to Effectiveness in the Face of Uncertainty: Indiocation Creep and Prevention Creep." *Journal of the American Medical Association* 305 (19): 2005-2006. doi:10.1001/jama.2011.650.

Doern, G. B., and T. Reed. 2000. "Canada's Changing Science-Based Policy and Regulatory Regime: Issues and Framework." In *Risky Business: Canada's Changing Science-Based Policy and Regulatory Regime,* edited by G. Bruce Doern and Ted Reed, 3-30. Toronto: University of Toronto Press.

Doshi, P. 2015. "No correction, no retraction, no apology, no comment: paroxetine trial reanalysis raises questions about institutional responsibility." *British Medical Journal* 351: h4629. doi: 10.1136/bmj.h4629

Doshi P., T. Jefferson, and C. Del Mar. 2012. "The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience." *PLoS Medicine* 9 (4): e1001201. doi: 10.1371/journal.pmed.1001201.

Feinstein, A. 1987. Clinimetrics. New Haven: Yale University Press.

Fuentes, A. 2010. "Blurring the Biological and Social in Human Becomings." Paper presented at the 11th European Association of Social Anthropologists meetings, Maynooth, Ireland, May 24-27.

Fuentes, A. 2013. "Blurring the Biological and Social in Human Becomings." In *Biosocial Becomings: Integrating Social and Biological Anthropology,* edited by Tim Ingold and Gisli Palsson, 42-58. Cambridge: Cambridge University Press.

Fugh-Berman, A., and D., Melnick. 2008. "Off-Label Promotion, On-Target Sales." *PLoS Medicine* 5 (10): e210. doi:10.1371/journal.pmed.0050210.

Geertz, C. 1983. *Local Knowledge.* United States: Basic Books.

Graham, J.E. and R. Bassett. 2006. “Reciprocal Relations: The recognition and co-construction of caring with Alzheimer’s disease.” *Journal of Aging Studies,* 20 (4):335-349. doi: 10.1016/j.jaging.2005.12.003.

Ghinai, I., C. Willott, I. Dadari, and H. J. Larson. 2013. “Listening to the Rumours: What the Northern Nigeria Polio Vaccine Boycott Can Tell Us Ten Years On.” *Global Public Health* 8 (10): 1138-1150. doi: 10.1080/17441692.2013.859720.

Giannini, A., R. Saravanan, and P. Chang. 2003. “Oceanic Forcing of Sahel Rainfall on Interannual to Interdecadal Time Scales.” *Science* 302 (5647): 1027–1030. doi: 10.1126/science.1089357.

Gilbert, D. 2006. *Stumbling on Happiness*. New York: Vintage Books.

Gluckman, P. and K. Allen. 2016. Chapter 10.The balancing act of science in public policy. In,_B.H. MacDonald, S.S. Soomai, E.M. De Santo, & P.G. Wells (Eds.), *Science, Information, and Policy Interface for Effective Coastal and Ocean Management* (Ch. 14). Pp. 325-349. Boca Raton, Florida, United States: CRC Press/Taylor & Francis Group.

Government of Canada. 2002. *The Canada We Want: Speech from the Throne to Open the Second Session of the Thirty-Seventh Parliament of Canada*. September 30. http://publications.gc.ca/site/eng/236442/publication.html

Graham, D. J., D. Campen, R. Hui, M. Spence, C. Cheetham, G. Levy S. Shoor, and W. A. Ray. 2005. “Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclo-Oxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Nested Case-Control Study.” *The Lancet* 365 (9458): 475-481. doi:10.1016/S0140-6736(05)17864-7.

Graham, J. E. 2001. “Harbinger of Hope or Commodity Fetishism: Re-cognizing Dementia in an Age of Therapeutic Agents.” *International Psychogeriatrics* 13 (2): 131-134. doi: 10.1017/S1041610201007529.

Graham, J. E. 2005. “Smart Regulation: Will the Government’s Strategy Work?” *Canadian Medical Association Journal* 173 (12): 1469-1470. doi: 10.1503/cmaj.050424.

Graham, J. E. 2008. “Facilitating Regulation: the Dance of Statistical Significance and Clinical Meaningfulness in Standardizing Technologies for Dementia.” *BioSocieties* 3 (3): 241-263. doi:10.1017/S1745855208006182.

Graham, J. E., and M. Jones. 2010. “Rendre evident: une approche symetrique de la réglementation des produits thérapeutiques (Determining Evidence: a Symmetrical Approach to the Regulation of Therapeutic Products).” *Sociologie et societies* 42 (2): 153-180.

Graham, J. E., and R. Nuttall. 2013. “Faster Access to New Drugs: Fault Lines Between Health Canada’s Regulatory Intent and Industry Innovation Practices.” *Ethics in Biology, Engineering & Medicine – An International Journal,* 4 (3): 231-239.

