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Toward a Jurisprudence of Drug Regulation

Matthew Herder

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Matthew Herder, BSc (hons), LLB, LLM, JSM, Assistant Professor, Health Law Institute
Faculties of Medicine and Law, Dalhousie University

Address for Correspondence:
Weldon Law Building
6061 University Avenue PO Box 15000
Halifax, Nova Scotia, Canada B3H 4R2
Work Telephone: (902) 494-2567
***Email: Matthew.Herder@Dal.ca**
***Preferred communication**

Author Bio: Matthew Herder is an Assistant Professor in the Faculties of Medicine and Law at Dalhousie University. He is a member of Dalhousie's Health Law Institute and holds a Bachelor of Science (hons.) degree from Memorial University, LLB and LLM degrees from Dalhousie, and a Master of the Science of Law (JSM) degree from Stanford Law School.

Précis of the article (50-200 words): Efforts to foster transparency in biopharmaceutical regulation are well underway: drug manufacturers are, for example, legally required to register clinical trials and share research results in the United States and Europe. Recently, the policy conversation has shifted toward the disclosure of clinical trial data, not just trial designs and basic results. Here, I argue that clinical trial registration and disclosure of clinical trial data are necessary but insufficient. There is also a need to ensure that regulatory decisions that flow from clinical trials—whether positive (*i.e.* product approvals) or negative (*i.e.* abandoned products, product refusals, and withdrawals)—are open to outside scrutiny. Further, a jurisprudence of drug regulation is needed. I develop two arguments motivated by 1) innovation concerns and 2) the value of good governance in support of openly publishing all final decisions for approved, abandoned, refused, and withdrawn products. After articulating why greater transparency in regulatory decision-making is needed, I distil four essential features of a jurisprudence of drug regulation that prescribe policy changes in terms not only of the transparency of regulatory outcomes and the underlying reasoning, but also regulatory organization.

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Efforts to ensure greater transparency in the regulation of "drugs" (used here as a catch-all for pharmaceuticals, biologics, medical devices, and biomarker-based technologies such as genetic testing paired with a pharmaceutical or biologic) are well underway. For example, laws in the United States and Europe now require registration of most clinical trials beyond phase 1.[1] Yet instances of avoidable harm to patients continue to arise.[2] In response, calls for disclosure of clinical trial data in the form of "clinical study reports," not just trial designs and basic results, are growing.[3] In this paper, I argue that disclosure of clinical trial data is necessary but insufficient. Rather, the regulatory decisions that flow from those trial data—whether positive (*i.e.* product approvals) or negative (*i.e.* abandoned products, product refusals, and withdrawals)[4]—should also be open to outside scrutiny provided they are final in nature. A jurisprudence of drug regulation is, in short, needed.

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[1] Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801, 121 Stat. 823, 904-22 (2007) [hereinafter FDAAA 2007]; European Commission, *Communication from the Commission Regarding the Guideline on the Data Fields Contained in the Clinical Trials Database Provided for in Article 11 of Directive 2001/20/EC to be Included in the Database on Medicinal Products Provided for in Article 57 of Regulation (EC) No 726/2004*, 2008 OFFICIAL J. EUR. UNION C 168/3, C 168/3 (2008), available at: <http://ec.europa.eu/health/files/eudralex/vol-10/2008_07/c_16820080703en00030004_en.pdf> (last visited: Aug. 22, 2013).

[2] The Lancet, Editorial, 'European Medicines Agency—More Transparency Needed,' The Lancet, 375 (2010): 1753; B.M. Psaty and C.D. Furberg, Editorial, 'Rosiglitazone and Cardiovascular Risk,' N. Engl. J. Med., 356 (2007): 2522-2524.

[3] P. Doshi, T. Jefferson and C. Del Mar, 'The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience,' PLoS Medicine, 9, no. 4 (2012): 1-6; P.C. Gøtzsche, Commentary, 'Why We Need Easy Access To All Data From All Clinical Trials and How To Accomplish It,' Trials, 12, no. 249 (2011): 1-14; P.C. Gøtzsche and A.W. Jorgensen, 'Opening Up Data at the European Medicines Agency,' British Medical Journal, 2011 May;342(may10 1):d2686 [hereinafter Gøtzsche and Jorgensen, Opening Up Data]; D. Strech and J. Littmann, Commentary, 'Lack of Proportionality. Seven Specifications of Public Interest That Override Post-Approval Commercial Interests on Limited Access to Clinical Data,' Trials, 13, no. 100 (2012): 1-5; T. Groves and F. Godlee, Editorial, 'The European Medicines Agency's Plans for Sharing Data from Clinical Trials,' British Medical Journal, 346 (2013): f2961; M.A. Rodwin and J.D. Abramson, 'Clinical Trial Data as a Public Good,' JAMA, 308 (2012): 871-872.

[4] For simplicity, I will refer to products that are withdrawn by the manufacturer during research and development as 'abandoned' products, and reserve the term 'withdrawn drugs' or 'withdrawals' for drugs that are removed from the market after they have received market authorization from a regulator. In the literature, however, the term 'withdrawn' is used in respect of drugs that are withdrawn pre- and post-market entry.

In legal parlance the term jurisprudence is used colloquially to encompass a body of court decisions relating to a given topic. For example, court cases in which a physician is sued for the provision of allegedly negligent patient care may be described as the "medical malpractice jurisprudence." Deciphering the boundaries of and controlling factors within a given legal jurisprudence can be difficult. In the context of drug regulation knowing the jurisprudence should, in principle, be more straightforward. "Like cases" can be readily identified by common active ingredient(s) and all regulatory authorities apply three core standards—safety, efficacy, and quality—to every product they evaluate. The immediate barrier to a jurisprudence of drug regulation is that not *all* decisions by regulatory authorities are open to outside scrutiny. Regulators in several countries, most notably the United States, selectively publish their decisions, specifically, only those decisions in which a given therapeutic product is approved. Only two regulators, the European Medicines Agency (EMA) and Australia's Therapeutic Goods Administration (TGA), currently publish negative decisions as well as positive ones.[5]

A jurisprudence of drug regulation requires, at a minimum, that all regulatory decisions and the reasons behind them be made transparent. Drug manufacturers are apt to contest regulators' legal authority to do so and suggest that negative decisions in particular are theirs to own in secret.[6] Here, I aim to shift the policy discussion away from

[5] European Medicines Agency, Committee for Medicinal Products for Human Use, Publication of CHMP Negative Opinion and Refusal of Marketing Authorisation Applications for Human Medicinal Products, Doc. Ref. EMA/311355/2005, adopted Jan. 24, 2007; European Medicines Agency, Committee for Medicinal Products for Veterinary Use, Reflections Paper on the Publication of the CHMP's Negative Opinion and Refusal to Recommend the Granting of a Marketing Authorisation for Veterinary Medicinal Products, Doc. Ref. EMA/CVMP/459912/2006, adopted Jul. 12, 2007; G. Tafuri, F. Trotta, H.G. Leufkens and L. Pani, 'Disclosure of Grounds of European Withdrawn and Refused Applications: A Step Forward on Regulatory Transparency,' British Journal of Clinical Pharmacology, 75 (2013): 1149-1151. [hereinafter Tafuri et al., Withdrawn and Refused Applications]

[6] *E.g.*, Government of Canada, Health Canada, *Summary Basis of Decision Phase II: Posting of the Summary Report of External Consultations*, May 7, 2012, at < http://www.hc-sc.gc.ca/dhp-

the trappings of these "jurisdiction" and "proprietary" arguments. I instead develop two arguments—one motivated by innovation concerns and the other grounded in the value of good governance—in support of openly publishing all products that are abandoned (by the manufacturer), refused (by the regulator), and/or withdrawn from the market (typically by both parties acting in concert) in addition to products approved for sale.[7] The first part of the paper provides some additional background about the transparency frameworks currently in place in the United States, Europe, and Canada, in which access to regulatory decision-making is but one element. After articulating why greater transparency is needed for reasons of innovation and governance in the second part of the paper, I distil four essential features of a jurisprudence of drug regulation in the third part of the paper that prescribe policy changes in terms not only of regulatory outcomes (openly publishing both positive and negative decisions) and the reasoning that supports them, but also in terms of the organization of regulatory institutions.

Transparency Transitioning

Concerns about the opacity of drug regulation are longstanding.[8] Prior to the patent medicines crisis in the early twentieth century, success in the (allegedly

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mps/prodpharma/sbd-smd/sbd_ext_consult_sbd-eng.php> (last visited Aug. 22, 2013). [hereinafter HC, *External Consultations*]

[7] These arguments build on recent work by other scholars, in particular, Rebecca Eisenberg and Trudo Lemmens. See R.S. Eisenberg, 'The Role of the FDA in Innovation Policy,' Michigan Telecommunications and Technology Law Review, 13 (2007): 345-388; M. Unlu, 'It is time: Why the FDA should start disclosing drug trial data,' Michigan Telecommunications and Technology Law Review, 16 (2010): 511-545; T. Lemmens, 'Pharmaceutical knowledge governance: A human rights perspective,' Journal of Law, Medicine & Ethics, 41(1): 163-184.