Graham, J. E., and K. Ritchie. 2006. “Mild Cognitive Impairment: Ethical Considerations for Nosological Flexibility in Human Kinds.” *Philosophy, Psychology and Psychiatry* 13 (2): 31-43. https://muse.jhu.edu/journals/philosophy_psychiatry_and_psychology/v013/13.1graham01.html.

Graham, J. E., A. Borda-Rodrigeuz, F. Huzair, and E. Zinck. 2012. “Capacity for a Global Vaccine Safety System: The Perspective of National Regulatory Authorities.” *Vaccine* 30 (33): 4953-4959. doi:10.1016/j.vaccine.2012.05.045

Haraway, D. 1997. *Modest_Witness@Second_Millenium.FemaleMan_Meets_OncoMouse:*

*Feminism and Technoscience*. New York: Routledge.

Hayden, C. 2003. *When Nature Goes Public: the Making and Unmaking of Bioprospecting in Mexico*. Princeton: Princeton University Press.

Health Canada. 2015. "Initial Development." http://www.hc-sc.gc.ca/ahc-asc/activit/strateg/mod/ini/index-eng.php (Accessed September 8, 2015).

Hébert, P. C., and M. Stanbrook. 2007. "Indication Creep: Physician Beware." *Canadian Medical Association Journal* 177 (7): 697 doi:10.1503/cmaj.071223.

Hobart, J. 2007. "A brief critique of clinimetrics." *The Lancet Neurology.* Online Publication. http://www.thelancet.com/cms/attachment/2000991592/2003658649/mmc1.pdf

Hofer, M. P., C. Jakobsson, N. Zafiropoulos, S. Vamvakas, T. Vetter, and J. Regnstrom. 2015. "Regulatory Watch: Impact of Scientific Advice from the European Medicines Agency." *Nature Reviews Drug Discovery* 14: 302-303. doi:10.1038/nrd4621.

Ingold, T. 2013a. *Making Anthropology, Archaeology, Art and Architecture.* Abington: Routledge.

Ingold, T. 2013b. "Prospect." In *Biosocial Becomings: Integrating Social and Biological Anthropology,* edited by Tim Ingold and Gisli Palsson, 1-21. Cambridge: Cambridge University Press.

Jasanoff, S. 2011. "The Practices of Objectivity in Regulatory Science." In *Social Knowledge in the Making,* edited by Charles Camic, Neil Gross, and Michèle Lamont, 307-337. Chicago: University of Chicago Press.

Jefferson, T., Jones, M., Doshi, P., Spencer, E. A., Onakpoya, I., and C. J. Heneghan J. 2014. "Oseltamivir for influenza in adults and children: systematic review of

clinical study reports and summary of regulatory comments." *British Medical Journal* 348: g2545. doi: http://dx.doi.org/10.1136/bmj.g2545

Jones, M., and J. E. Graham. 2009. "Multiple Institutional Rationalities in the Regulation of Health Technologies: An Ethnographic Examination." *Science and Public Policy* 36 (6): 445-455. doi: 10.3152/030234209X460980.

Kassirer, J.P. 2007. Financial conflicts in the medical profession: an ongoing, unresolved problem. Open Medicine 1 (3); http://www.openmedicine.ca/article/view/133/64

Kesselheim A. S., M. M. Meloo, and D. M. Studdert. 2011. "Strategies and Practices in Off-Label Marketing of Pharmaceutical: a Retrospective Analysis of Whistleblower Complaints." *PLoS Medicine* 8 (4): e1000431. doi: 10.1371/journal.pmed.1000431.

LaForce, F. M., K. Konde, S. Viviani, and M. P. Préziosi. 2007. "The Meningitis Vaccine Project." *Vaccine* 3 (25) Suppl 1: A97–100. doi: 10.1016/j.vaccine.2007.04.049.

LaForce, F. M., and J. M. Okwo-Bele. 2011. "Eliminating Epidemic Group A Meningococcal Meningitis in Africa Through a New Vaccine." *Health Affairs* 30 (6): 1049–1057. doi: 10.1377/hlthaff.2011.0328.

LaForce, F. M., N. Ravenscroft, M. Djingarey, and S. Viviani. 2009. "Epidemic Meningitis Due to Group A Neisseria Meningitidis in the African Meningitis Belt: A Persistent Problem with an Imminent Solution." *Vaccine* 24 (27) Suppl 2: B13–19. doi: 10.1016/j.vaccine.2009.04.062.

Lampland, M. and S.L. Star. 2008. Standards and their stories: how quantifying, classifying, and formalizing practices shape everyday life. Cornell University Press.

Larson, H. 2014. "Underlying Issues are Key to Dispelling Vaccine Doubts." *Bulletin World Health Organization* 92: 84-85 http://dx.doi.org/10.2471/BLT.14.030214

Latour, B. 1993. *We Have Never Been Modern.* Cambridge, MA: Harvard University Press.

Latour, B. 2003. "The Promises of Constructivism." In *Chasing Technoscience: Matrix for Materiality,* edited by Don Ihde and Evan Selinger, 27-46. Bloomington: Indiana University Press.

Leach, M., and J. Fairhead. 2007. *Vaccine Anxieties: Global Science, Child Health and Society*. London: Earthscan.

Le Noury, J., Nardo, J. M., Healy, D., Jureidini, J., Raven, M., Tufanaru, C., and E. Abi-Jaoude. 2015. "Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence." *British Medical Journal* 351: h4320. doi: http://dx.doi.org/10.1136/bmj.h4320

Lexchin, J. 2012. "Those Who Have the Gold Make the Evidence: How the Pharmaceutical Industry Biases the Outcomes of Clinical Trials of Medication." *Science Engineering Ethics* 18 (2): 247-261. doi:10.1007/s11948-011-9265-3.

Lezaun, J., and C. M. Montgomery. 2015. "The Pharmaceutical Commons: Sharing and Exclusion in Global Health Drug Development." *Science, Technology & Human Values* 40 (1): 3-29. doi: 10.1177/0162243914542349.

Light, D. W. 2009. *Advanced Market Commitments. Current Realities and Alternate Approaches*. Health Action International (HAI) Europe. Paper series reference 03-2009/01. http://haieurope.org/wp-content/uploads/2010/12/27-Mar-2009-Report-AMC-Current-Realities-Alternate-Approaches.pdf

Longino, H.E. 2002. The fate of knowledge. New Jersey: Princeton University Press.

Lundh, A., S. Sismondo, J. Lexchin, O.A. Busuic and L. Bero. 2013. Industry sponsorship and research outcome. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: MR000033. DOI:10.1002/14651858.MR000033.pub2.

Maund, E., B. Tendal, A. Hróbjartsson, K. J. Jørgensen, A. Lundh, J. Schroll, and P. C. Gøtzsche. 2014. "Benefits and Harms in Clinical Trials of Duloxetine for Treatment of Major Depressive Disorder: Comparison of Clinical Study Reports, Trial Registries, and Publications." *British Medical Journal* 348: g3510. doi:10.1136/bmj.g3510.

Maurice G. 1999. *The Enigma of the Gift.* Chicago: University of Chicago Press.

Mazzucato, M. 2011. *The Entrepreneurial State*. London: Demos.

McGoey, L. 2012a. "Strategic Unknowns: Towards a Sociology of Ignorance." *Economy and Society* 41 (1): 1-16. doi*:* 10.1080/03085147.2011.637330

McGoey, L. 2012b. "Logic of Strategic Ignorance." *British Journal of Sociology* 63 (3): 553-576. doi: 10.1111/j.1468-4446.2012.01424.x.

McGoey, L. 2014. "The Philanthropic State: Market Hybrids in the Philanthrocapitalist Turn." *Third World Quarterly* 35 (1): 109-125. doi: 10.1080/01436597.2014.868989.

Mounier-Jack, S., H. E. D. Burchett, U. K. Griffiths, M. Konate, and K. S. Diarra. 2014. "Meningococcal Vaccine Introduction in Mali through Mass Campaigns and Its Impact on the Health System." *Global health: Science and Practice* 2 (1): 117-29. doi:10.9745/GHSP-D-13-00130.

Muir Gray, J. A. 2012. Address to the APAC Forum on Quality Improvement in Health Care. September 19-21. http://www.vimeo.com/49892096. 2015. "One Health Global Network." http://www.onehealthglobal.net (accessed September 8, 2015).

"One Health." 2015. Centers for Disease Control and Prevention. http://www.cdc.gov/onehealth/ (accessed September 8, 2015).

One Health Global Network. 2015. "What is One Health?" http://www.onehealthglobal.net/what-is-one-health/ (accessed September 15, 2015).

One Health Initiative. n.d. “About the One Health Initiative.” http://www.onehealthinitiative.com/about.php (accessed February 4, 2015).

O’Neill, O. 2014. “Trust, Trustworthiness, and Accountability.” In, *Capital Failure: Rebuilding Trust in Financial Services*, edited by Nicholas Morris and David Vines, 172-192. Oxford: Oxford University Press.

Oreskes, N., and E. M. Conway. 2010. *Merchants of doubt. How a handful of scientists obscured the truth on issues from tobacco smoke to global warming.* New York: Bloomsbury Press.

Public Health Agency of Canada. 2015. “One Health.” http://www.phac-aspc.gc.ca/owoh-umus/index-eng.php (accessed September 8, 2015).