[8] A.K. Asamoah and J.M. Sharfstein, 'Transparency at the Food and Drug Administration,' N. Engl. J. Med., 362 (2010): 2341–2343; R.A. Merrill, 'The Architecture of Government Regulation of Medical Products' Virginia Law Review, 82 (1996): 1753-1866. [hereinafter Merrill, The Architecture of Government Regulation]

therapeutic) drug trade was premised on secrecy and advertising.[9] When government oversight was imposed circa the First World War, regulators began policing fraudulent advertising claims by manufacturers, but secrecy was carried through exchanges between the two.[10] In the United States, the regulatory practice of treating information shared by manufacturers as confidential continued after 1962 when the Food and Drug Administration (FDA) was first empowered to require "substantial evidence" of safety and efficacy before a medical product could be sold on the market.[11] This, in turn, protected a space for private dialogue between manufacturers and the regulator. For decades, in cases where market approval has appeared unlikely manufacturers have used this private space to appeal to the FDA for a reassessment, or, alternatively, abandon the application without fear of immediate market repercussions.

In this way the very idea of a "negative decision" is a misnomer. The regulatory process is highly *iterative* with the potential to stop, pause, re-start, and change applications for market approval along the way. Those concerned about the excessive costs of drug development have characterized this iterative exchange between the FDA and manufacturers as unduly adversarial.[12] From a patient safety perspective, the worry is that the regulator and industry are working too hand in hand.[13] Regardless, the fact that only three denied applications for market approval have been challenged in court by a

[9] J.H. Young, The Toadstool Millionaires: A Social History of Patent Medicines in America before Federal Regulation (Princeton: Princeton University Press, 1961), at 93-124; D.B. Haycock and P. Wallis, 'Quackery and commerce in seventeenth-century London: the proprietary medicine business of Anthony Daffy,' Medical History Supplement, 25 (2005):1-216.
[10] See Merrill, The Architecture of Government Regulation, *supra* note 8.
[11] *Id.*
[12] *Id.*
[13] E.J. Topol, 'Failing the Public Health–Rofecoxib, Merck, and the FDA,' N. Engl. J. Med., 351 (2004): 1707-1709.

brand-name company during the first thirty years of regulation in the US[14] attests to the value that industry places on the private, iterative nature of regulators' decision-making. The decision-making of regulatory bodies in Europe and Canada, which, like their American counterparts assumed market approval responsibilities through the 1960s,[15] has for a long time closely resembled the private, iterative processes followed by the FDA.

Recently, these jurisdictions have begun to make their respective regulatory systems more transparent, but the specific elements of these transparency frameworks vary in both principle and practice.[16] In Canada, for example, gestures at transparency have largely happened in a legislative vacuum. There is a policy requirement that all clinical trials be publicly registered but it is limited to research conducted by publicly funded researchers or institutions in receipt of public funds.[17] Efforts by the regulator, Health Canada, to disclose its decision-making have largely been limited to approved pharmaceutical products and high-risk medical devices, and an internal review of the program has shown that this level of transparency has seldom added value to information already available in the public domain.[18] Transparency requirements in Europe and United States, by contrast, are more comprehensive in scope and generally carry the force of law. As of September 2007, all clinical trials of drugs, biologics, and devices beyond phase 1 that are within the purview of the FDA must be registered on

[14] See Merrill, *supra* note 8.
[15] L.I. Pugsley, 'The administration and development of federal statutes on foods and drugs in Canada,' Medical Services Journal Canada, 23 (1967):387-449.
[16] *E.g.*, A. Vitry, J. Lexchin, L. Sasich, T. Dupin-Spriet, T. Reed, V. Bertele, S. Garattini, L. Toop, E. Hurley, 'Provision of Information on Regulatory Authorities' Websites,' Internal Medicine Journal, 38 (2008): 559–567.
[17] Government of Canada. *Interagency Advisory Panel on Research Ethics*. TRI-COUNCIL POLICY STATEMENT: ETHICAL CONDUCT FOR RESEARCH INVOLVING HUMANS 2010, Article 11.3; at: <http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/>. [hereinafter TCPS2]
[18] Government of Canada, Health Canada, *Evaluation of Phase I of the Summary Basis of Decision Project*, Jan. 29, 2010, at: <http://www.hc-sc.gc.ca/dhp-mps/pubs/drug-medic/sbd_er_smd-eng.php> (last visited: Aug. 22, 2013). [hereinafter HC, *Evaluation of Phase I*]

ClinicalTrials.gov.[19] Amendments to the United States' *Food, Drug and Cosmetic Act* also require the National Institutes of Health to maintain a "basic results" database into which manufacturers must disclose several pieces of key information (*e.g.* primary and secondary outcomes of the trial and statistical methods employed) within 12 months of trial completion or within 30 days of FDA approval.[20] As well, FDA advisory committees, comprised of persons outside the FDA, conduct part of their business in public hearings.[21] The European Medicines Agency (EMA) does not entertain outside groups as part of its deliberations, nor release "preparatory documents, i.e. working documents, internal notes, and documents containing opinions for internal use or related to preliminary consultations within the Agency."[22] But on the heels of the amendments to the FDA's parent legislation, the EMA began to impose mandatory clinical trial registration as of 2008[23] and, since 2004, it has published assessment reports for approved medical products (known as "European Public Assessment Reports" or "EPARs"), "information about all refusals and the reasons for them," and information pertaining to withdrawn applications.[24] The latter two practices are unique to the EMA, although the prospect of a negative outcome can surface at the FDA's advisory committee hearings, and the FDA is contemplating whether to formalize the authority to

[19] FDAAA 2007, *supra* note 1.
[20] *Id.*
[21] United States Government Accountability Office, *FDA Advisory Committees: Process for Recruiting Members and Evaluating Potential Conflicts of Interest*, Sept. 2008, at: <http://www.gao.gov/new.items/d08640.pdf>. [hereinafter GAO, *FDA Advisory Committees*]
[22] European Medicines Agency, *European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use),* Nov. 30, 2010, available at: < http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf> (last visited: Aug. 22, 2013).
[23] European Commission, *Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency*, 2004 O.J. (L136)1. [hereinafter *Regulation (EC) No. 726/2004*]
[24] *Id.,* articles 13(3), 12(3), and 11, respectively.

disclose negative decisions as well as abandoned and withdrawn applications.[25] As well, the EMA has announced plans to begin publishing agendas and minutes from all its committee meetings.[26] Thus, even though the level of transparency observed in Canada is lacking compared to the US and Europe, globally, there is an emergent transparency due to the transnational nature of the development and regulation of drugs.[27]

Significant problems remain. First, there is evidence that manufacturers continue to game clinical trial registration. According to one study, registration of one in eight clinical trials is delayed beyond the statutory deadline imposed in the United States.[28] Others have repeatedly documented the poor quality of the information provided in the registration, whether the details about the persons responsible for conduct of the trial, or information about the intervention or primary and secondary outcomes of interest.[29]

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[25] United States Food and Drug Administration, *Phase II Transparency Report*, May 19, 2010, available at: <http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212110.pdf> (last visited: Aug. 22, 2013). [hereinafter FDA, *Transparency Report*]

[26] European Medicines Agency, *Press release: European Medicines Agency announces plan to publish committee agendas and minutes*, Jul. 18, 2012, available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/07/WC500130054.pdf> (last visited: Aug. 22, 2013).

[27] A recent decision by the Supreme Court of Canada is illustrative of this emergent transparency. The majority held that the confidential business information exemption from disclosure under the *Access to Information Act*, R.S.C. 1985, C. A-1, s. 20(1)(b), did not apply on the facts of the case because the information in dispute was, to a large extent, publicly available via the FDA's website. See *Merck Frosst Canada Ltd. v. Canada (Health)* 2012 SCC 3 at para. 182. [hereinafter *Merck Frosst*] Also, in draft proposals intended to increase the transparency of its decision-making, the FDA has specifically highlighted greater levels of transparency at the EMA as a reason to pursue policy change. See FDA, *Transparency Report*, *supra* note 25.

[28] M.R. Law, Y. Kawasumi, S.G. Morgan, 'Despite Law, Fewer Than One In Eight Completed Studies Of Drugs And Biologics Are Reported On Time On ClinicalTrials.gov,' Health Affairs, 30 (2011): 2338-2345; see also C.J. Gill, 'How often do US-based human subjects research studies register on time, and how often do they post their results? A statistical analysis of the Clinicaltrials.gov database,' 2 BMJ Open (2012), http://bmjopen.bmj.com/content/2/4/e001186 (last visited Jul 5, 2013).

[29] S. Mathieu, I. Boutron, D. Moher, D.G. Altman, P. Ravaud, 'Comparison of registered and published primary outcomes in randomized controlled trials,' JAMA 302 (2009): 977-984; M. Sekeres, J.L. Gold, A-W. Chan, J. Lexchin, D. Moher, M.L.P Van Laethem, J. Maskalyk, L. Ferris, N. Taback, P.A. Rochon, 'Poor Reporting of Scientific Leadership Information in Clinical Trial Registers,' PLoS ONE, 3, no. 2 (2008): e1610; R.F. Viergever, D. Ghersi, 'The Quality of Registration of Clinical Trials,' PLoS ONE, 6, no. 2 (2011): e14701; C.W. Jones, T.F. Platts-Mills, 'Quality of Registration for Clinical Trials Published in Emergency Medicine Journals,' Annals of Emergency Medicine, 60 (2012): 458–464.e1; R.W. Scherer et al., 'Can We Depend on Investigators to Identify and Register Randomized Controlled Trials?,' PLoS

Second, legally-binding clinical trial registration requirements are either lacking (in Canada)[30] or poorly enforced (in the US and Europe), and limited in scope. Unlike registration policies issued by the World Health Organization and International Committee of Medical Journal Editors, which do not discriminate based on the type of intervention, the exclusion of phase 1 clinical trials and observational studies from the ambit of the registration requirements in the United States and Europe omits valuable safety data.[31] Third, the amount of information that is made available, for example, in the FDA's "basic results" database or communicated via the EMA's European Public Assessment Reports is often insufficient to assess the merits of the research protocols, specifically, the statistical techniques, comparators, and end points chosen by the researchers. Fourth, while conflicts of interest amongst advisory committee members are now more readily disclosed they seldom result in recusals.[32] This suggests that decision-makers continue to underestimate the subtle, but powerful ways in which conflicting interests can compromise their reasoning.[33] Fifth, nearly every provision for transparency is qualified by protection for industry's "confidential information."[34] Regulators have

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ONE 7 (2012): e44183; A.P. Prayle, M.N, Hurley, A.R. Smyth, 'Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study,' BMJ 344 (2012): d7373; *cf.* V. Huser, J. J. Cimino, 'Evaluating adherence to the International Committee of Medical Journal Editors' policy of mandatory, timely clinical trial registration,' Journal of the American Medical Informatics Association 20 (2013): e169–e174.

[30] TCPS2, *supra* note 12.

[31] D.A. Zarin and T. Tse, Commentary, 'Moving Toward Transparency of Clinical Trials,' Science, 319 (2008): 1340-1342; J. Kimmelman and J.A. Anderson, 'Should Preclinical Studies Be Registered?' Nature Biotechnology, 30 (2012): 488–489. [hereinafter Kimmelman and Anderson, Preclinical Studies]

[32] P. Lurie, C.M. Almeida, N. Stine, A.R. Stine, S.M. Wolfe, 'Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings,' JAMA, 295 (2006): 1921-1928. [hereinafter Lurie et al., Financial Conflict of Interest Disclosure]

[33] J. Lexchin and O. O'Donovan, 'Prohibiting or "Managing" Conflict of Interest? A Review of Policies and Procedures in Three European Drug Regulation Agencies,' Social Science & Medicine, 70 (2010): 643–647. [Lexchin and O'Donovan, Prohibiting or Managing]

[34] For instance, *Regulation (EC) No. 726/2004*, *supra* note 23, art. 13(3), states:

> The Agency shall immediately publish the assessment report on the medicinal product for human use drawn up by the Committee for Medicinal Products for Human Use and the reasons for its

implemented procedures of vetting information with manufacturers before broader disclosure, meaning that the boundaries of "confidential information" are shaped in concert with those asserting it, which results in delayed disclosure and, in some cases, preventable harm to patients.[35]

Various policy solutions to these problems have been put forward, including the expansion of clinical trial registration to pre-clinical studies and more "energetic enforcement" of registration requirements.[36] The most controversial proposal would see regulators disclosing all clinical trial data codified in the form of clinical study reports in order to allow for independent assessment of the evidence base behind a given medicine.[37] The EMA's stated intention of doing so triggered a court challenge by two manufacturers, which resulted in an injunction precluding data disclosure for the time being.[38] Whether the EMA will appeal the court decision or otherwise succeed in making clinical trial data more broadly available, let alone whether other regulators like the FDA and Health Canada will follow suit, is in doubt.[39] Biopharmaceutical companies continue

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opinion in favour of granting the authorization, *after deletion of any information of a commercially confidential nature*. [emphasis added]

[35] G. Sinha, 'Trade Secrets in Balance as Agencies Issue New Transparency Rules,' Nature Biotechnology, 29 (2011): 98-99.

[36] J.M. Drazen, 'Transparency for Clinical Trials—The TEST Act,' New England Journal of Medicine, 367 (2012): 863-864; K. Dickersin and D. Rennie, 'The Evolution of Trial Registries and Their Use to Assess the Clinical Trial Enterprise,' JAMA, 307 (2012): 1861–1864; Kimmelman and Anderson, Preclinical Studies, *supra* note 31.

[37] H-G. Eichler, E. Abadie, A. Breckenridge, H. Leufkens, G. Rasi, 'Open clinical trial data for all? A view from regulators,' PLoS Medicine 9(4) (2012): e1001202.

[38] See *Abbvie Inc and Abbvie Ltd v European Medicines Agency,* Order of 25 April 2013, T-44/13. The EMA is nevertheless moving forward with public consultations surrounding open access to clinical trial data. See European Medicines Agency, *Press release: European Medicines Agency receives interim decisions of the General Court of the EU on access to clinical and non-clinical information*, Apr. 30, 2013), available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/04/WC500142837.pdf> (last visited July 5, 2013).

[39] See D. Holmes, 'Transparency battle resurfaces as EU trial revamp wraps up,' Nature Medicine 19 (2013): 797.

to assert that such data is proprietary, the disclosure of which will significantly discourage production of new biopharmaceutical therapies.[40]

Remarkably, almost entirely absent from the present policy discussion is a call for greater transparency in regulatory decision-making—information which, by definition, biopharmaceutical firms should be harder pressed to claim as theirs to own.[41] With the exception of the EMA, the current level of transparency in regulators' decision-making is bleak. (see **Table 1**) The FDA has recently proposed potential improvements,[42] but it is not clear whether these proposals will move forward.[43] In the next part of the paper, I develop two arguments in support of greater transparency in regulators' decision-making, a move intended to complement the ongoing push for clinical trial data openness.

[INSERT TABLE 1 ROUGHLY HERE]

Two Arguments for a Jurisprudence of Drug Regulation

Industry has resisted every policy effort to increase the transparency of the drug research and development process, whether the registration of clinical trials, disclosure of trial results or data, or regulatory decision-making, on the grounds of innovation. Transparency, industry has claimed in each instance, will weaken the incentives for drug

[40] J. Castellani, 'Are clinical trial data shared sufficiently today? Yes,' BMJ 347 (2013): f1881; [hereinafter Castellani] *cf*. B. Goldacre, 'Are clinical trial data shared sufficiently today? No,' BMJ 347 (2013): f1880.
[41] In Canada, for example, it should be difficult to establish that such information is "confidential information" because regulators' decisions are not "supplied by" manufacturers per se, although the decisions may be based, in part, on information that is in fact supplied by manufacturers. See *Merck Frosst*, *supra* note 27 at para. 152-158.
[42] FDA, *Transparency Report*, *supra* note 25.
[43] None of the draft proposals relating to the FDA's decision-making (*e.g.* abandoned products) have been implemented to date. The last update provided by the FDA is dated 2011. See United States Food and Drug Administration, *Phase II Progress* Report, available at: <http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm273854.htm> (last visited: Aug. 22, 2013).

development, resulting, over time, in less therapeutic innovations.[44] The first argument in favour of greater regulatory transparency turns this claim on its head, highlighting the waste in innovation associated with maintaining the status quo. The second argument developed below centres on governance.

The innovation argument

Several drug regulators now have a practice of drafting and disseminating summaries of some of their decisions on drug submissions. For example, the Canadian regulator, Health Canada, has published "Summary Basis of Decisions" (SBDs) online since 2005.[45] With the exception of two regulators (the EMA and Australia's TGA), only decisions accompanying a product approval are openly published.[46] Knowledge of those outcomes and their supporting rationale(s) are instead kept in confidence between the manufacturer and regulator. The private, iterative nature of the exchange between the manufacturer and regulator similarly masks any decisions made during the evaluation process, for example, to narrow the drug's indication to a more specific patient population. The regulator does not disclose the fact of such indication changes (and the reasons for them) when the product is subsequently approved.

The lack of transparency in respect of each of these decision points—when products fail to reach the market, or do, but only after considerable, and clinically-

[44] Castellani, *supra* note 40.
[45] The SBD project has recently undergone significant changes, which will be discussed *infra*. See Government of Canada, Health Canada, *Notice – Launch of Phase II of the Summary Basis of Decision Project*, Jun. 29, 2012, available at: < http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/announce-annonce/sbd_notice_launch_phaseii_smd_lance_avis-eng.php> (last visited: Aug. 22, 2013). [hereinafter HC, *Launch of Phase II*] For further information regarding SBDs, see HC, *Evaluation of Phase I*, *supra* note 18; and, J. Lexchin and B. Mintzes, 'Transparency in drug regulation: Mirage or oasis?' CMAJ, 171 (2004): 1363-1365.
[46] Tafuri et al., Withdrawn and Refused Applications, *supra* note 5.

relevant, changes to the product's indication(s)—represents a colossal waste of knowledge. Consider the rate of attrition in drug development. Approximately 95% of all drugs that enter clinical trials fail or, to be more precise, fail *to reach the market*.[47] Some fail for reasons of safety and/or efficacy. A significant percentage of all failed drugs (nearly one third) also fail to reach market for strictly business reasons (specially referred to as "abandoned drugs" below).[48] In every case, where a drug is found to have safety and/or efficacy shortcomings, or where the drug appears safe and efficacious, but the company decides to shelve it for unrelated reasons, much of the knowledge generated in connection with the drug's development and the regulator's evaluation of that body of evidence—potentially spanning several years of research involving hundreds if not thousands of human research participants—is wasted.[49] This is because only half of all clinical trials conducted in respect of all medicines in use today have been published, and those that have are twice as likely to contain positive findings (i.e. the drug is safe and/or efficacious). Absent disclosure of the evidence associated with failed and abandoned drugs, the published medical literature is left grossly distorted.[50]

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[47] J.A. DiMasi, L. Feldman, A. Seckler, A.Wilson, 'Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs,' Clinical Pharmacology & Therapeutics, 87 (2010): 272–277. [hereinafter DiMasi et al., Trends in Risks]

[48] DiMasi et al., Trends in Risks, *id.*, unfortunately does not provide new data in this regard. The one-third figure is based upon research published in 2001. See J.A. DiMasi, Commentary, 'Risks in New Drug Development: Approval Success Rates for Investigational Drugs,' Clinical Pharmacology & Therapeutics, 69 (2001): 297–307.