Rabinowitz, P., and L. Conti. 2012. “Links among Human Health, Animal Health, and Ecosystem Health.” *Annual Review of Public Health* 34: 1-16. doi: 10.1146/annurev-publhealth-031912-114426.

Riggs K. R., and P. A. Ubel. 2015. “The Role of Professional Societies in Limiting Indication Creep.” *Journal of General Internal Medicine* 30 (2): 249-52. doi: 10.1007/s11606-014-2980-0.

Sackett D. L., W. M. C. Rosenberg, J. A. Muir Gray, R. B. Haynes, and W. S. Richardson. 1996. “Evidence Based Medicine: What It Is and What It Isn't.” *British Medical Journal* 312 http://dx.doi.org/10.1136/bmj.312.7023.71.

Sahlins, M. 1972. “The Original Affluent Society.” In *Stone Age Economics.* London: Routledge.

Sanou, A., S. Simboro, B. Kouyate, M. Dugas, J. E. Graham, and G. Bibeau. 2009. “Assessment of Factors Associated with Complete Immunization Coverage in Children Ages 12-23 Months: A Cross Sectional Study in Nouna District, Burkina Faso.” *BMC International Health and Human Rights* 9, S10. http://www.biomedcentral.com/1472-698X/9/S1/S10

Sarkki, S., J. Niemelä, R. Tinch, S. van den Hove, A. Watt, and J. Young. 2014. "Balancing Credibility, Relevance and Legitimacy: A Critical Assessment of Trade-Offs in Science-Policy Interfaces." *Science and Public Policy* 41, 194-206.

Scherer, R. W., P. Langenberg, and E. von Elm. 2007. "Full Publication of Results Presented in Abstracts." *Cochrane Database Systematic Review* 2: MR000005. doi: 10.1002/14651858.

Sismondo, Sergio. 2008. "How pharmaceutical industry funding affects trial outcomes: causal structures and responses." *Social Science & Medicine* 66: 1909-1914. doi:10/1016/j.socscimed.2008.01.010.

Stengers, I. 1997. *Power and Invention: Situating Science*. Minneapolis: University of Minneapolis Press.

Stengers, I. 2005. "The Cosmopolitical Proposal." In *Making Things Public: Atmospheres of democracy*, edited by Bruno Latour, 994-1003. Cambridge, MA: The MIT Press.

Stern, N. 2006. *Stern Review on the Economics of Climate Change*. London: HM Treasury.

Therapeutics Initiative. "Selective COX-2 Inhibitors: Are They Safer?" January – February 2001, Newsletter 39. http://www.ti.ubc.ca/newsletter/selective-cox-2-inhibitors-are-they-safer (accessed September 8, 2015).

Therapeutics Initiative. "COX-2 Inhibitors Update: Do Journal Publications Tell the Full Story?" November 2001- January 2002, Newsletter 43. http://www.ti.ubc.ca/newsletter/cox-2-inhibitors-update-do-journal-publications-tell-full-story (accessed September 8, 2015).

Therapeutics Initiative. "Rofecoxib (Vioxx®) Withdrawal Generates Uncertainty about COX-2s – Do Product Monographs Adequately Inform?" July - October 2004, Newsletter 53. http://www.ti.ubc.ca/newsletter/rofecoxib-vioxx%C2%AE-withdrawal-generates-uncertainty-about-cox-2s-%E2%80%93-do-product-monographs-ad (accessed September 8, 2015).

Turnpenny, J., M. Jones and I. Lorenzoni. 2011. “Where now for post-normal science?: A critical review of its development, definitions, and uses. *Science, Technology and Human Values* 36(3): 287-306.

van Eeckhout, L. 2015. “Winds of Climate Change Blast Farmers Hopes of Sustaining a Livelihood in Burkina Faso.” *The Guardian*, July 7. http://www.theguardian.com/world/2015/jul/07/winds-climate-change-blast-burkina-faso-farmers.

Weiner, T. 2011. "A Report on the 2010 4S Conference in Tokyo.” January 4. http://somatosphere.net/2011/01/report-on-2010-4s-conference-in-tokyo.html

Wright, J. M., T. L. Perry K. L. Bassett, and G. K. Chambers. 2001. “Reporting of 6-month vs 12-month Data in a Clinical Trial of Celecoxib.” *Journal of the American Medical Association* 286 (19): 2398-2400. doi:10.1001/jama.286.19.2398.

Wynne, B. 1996. “May the Sheep Safely Graze? A Reflexive View of the Expert-Lay Knowledge Divide.” In *Risk, Environment and Modernity: towards a New Ecology*, edited by S. Lash, B. Szerszynski, and B. Wynne, 186-226. London: SAGE Publications.