[49] It also raises a series of ethical issues, including breach of informed consent, respect for participants, and harm to downstream users. See M.A. Rogwaski and H.J. Federoff, 'Disclosure of Clinical Trial Results When Product Development is Abandoned,' Science Translational Medicine, 3 (2011): 102cm29 [hereinafter Rogwaski and Federoff, When Product Development is Abandoned]; Kimmelman and Anderson, Preclinical Studies, *supra* note 31; R.C. Cleophas and T.J. Cleophas, 'Is selective reporting of clinical research unethical as well as unscientific?' International Journal of Clinical Pharmacology and Therapeutics, 37 (1999): 1-7.

[50] *Id.*; K. Rising, P. Bachetti, L. Bero, 'Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation,' PLoS Medicine, 5 (2008): e217; E.H. Turner, A.M. Matthews, E. Linardatos, R.A. Tell, R. Rosenthal, 'Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy,' N. Engl. J. Med., 358 (2008): 252–260.

This problem of waste is exacerbated by the fact that there is a strong chance that another research outfit could benefit from a regulator's evaluation of abandoned or otherwise failed drugs. There is mounting evidence that scientific research—as measured by what gets funded, published, and patented—tends to be highly concentrated in discrete areas within a given field.[51] Likewise, biopharmaceutical firms do not operate in disparate therapeutic areas.[52] Therefore it is difficult to suggest that the knowledge that is not shared would go to waste even if disclosed. On the contrary, other researchers and firms, it seems, stand to learn a great deal from regulatory reviews of drugs that do not see the light of day for reasons of safety, efficacy, or commerce. Less research would be duplicated and fewer research participants would be unnecessarily exposed to risks of, or actual, harm.[53]

Openly publishing regulatory reviews regardless of their outcome could significantly facilitate innovation. Repurposing drugs for new indications is becoming more common.[54] Disclosing regulators negative evaluations could thus help inform repurposing efforts. As well, if clinical trial data becomes available for re-use in tandem with regulatory decisions, firms may be able to aggregate that data with findings of their

[51] A.M. Edwards, R. Isserlin, G.D. Bader, S.V. Frye, T.M. Willson, F.H. Yu, 'Too Many Roads Not Taken,' Nature, 470 (2011): 163–165; K. Boudreau, E. Guinan, K. Lakhani, C. Riedl, 'The Novelty Paradox & Bias for Normal Science: Evidence from Randomized Medical Grant Proposal Evaluations', *Social Science Research Network*, available at <<ahref='http://papers.ssrn.com/abstract=2184791'>http://papers.ssrn.com/abstract=2184791> (last visited Feb. 15, 2013).

[52] For instance, most R&D in the realm of rare diseases (which now make up approximately one third of FDA drug approvals) is clustered in the area of oncology. See O. Wellman-Labadie and Y. Zhou, 'The US Orphan Drug Act: rare disease research stimulator or commercial opportunity?' Health Policy, 95 (2010): 216-228.

[53] A.J. Cowley, A. Skene, K. Stainer, J.R. Hampton, 'The Effect of Lorcainide on Arrhythmias and Survival in Patients with Acute Myocardial Infarction: An Example of Publication Bias,' International Journal of Cardiology, 40 (1993): 161–166 [hereinafter Crowley et al., Publication Bias]; Rogwaski and Federoff, When Product Development is Abandoned, *supra* note 49.

[54] See generally, M.J. Barratt and D.E. Frail, Drug Repositioning: Bringing New Life to Shelved Assets and Existing Drugs (Hoboken, NJ: John Wiley & Sons, 2012).

own, for instance, to predict whether patients will respond well to other treatments under investigation.[55] Opening up regulatory decision-making could thus be part in parcel of a larger strategy to encourage new, more innovative business models within the biopharmaceutical sector.

Importantly, opening up regulatory decision-making and even the accompanying trial data does not mean that any and every competitor will be able to free ride on that knowledge. A variety of intellectual property related statutory protections, including patent rights tied to the drug in question, data exclusivity in respect of the trial data, and, in the case of orphan drugs, market exclusivity for a set period of time, may preclude competitors from bringing a competing drug to market until several years have elapsed.[56] Given these other potential constraints on competitors' freedom to operate, why should manufacturers expect that regulatory decisions be kept secret? Unlike clinical trial data, which, in a certain percentage of—but by no means all—cases manufacturers can claim to have generated, regulatory decisions are the work product of regulators.[57] Thus,

[55] Crowley et al., Publication Bias, *supra* note 53; H.P. Selker, R. Ruthazer, N. Terrin, J.L. Griffith, T. Concannon, D.M. Kent, 'Random Treatment Assignment Using Mathematical Equipoise for Comparative Effectiveness Trials,' Clinical and Translational Science, 4 (2011): 10–16; D.M. Kent, R.A. Hayward, J.L. Griffith, S. Vijan, J.R. Beshansky, R.M. Califf, H.P Selker, 'An Independently Derived and Validated Predictive Model For Selecting Patients with Myocardial Infarction Who are Likely to Benefit From Tissue Plasminogen Activator Compared with Streptokinase,' The American Journal of Medicine, 113 (2002): 104–111.

[56] Several commentators have pointed out that these various forms of market protection can be co-extensive. See R. Eisenberg, 'Data Secrecy in the Age of Regulatory Exclusivity,' in R.C. Dreyfuss and K.J. Strandburg, eds., The Law and Theory of Trade Secrecy: A Handbook of Contemporary Research (United Kingdom: Edward Elgar Publishing, 2012); M. Herder, 'Unlocking Health Canada's cache of trade secrets: mandatory disclosure of clinical trial results,' Canadian Medical Association Journal, 184 (2012): 194-199; T. Lemmens and C. Telfer, 'Access to Information and the Right to Health: The Human Rights Case for Clinical Trials Transparency,' American Journal of Law & Medicine, 38 (2012): 63-112.

[57] See *supra* note 41.

whether positive or negative, manufacturers cannot claim ownership over the regulatory decision per se.[58]

In sum, current shortcomings in the transparency of regulatory decision-making contribute to significant waste in the development of therapeutic innovations. Wasted opportunities to strengthen regulatory decision-making underpin the second, governance-driven argument in favour of a jurisprudence of drug regulation.

The governance argument

The second argument is less straightforward; though ideas of transparency and governance have long been intertwined, their relation remains unclear, both in principle and in practice.[59] According to one popular account of the relationship between the two, transparency renders government accountable to the populace as a whole, building trust and stability in a state owing to openness' check on arbitrary decisions.[60] In 1978, then FDA Commissioner Donald Kennedy invoked this kind of democratic, accountability rationale for more open governance at the FDA:

> [G]overnmental decisions, particularly regulatory decisions, should be based on publicly available information…This premise underlies the Freedom of Information Act, the Federal Advisory Committee Act, and the Government in the Sunshine Act. In enacting each of these statutes, the Congress implemented a basic principle of our political system: that people affected by governmental

[58] Canadian courts have excluded information that provides insight into the regulatory process such as reviewer's notes from the scope of "confidential information" or information that would harm a company's competitive position. See *AstraZeneca Canada Inc. v. Canada (Health),* 2005 FC 1451 at para. 95, aff'd 2006 FCA 241, and endorsed in *Merck Frosst Ltd. v. Canada (Health)*, [2012] 1 S.C.R. 23 at para. 218.
[59] C. Hood, 'Transparency in Historical Perspective,' in C. Hood and D. Heald, eds., Transparency: The Key to Better Governance? (New York: Oxford University Press, 2006): 3-23. [hereinafter Hood, Historical Perspective]
[60] *Id.*, at 5-7.

> decisions have a right to know the basis on which they are made. Anyone who questions the wisdom of a regulatory decision should be able to examine the factual foundation of the decision.[61]

This democratic rationale for greater transparency continues to be invoked in policy discourse, with emphasis on the idea that *the* "public" is entitled to government held information generally, and about therapeutic medicines in particular.[62] However, it is questionable whether this rationale has improved, in meaningful ways, the transparency of regulators' institutional practices.[63]

The governance argument that I offer is more pragmatic in its orientation. In my view, regulatory decision-making should be more transparent because transparency promises to improve decision-making performance, both internally, within a regulatory institution, and over time, in dialogue with outside actors.[64] This performance-based argument for more transparent governance thus has two parts.

The first part of the argument focuses on what could be called the generic benefits to be gained from "giving reasons," a requirement that governmental agencies in Canada, the United States, and Europe must meet to varying degrees.[65] Numerous commentators

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[61] FDA, *Transparency Report*, *supra* note 25.
[62] A. Roberts, 'Dashed Expectations: Governmental Adaptation to Transparency Rules,' in C. Hood and D. Heald, eds., Transparency: The Key to Better Governance? (New York: Oxford University Press, 2006): 107-125 [hereinafter Roberts, Dashed Expectations]; HC, *External Consultations*, *supra* note 6; FDA, *Transparency Report*, *supra* note 25.
[63] For example, FDA advisory committee deliberations are publicly available but they tend to be populated by individuals that are invested, as patient representatives or expert researchers, to some degree, in the regulatory outcome. Deciphering whether advisory committees are shaped by special interests versus accountable to otherwise interested publics is therefore difficult. S.F. Wood and J.K. Mador, 'Uncapping Conflict of Interest?' Science, 340 (2013): 1172-1173. [hereinafter Wood and Mador, Uncapping Conflict]
[64] The English philosopher Jeremy Bentham's "panopticon" took this performance-based rationale for transparency to the extreme, advocating in the late eighteenth and early nineteenth centuries for exposure of every government agent to outside scrutiny through an all "inspective-architecture." See Hood, Historical Perspective, *supra* note 59, at 9-10.
[65] In Canada, for example, several recent decisions by the Supreme Court of Canada acknowledge that, depending on the administrative context, limited reasons may suffice or a duty to give reasons may not

and courts have recognized the generic benefits that flow from the process of furnishing reasons:

> Giving reasons requirements are a form of *internal improvement* for administrators. A decisionmaker required to give reasons will be more likely to weigh pros and cons carefully before reaching a decision than will a decisionmaker able to proceed by simple fiat.[66] [emphasis added]

The Supreme Court of Canada has similarly recognized that reasons "foster better decision making by ensuring that issues and reasoning are well articulated and, therefore, more carefully thought out. The process of writing reason for decision by itself may be a guarantee of a better decision."[67] I see no reason why this basic logic does not apply to regulatory decisions such as conditional drug approvals and drug withdrawals, the reasoning and evidence behind which is seldom transparent at present.[68]

The second part of my governance argument underscores the performance benefits to be gained from opening up regulatory decisions to more independent scrutiny (*i.e.* disinterested, in important ways, and sceptical in a scientific sense) as opposed to only immediately affected (*e.g.* the manufacturer) or interested parties (*e.g.* researchers with a financial stake in the product; members of the target patient population). Administrative law's recognition of the benefits of independent scrutiny is weak to non-

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even exist. See for e.g., *Canada (Attorney General) v. Mavi*, [2011] 2 S.C.R. 504; *Alberta (Information and Privacy Commissioner) v. Alberta Teachers' Association*, [2011] 3 S.C.R. 654; and, *Newfoundland and Labrador Nurses' Union v. Newfoundland and Labrador (Treasury Board)*, [2011] 3 S.C.R. 708.

[66] M. Shapiro, 'The Giving Reasons Requirement,' Univ. Chi. Legal Forum (1992): 179-220 at 180.

[67] *Baker v. Canada (Minister of Citizenship and Immigration)*, [1999] 2 S.C.R. 817 at para. 39.

[68] J. Lexchin, 'Withdrawals of drugs for safety reasons: how do regulators decide if they are too unsafe?' Adverse Drug Reaction Bulletin (Feb. 2006) [hereinafter Lexchin, Withdrawals]; A. Clarke, J.J. Deeks, S.A.W. Shakir, 'An Assessment of the Publicly Disseminated Evidence of Safety Used in Decisions to Withdraw Medicinal Products From the UK and US Markets,' Drug Safety, 29 (2006): 175–181 [hereinafter Clarke et al., An Assessment; J. Lexchin, 'Notice of Compliance with Conditions: A Policy in Limbo,' Healthcare Policy, 2 (2007): 114-122.

existent.[69] However, the entire edifice of modern science is constructed around peer review, and the independent scrutiny it is thought to provide.[70] Scientific knowledge is legitimated, and scientific progress is achieved, in significant part, because of science's normative commitments to open, disinterested, sceptical inquiry.[71] The everyday reality of science has, of course, shown to be much more complicated. Some scientists appear to subscribe to "counternorms" and, for example, have a vested interest in one scientific theory gaining traction over others.[72] No scientist, moreover, can claim absolute impartiality, and many nowadays have strong ties to the biopharmaceutical industry, which can create clear conflicts of interest.[73] These complexities create problems for any

[69] The core focus in administrative law disputes regarding the purpose and scope of the requirement to give reasons is on the party immediately affected by a given administrative decision. In some cases, courts have broadened the rationale for giving reasons to include providing guidance to other members of a regulated industry. For instance, the Canadian Federal Court of Appeal has explained:

> …in the case of a regulated industry, the regulator's reasons for making a particular decision *provide guidance to others* who are subject to the regulator's jurisdiction. *They provide a standard by which future activities of those affected by the decision can be measured.*

See *VIA Rail Canada Inc. v. Lemonde*, [2001] 2 F.C. 25 (F.C.A.), at para 20.
But there is little attention to the idea that giving reasons might, by opening up those reasons to scrutiny by independent experts, improve the quality of the administrative agency's decision-making over time.

[70] H. Zuckerman and R.K. Merton, 'Patterns of Evaluation in Science: Institutionalisation, Structure and Functions of the Referee System,' Minerva 9 (1971): 66-100. Zuckerman and Merton write in reference to the institution of peer review at the Royal Society:

> The practice of having scientific communications assessed by delegated members of the Royal Society might have affected the quality of those communications. Communications intended for publication would ordinarily be more carefully prepared than private scientific papers, and all the more so, presumably, in the knowledge that they would be scrutinized by deputies of the Society.

Id. at 73.

[71] These normative commitments to 'open, disinterested, sceptical' inquiry are meant to map onto three of the four norms (communism, disinterestedness, and organized skepticism) as originally described by Robert Merton. R.K. Merton, 'A note on science and democracy,' Journal of Legal and Political Sociology, 1 (1942): 115-126. Merton's fourth norm, universalism, which holds that scientific work is to be judged by pre-established criteria, has less relevance in the context of this paper because determining what criteria should be used to judge the adequacy of a regulatory decision-making is premature in the absence of greater transparency.

[72] I.I. Mitroff, 'Norms and counter-norms in a select group of the Apollo moon scientists: A case study of the ambivalence of scientists,' American Sociological Review, 39 (1974): 579-595; R.K. Merton, 'Priorities in Scientific Discovery: A Chapter in the Sociology of Science,' American Sociological Review, 22 (1957): 635-659.

[73] J. Neuman, D. Korenstein, J.S. Ross, S. Keyhani, 'Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study,' BMJ, 343 (2011):d5621; D.E. Zinner, D. Bolcic-Jankovic, B. Clarridge, D. Blumenthal, E.G. Campbell,

system of peer review and demand careful attention. However, not all competing interests are equivalent, much less pre-empt scientists' capacity to review research findings and conclusions from a position of relative disinterestedness and scepticism. The observation that scientists' have agendas and interests of their own thus does not obviate, in all cases, the benefits that peer review can potentially confer. The challenge is to determine what the appropriate thresholds of disinterestedness and scepticism should be in a given context.

Regulators' use of advisory committees might be understood as tacit acceptance of the idea that regulatory decisions can benefit from independent peer review. Regulators, particularly the FDA, explicitly justify the involvement of an advisory committee in their decision-making process when a given drug submission surpasses the available institutional expertise,[74] and regulators have lauded advisory committees' ability to improve their decision-making performance.[75] For at least two reasons, however, advisory committees cannot provide the decision-making performance benefits that more independent scrutiny potentially can. First, there is evidence that advisory committees are not in fact independent from regulators. The FDA exercises tight control

'Participation Of Academic Scientists In Relationships With Industry,' Health Affairs, 28 (2009):1814–25; Lurie et al., Financial Conflict of Interest Disclosure, *supra* note 32.

[74] GAO, *FDA Advisory Committees*, *supra* note 21; Government of Canada, *Health Canada Policy on External Advisory Bodies (2011)*, Nov. 7, 2011, available at: < http://www.hc-sc.gc.ca/ahc-asc/public-consult/res-centre/poli-eab-oce-eng.php> (last visited: Aug. 22, 2013). Some scholars have argued that, rather than reflecting a genuine attempt to engage experts and members of the public in its decision-making, the FDA's use of advisory committees are instead better characterized as an attempt by the FDA to enhance its reputation and power while being seen as consultative. See S.L. Moffitt, 'Promoting Agency Reputation through Public Advice: Advisory Committee Use in the FDA,' Journal of Politics, 72 (2010): 880-893. [hereinafter Moffitt, Promoting Agency Reputation]

[75] United States Food and Drug Administration, *Advisory Committees: Critical to the FDA's Product Review Process*, Aug. 12, 2011, available at: <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143538.htm > (last visited: Aug. 22, 2013).

over who is named to committees, and what clinical data committees are supplied with.[76] Second, empirical studies suggest that members with clear conflicts of interest often populate FDA advisory committees.[77] It is therefore also not possible to describe those who sit on advisory committees as disinterested, raising doubts as to whether conflicting interests reduce the level of scepticism committee members bring to bear on any given drug submission.

Apart from the (problematic) role played by advisory committees, drug regulators have traditionally maintained that transparency and, in turn, independent scrutiny of their decisions had little to offer in return for regulatory science. Regulators sought instead to refine their craft amongst themselves, sharing information through closed channels such as the "International Conference on Harmonization."[78] When asked to share information with independent researchers such as the Cochrane Collaboration, an international network of researchers devoted to preparing systematic reviews regarding medical interventions, regulators have tended to flatly refuse. The EMA has, for instance, repeatedly refused to disclose clinical trial data and accompanying decisions because, *inter alia*, "the evaluation of safety and efficacy of drugs is *its* responsibility."[79]

However, more recently regulators are beginning to appreciate that greater openness may, over time, have a positive effect upon their decision-making. In the

[76] S. Okie, 'What Ails the FDA?' New England Journal of Medicine, 352 (2005): 1063-1066 [hereinafter Okie, What Ails]; A. Mundy, 'Political Lobbying Drove FDA Process,' Wall Street Journal, Mar. 6, 2009, at A1; J. Avorn, 'Keeping Science on Top in Drug Evaluation,' New England Journal of Medicine, 357 (2007): 633-635.

[77] Lurie et al., Financial Conflict of Interest Disclosure, *supra* note 32; Wood and Mador, Uncapping Conflict, *supra* note 63.

[78] The International Conference on Harmonization is a private forum originally comprised of representatives from the FDA, the EMA, and Japan's medicines regulator, as well as regional associations of the pharmaceutical industry, which meets to discusses regulatory challenges and advocate for the application of common technical standards, including safety and efficacy. See International Conference on Harmonization, History, available at: <http://www.ich.org/about/history.html> (last visited: Aug. 22, 2013).

[79] Gøtzsche and Jorgensen, Opening Up Data, *supra* note 3.

context of public consultations regarding access to clinical trial data and the decisions that flow from them, the EMA has taken a very different tone from the past:

> Access to [clinical trial] data in an analysable format will benefit public health in future. It will make drug development more efficient by establishing a level playing field that allows all drug developers to learn from past successes and failures, and it will enable the wider scientific community to make use of detailed and high-quality [clinical trial] data to develop new knowledge in the interest of public health. The [EMA] also takes the view that a high degree of transparency will take regulatory decision-making one step closer to EU citizens and patients, and promote better-informed use of medicines. Independent replication of [clinical trial] data analysis is a legitimate scientific and societal goal. *Access to [clinical trial] data will enable third parties to verify the regulatory authority's positions and challenge them where appropriate*.[80]

Similarly, the FDA recently acknowledged that allowing outsiders to "independently assess information about a medical product…may allow for new perspectives about the safety and efficacy of medical products" and, by implication, strengthen the credibility and quality of its decision-making over time.[81] In short, there appears to be a new line of thinking amongst regulators to the effect that greater openness can enhance governance.

This governance argument also has an innovation dimension that stems from the growing complexity of drug products. Increasingly, new drug submissions integrate genetic and epigenetic information, for example, in the form of a companion diagnostic

[80] European Medicines Agency, *Publication and access to clinical-trial data, Policy/0070: Draft for public consultation*, Jun. 24, 2013, available at: <http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf> (last visited: Aug. 22, 2013).
[81] FDA, *Transparency Report*, *supra* note 25 at 39.

test.[82] Though the clinical validity and utility of the test may be unclear, drug developers use genetic and epigenetic data to more narrowly define a target patient population and, in turn, demand greater regulatory flexibility around what evidence of safety and efficacy should suffice for market approval.[83] In response, regulators have become more receptive to "alternative trial designs" given, for example, the difficulties of conducting large clinical trials with small sub-populations or individuals afflicted with rare diseases. As a result, the scientific standards by which the safety and efficacy drugs are judged are now in considerable flux.[84] If regulatory flexibility is necessary to accommodate newer, more complex drugs, greater candour from regulators about the limits and intricacies of the experimental evidence they possess and base their decisions upon should follow. Only in those circumstances can independent scrutiny of regulatory decisions occur.

To summarize my second argument for greater transparency in regulatory decision-making: opening up regulatory decision-making (and the clinical evidence upon which regulatory assessments of safety and efficacy are based) to independent scrutiny by critically engaged research communities promises to improve decision-making performance. Such independent scrutiny is especially essential now as the standards of

[82] United States Food and Drug Administration, Guidance for Industry and Food and Drug Administration Staff – In Vitro Companion Diagnostic Devices, Jul. 14, 2011, available at: <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm>, (last visited Aug. 22, 2013).

[83] M. Dunoyer, 'Accelerating Access to Treatments for Rare Diseases,' Nature Reviews Drug Discovery, 10 (2011): 475-476; P.L. Saltonstall, Letter to the Editor, 'Clinical Trials of Orphan Drugs for Cancer,' JAMA, 306 (2011): 1545; D.J. Stewart, S.N. Whitney, P. Kurzrock, 'Equipoise Lost: Ethics, Costs, and the Regulation of Cancer Clinical Research,' Journal of Clinical Oncology, 28 (2010): 2925-2935.

[84] Two recent studies suggest the evidence behind approved orphan medicines for cancers and neurological conditions depart significantly from important experimental standards, including randomization and blinding. See A.S. Kesselheim, J.A. Myers, J. Avorn, 'Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer,' JAMA, 305 (2011): 2320-2326; J. Mitsumoto, E.R. Dorsey, C.A. Beck, K. Kieburtz, R.C. Griggs, 'Pivotal Studies of Orphan Drugs Approved for Neurological Diseases,' Annals of Neurology, 66 (2009): 184-190.

safety and efficacy are being renegotiated under increasing pressure to accommodate targeted drug therapies.

Before moving to the final part of the paper, it is important to highlight a difficult question lurking beneath the surface of this governance argument for enhanced transparency. The question is: will the reasons that are publicly articulated accurately reflect regulatory decision-making? Analysis of past efforts to establish greater transparency amongst government institutions suggests they may not. As detailed by Alasdair Roberts, government actors such as regulatory agencies may adopt several "informal methods of resistance" in the face of new transparency requirements.[85] They may change record-keeping practices, such as decreasing the level of candour contained in records of governmental deliberations (*e.g.* omitting dissenting opinions), manipulating records (*e.g.* destroying meeting transcripts), or electing not to create records in the first place.[86] If adopted, any of these practices will distort the public record of regulatory decision-making. Short of outright omission, distortion, or destruction, the prospect of transparency can also create a perverse incentive for those who are more cognizant of inappropriate influences on their decision-making to reframe, couch, or bury the reasons that are actually determinative of the decision amongst accepted criteria.

A recent study comparing FDA and EMA outcomes suggests that the real reasons for regulatory decision-making—or at least the factors capable of explaining the discrepant outcomes—appear to escape the reasons on open offer.[87] Francesco Trotta et

[85] Roberts, Dashed Expectations, *supra* note 62.
[86] *Id.* at 111-114.
[87] F. Trotta, H.G.M. Leufkens, J.H.M. Schellens, R. Laing, G. Tafuri, 'Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When Differences Have an Impact on Clinical Practice,' Journal of Clinical Oncology, 29 (2011): 2266–2272. Other studies have similarly revealed differences between regulatory outcomes, but are not able to explain why the differences occurred

al. examined 42 cancer medications approved by both the FDA and EMA from 1995 to 2008, and found that only half the common indications tied to those 42 therapies (52/100) were identical or "virtually identical" to one another. Nineteen of the remaining 47 indications were approved by only one of the two regulators. In 28 indications some other clinically-relevant difference between the two approvals, such as a more specific patient population, line of treatment, type of treatment (combination therapy versus monotherapy), was found. Strikingly, "no clear associations" between the clinical data being evaluated and the discrepant outcomes was identified. On the contrary, twenty-two of the 28 indications with clinically relevant differences were based on the same pivotal study. Trotta et al. could not explain the discrepancies in decision-making in light of the publicly available information before the two regulators, leaving the authors to conclude:

> Because no clear predictors of regulatory outcomes have been identified, there must be other driving forces causing such heterogeneity in the approval between the EMA and FSA [sic]. *Economic, political, and sociocultural factors, possibly influencing regulatory decision making, need to be investigated.*[88] [emphasis added]

In this regard, social scientists have assembled a sizeable body of qualitative data. Although dated, a case study of the sleeping pill Halcion (triazolam) offers a powerful example.[89] The Upjohn Company received market approval for Halcion from the United Kingdom's medicines regulator in 1978 and the FDA in 1982. By the mid-1980s Halcion had become the world's "leading hypnotic" with world sales reaching $237 million in

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due to a lack of transparent information. See J. Lexchin, 'International comparison of assessments of pharmaceutical innovation,' Health Policy, 105 (2012): 221-225.

[88] Trotta et al., Evaluation of Oncology Drugs, *id.*, at 2271.

[89] J. Abraham and J. Sheppard, 'Complacent and Conflicting Scientific Expertise in British and American Drug Regulation: Clinical Risk Assessment of Triazolam,' Social Studies of Science, 29 (1999): 803-843.

1991. As early as 1979 a significant number of adverse events associated with the drug were reported, and safety concerns continued to come to the attention of regulators through 1980s. Yet when confronted with the same evidence, "British and American regulatory authorities 'changed their minds' in contradictory ways *over time* about triazolam risks."[90] By 1993 the British agency had revoked all manufacturing licenses for Halcion whereas the FDA simply required Upjohn to half the recommended dose on the product label. The authors of the case study, John Abraham and Julie Sheppard, show that it is impossible to account for this difference in outcome in terms of technical safety and efficacy standards:

> The conflicting risk assessments and regulatory outcomes were substantially mediated and constructed by social judgments about 'acceptable risk', rather than by merely technical calculations. For example, there was no technical solution to the fact that the [British regulator] took a more serious view of the number of postmarketing adverse reactions associated with triazolam than did the FDA; nor to the fact that the [British regulator] considered 30 mg flurazepam and 0.5 mg triazolam to be equipotent, while the [American regulator] accepted an analysis based on Upjohn's claim that 30 mg flurazepan was equipotent to just 0.25 mg triazolam.[91]

Rather, to explain what occurred, attention to a) the continuing influence of those with a professional stake in the initial approval of Halcion in the United States; b) the level of conflicts of interest feeding into the FDA's advisory committee (all of the invited experts were past or current advisors to Upjohn and ten of 11 members of the committee were

[90] *Id.*, at 823. [emphasis in original]
[91] *Id.*, at 831-832.

either recipients of Upjohn grants or stockholders); and, c) a "particularly powerful deregulatory climate" in the United States, was needed.[92]

Subsequent amendments to the FDA's governing legislation preclude, in theory, the level of conflicts that became apparent in the Halcion case.[93] However, it is doubtful that those changes combined with added transparency requirements can preclude social, political, and economic considerations, both minor and major in nature, from infiltrating the regulatory process. In the minor category, a firm's status as an established player seems to be a predictor of approvals.[94] In the major category, more recent work by John Abraham posits that regulators' receptivity to commercial interests, driven in part by political influence, has coloured regulators' definition of a carcinogenic drug, and institutionalized a "permissive" (rather than "precautionary") approach to regulation.[95] In perhaps the most powerful example of all, members of the HIV/AIDS community were instrumental in the creation of accelerated and conditional approval regulatory pathways in the early 1990s[96]—pathways into which an increasing number of biopharmaceuticals are now funnelled.

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[92] *Id.*, at 828-831.

[93] However, several news reports document instances where advisory committees, replete with conflicts of interest, played a key role in getting a drug to market. G. Harris and A. Berenson, '10 Voters on Panel Backing Pain Pills Had Industry Ties,' New York Times, Feb. 25, 2005, at A1; D. Willman, 'New FDA: How a New Policy Led to Seven Deadly Drugs,' Los Angeles Times, Dec. 20, 2000, at A1. [hereinafter Willman, New FDA]

[94] J.W. Kim, 'Arbiter of Science: Institutionalization and Status Effects in FDA Drug Review 1990–2004,' Strategic Organization, 10 (2012): 128–157.

[95] J. Abraham, C. Davis, 'Drug Evaluation and the Permissive Principle: Continuities and Contradictions between Standards and Practices in Antidepressant Regulation,' Social Studies of Science, 39 (2009): 569-598; J. Abraham, R. Ballinger, 'The Neoliberal Regulatory State, Industry Interests, and the Ideological Penetration of Scientific Knowledge: Deconstructing the Redefinition of Carcinogens in Pharmaceuticals,' 37 (2011): 443-477; see also, J. Abraham and T. Reed, 'Progress, Innovation and Regulatory Science in Drug Development: The Politics of International Standard-Setting,' Social Studies of Science, 32 (2002): 337-369.

[96] S. Epstein, 'Activism, Drug Regulation, and the Politics of Therapeutic Evaluation in the AIDS Era: A Case Study of ddC and the 'Surrogate Markers' Debate,' Social Studies of Science, 27 (1997): 691-726.

As explained in the final substantive part of the paper, rather than defeating the call for greater transparency in regulatory decision-making, the foregoing findings from the social science literature help to delineate what a jurisprudence of drug regulation should look like, and underscore its role as one element in a larger system of transparency. Writing in relation to the limits of clinical trials, Steven Epstein writes:

> …the whole history of clinical trials is a story of how the fetishization of method tends to bracket or disguise a series of social decisions about values, priorities, goals, and resources…the solution is therefore not to solidify the reification and further the myth that clinical knowledge-production is a fully rule-bound exercise. *Rather, the only way forward is to open the black box, expose the uncertainty and the value choices*, and then convince people of the considerable importance of participating in such research, even after they understand just how messy it truly is, and how bounded is the usability of the knowledge thereby produced…this educational process presupposes the cooperation of the experts in their own partial dethronement; however 'the expert would exchange lost power for greater legitimacy'."[97] [emphasis added]

In my view, the same reasoning holds with respect to regulatory decision-making. It cannot and should not be reduced to a technocratic exercise. Revealing the full complexity, contingency, and contested nature of regulatory decision-making can enhance the legitimacy of regulators. The following four essential features of what I term a jurisprudence of drug regulation suggest a way how.

A Jurisprudence of Drug Regulation: Four Essential Features

[97] *Id*., at 719.

Operationalizing a commitment to transparency in an institutional context such as drug regulation entails answering several substantive questions, including: 1) Why should something be transparent? 2) What exactly should be transparent? 3) When should something be transparent? 4) What should trigger transparency? 5) What are the institutional mechanisms of transparency? and, 6) Who are the audiences of transparency?[98] Above, I spoke primarily to the first question. Below, I speak to the latter five questions while outlining four essential features of a jurisprudence of drug regulation, and its place within a broader system of transparency. To make the discussion concrete, I juxtapose the four features against Health Canada's Summary Basis of Decision (SBD) project.[99] In contrast to past studies, which focus exclusively on the quality of the information contained within the four corners of summary reports and accompanying documentation published by regulators,[100] the four following features engage not only the contents of regulatory decisions but also the institutional machinery that generates them. The four features are: comprehensiveness, process, audience, and independence.

COMPREHENSIVENESS: *Regulators must openly publish both positive and negative decisions (broadly defined) in a timely fashion*

To avoid massive waste in drug development and enhance regulatory science, all regulators should begin publishing negative decisions, which should be broadly interpreted to include a) any changes made to a drug's medical indication(s) during the

[98] E. Fisher, 'Transparency and Administrative Law: A Critical Evaluation,' Current Legal Problems, 63 (2010): 272–314; S. Jasanoff, 'Transparency in Public Science: Purposes, Reasons, Limits,' Law & Contemporary Problems, 69, no. 3 (2006): 21-46.
[99] For background information about this project see references provided at note 45, *supra*.
[100] Vitry et al., Regulatory Authorities' Websites, *supra* note 16; L.M. Schwartz and S. Woloshin, 'Lost in Transmission — FDA Drug Information That Never Reaches Clinicians,' N. Engl. J. Med., 361 (2009): 1717–1720 [hereinafter Schwartz and Woloshin, Lost in Transmission]; Personal communication from Joel Lexchin to author (Aug. 23, 2013).

review process, b) any drugs that are abandoned by the manufacturer for reasons of safety, efficacy, or business during the review process, c) any drugs that are refused by the regulator for reasons of safety or efficacy, and d) any drugs that are withdrawn from the market after they have been approved for sale.[101]

The caveat is that negative decisions need not be published unless they are *final* in nature. Determining whether a given negative decision is final will depend upon the circumstances. In the case of changes made to a drug's medical indication(s) during the review process, the decision to do so, and the reasons for it, should only be communicated in the event of the drug's approval for a different indication or set of indications. Delaying publication of any changes made until the point of approval will preserve an opportunity for the drug's developer to generate more evidence in support of the indication(s) originally sought. Similarly, a reasonable period of delay should also be allowed in the case of abandoned drugs. Regulators should set a specific timeframe for constructive abandonment; if a manufacturer does not furnish new evidence to overcome any safety and efficacy concerns that have been raised, or simply fails to move forward for commercial reasons, abandonment should be assumed, allowing a negative decision to be published. In the case of drug refusals and withdrawals, the intervening delay should be significantly reduced by comparison. Months, if not years, of correspondence between the manufacturer and regulator has likely preceded a decision to refuse market authorization for a given drug, leaving little justification for additional delay. Likewise, if

[101] Note that prior events, such as the filing of an application to investigate a drug in a clinical trial, or halt a trial, also typically invite responses from regulators. These prior events in the research and development process are not the focus here, however, as existing clinical trial registration requirements should, in principle, make the pertinent details (e.g. indications being tested) transparent.

a product is withdrawn from the market due to newly identified safety concerns, there is no reason to stall disclosure of this fourth type of negative decision.

Although Health Canada was encouraged to expand SBDs to encompass negative decisions, it declined to do so for Phase II of the project, which began in September 2012.[102] Health Canada offered no particular justification for this decision, stating simply "SBDs are not drafted for negative decisions at this time, though they may be considered for future phases of the project."[103] In a summary of consultations leading up to Phase II, Health Canada noted that "some stakeholders" favoured disclosure of negative decisions in order to protect patients' safety whereas others expressed concerns about "the competitive impact of disclosing information about products which had been rejected" or "taint[ing] a product's image."[104] It appears the latter set of concerns were persuasive to Health Canada.

Whatever the underlying rationale, this policy choice precludes the development of a jurisprudence of drug regulation. If the only decisions available for outside scrutiny are positive, the strengths and weaknesses of a regulator's reasoning and evaluative processes cannot be assessed, and variations in regulatory outcomes cannot be fully understood (not to mention the risks to patient safety).

PROCESS *Decisions should communicate the procedural history behind each drug approval (abandonment, refusal, or withdrawal) as well as the regulator's reasoning as to why the combined safety, efficacy, and quality profile of a drug is favourable (or not)*

[102] One of the guidance documents regarding Phase II of the SBD initiative notes that "submissions/applications for a new use of [an already approved] product [will be published] whether Health Canada's decision was negative or positive…" As a result, this limited subset of negative decisions may, with time, become publicly known. See HC, *External Consultations*, *supra* note 6.

[103] Government of Canada, Health Canada, *Frequently Asked Questions: Summary Basis of Decision (SBD) Project: Phase II*, available at: <<a href='http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/sbd_qa_smd_fq-eng.php#a11' >http://www.hc-sc.gc.ca> (last visited Aug. 9, 2013). [hereinafter HC, *Frequently Asked Questions*]

[104] HC, *External Consultations*, *supra* note 6.

Drug approvals (or refusals) are supposed to reflect a judgment by a regulator that the benefits of the drug outweigh its risks (or not). Sometimes that judgment is strongly supported by the available evidence of safety and efficacy from clinical trials and demonstrated compliance with good manufacturing practices. Sometimes a great degree of uncertainty remains yet the regulator determines that the benefit/harm ratio is nevertheless favourable, for instance, where no other treatment is available for the condition in question. Drug labels tend not to convey these uncertainties and nuances, and while they may be found in the voluminous approval packages posted online by the FDA,[105] there is a need to bring them to the fore in a more accessible format regardless of whether the regulatory outcome is positive or negative.

A drug must, by law, meet all three requirements of safety, efficacy, and quality to be licensed for sale. In practice, regulators tend to consider these requirements in relation to one another. For example, a drug with limited efficacy may be deemed to have an acceptable benefit/harm ratio if it lacks significant risks of harm. Furthermore, the level of evidence required to establish safety, efficacy, and quality will inevitably vary depending on various other considerations. The absence of treatment alternatives, the rarity, morbidity, and mortality of the condition, or the adoption of a post-market "risk management plan," may buoy a regulator's decision to approve a drug with limited evidence of safety and/or efficacy.[106] What evidence will trigger a drug's withdrawal from the market is also unclear.[107]

[105] Schwartz and Woloshin, Lost in Transmission, *supra* note 100.
[106] P. Frey, United States Food and Drug Administration, Center for Drug Evaluation and Research (CDER), *Benefit-Risk Considerations in CDER: Development of a Qualitative Framework*, Jun. 28, 2012: available at:

Both the FDA and EMA have acknowledged the need for better communication of the benefit-risk reasoning behind its decisions. Each is currently developing new "benefit-risk" frameworks and methodologies to increase the transparency of which benefits, risks and other factors were considered, how the evidence was interpreted, and how the risks and benefits were weighed.[108] In keeping with the governance argument above, having to articulate the underlying reasoning behind a drug approval, abandonment, refusal, or withdrawal, should, with time, strengthen the quality of a regulator's decision-making. As also noted above, in principle, the regulator's reasons are its own work product—not the manufacturer's proprietary information—and thus amenable to public disclosure.[109]

Yet distinguishing the regulator's reasons from information contained in the manufacturer's submission may prove difficult in practice. Studies have shown that regulators have at times worked almost in collaboration with manufacturers during the review process to secure approval, advising about how to present their evidence in "pre-submission meetings," even re-drafting key components of the drug submission.[110] This highlights another component of what regulatory decisions should strive to make transparent: the procedural history of a given decision.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM317788.pdf> (last visited: Aug. 23, 2013). [hereinafter Frey, *Benefit-Risk Considerations*]

[107] Lexchin, Withdrawals, *supra* note 68; Clarke et al., An Assessment, *supra* note 68.

[108] FDA, Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, at <<www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf> (last visited Aug. 9, 2013); Frey, *Benefit-Risk Considerations*, *supra* note 106; E. Sukkar, 'Sunshine at the European regulator,' BMJ 344 (2012): e976. [hereinafter Sukkar, Sunshine]

[109] Note that these reasons do not encompass information that has been found to be proprietary, such as details of manufacturing processes and any sales or marketing related information.

[110] If this type of coaching is common, it arguably underscores the claim that regulator's reasons are not manufacturer's proprietary information.

The procedural history of a given regulatory decision is likely to be opaque at present. Health Canada's SBD Project (both Phase I and Phase II) describes the steps that led to a drug product's approval, but nothing more. For example, in May 2012, Health Canada approved Prochymal® (an adult human mesenchymal stem cell product) for the management of acute Graft versus Host Disease in children.[111] It is only one of two regulators in the world to do so and the decision met with some alarm.[112] In October 2012, an SBD for Prochymal was published on Health Canada's website along with other documentation, including a detailed report of an advisory committee's opinion in support of Prochymal.[113] Under the heading of "Submission Milestones," the SBD discloses that Prochymal was actually rejected twice for reasons of safety and efficacy, first in January 2011, and six months later, in late June 2012. In early August, a pre-submission meeting was held, presumably with representatives of Prochymal's manufacturer, Osiris Therapeutics, Inc., and Health Canada present. Less than six weeks after that meeting Prochymal was accepted for "Advance Consideration under the Guidance document: Notice of Compliance with Conditions (NOC/c)."[114] There is no information in the SBD about what happened in the pre-submission meeting. Did the manufacturer present new data? Did Health Canada officials offer advice about what additional data was needed or how to present the data already in hand? Health Canada's decision to approve Prochymal

[111] Government of Canada, Health Canada, *Prochymal: Notice of Compliance with Conditions - Qualifying Notice*, May 17, 2012, available at: < http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/prochymal_qn_aa_150026-eng.php > (last visited Aug. 23, 2013); Government of Canada, Health Canada, *Summary Basis of Decision (SBD) for PROCHYMAL*, Oct. 5, 2012, available at: < http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_prochymal_150026-eng.php > (last visited Aug. 23, 2013). [hereinafter HC, Prochymal SBD]

[112] D. Cyranoski, 'Canada Approves Stem Cell Product,' Nature Biotechnology, 30 (2012): 571–571. [hereinafter Cyranoski, Canada Approves]

[113] HC, Prochymal SBD, *supra* note 111; Government of Canada, Health Canada, *Report of the Expert Advisory Panel on Prochymal*, Jan. 26, 2012, available at: < http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/sci-consult/prochymal/report-rapport-eng.php > (last visited Aug. 23, 2013).

[114] HC, Prochymal SBD, *supra* note 111.

thus remains a puzzle to outsiders; it failed to satisfy efficacy endpoints during phase 3 trials in 2009, and the retrospective analysis of a subset that data upon which Health Canada's approval appears to turn is unpublished.[115] Making the substantive exchanges involved in a drug's procedural history transparent is necessary to understand Prochymal's positive outcome.

Outing a drug's procedural history may also repair how regulator-manufacturer interactions are perceived, though it cannot completely resolve the potential conflicts of interest infused in that dialogue (organizational changes described below are also needed). Nor can it fully answer the concerns (noted above stemming from Abraham and Sheppard's case study of the sleeping pill, Halcion®) from social science scholars about what the *real* reasons for regulatory decisions really are. That concern, however, underscores the idea that a jurisprudence of drug regulation should complement other measures of transparency, in particular, open access to clinical trial data in the form of clinical study reports. Transparency of clinical trial data can allow independent researchers to analyze the scientific basis for regulatory decisions. Yet study after study points to the importance of interpreting the data; it is not simply a technical exercise, but rather an invariably human one, subjective in nature, and thus vulnerable to error, bias, and influence.[116] Thus, access to regulators' interpretation of scientific evidence, encompassing both the process followed and lines of reasoning applied, is equally necessary.

AUDIENCE: *Decisions should be generated with drug developer, independent researcher, and fellow regulator audiences primarily in mind (not practising clinicians or the general public)*

[115] Cyranoski, Canada Approves, *supra* note 112.
[116] See notes 95 and 96 and corresponding text.

Determining what and how much information to incorporate into a regulatory decision depends on its primary intended audience(s). Regulators have been critiqued for failing to reach clinicians, lay publics, and researchers in their decision-making offerings.[117] Lisa Schwartz and Steve Woloshin, for example, have argued that the FDA's drug approval packages are unlikely to be mined by busy clinicians due to their voluminous size.[118] In an analysis of 161 of Health Canada's SBDs, Roojin Habibi and Joel Lexchin found that the vast majority of SBDs provided insufficient information for physicians to assess whether those who participated in the clinical trials that led to a drug's approval resemble patients under their care (*e.g.*, in terms of age and gender), thus limiting the utility of SBD for clinicians.[119] Barbui et al. examined a small set of the EMA's European Public Assessment Reports (EPARs) for psychiatric drugs. They found that key information pertaining to "the number of patients randomised to each treatment arm, losses during follow-up (plus the reasons), number of patients included in the primary outcome analysis, and absolute numbers and effect size (with precision) for the primary outcome analysis" was often missing.[120] The value of EPARs to clinicians, patients, and especially researchers engaged in systematic reviews and meta-analyses, was therefore judged to be poor.

While regulatory decisions should be freely available online to all audiences, in my view, they should be drafted with drug developers, independent researchers, and

[117] Schwartz and Woloshin, Lost in Transmission, *supra* note 100; C. Barbui, C. Baschirotto, A. Cipriani, 'EMA Must Improve the Quality of its Clinical Trial Reports,' British Medical Journal, 342 (2011): d2291 [hereinafter Barbui et al., EMA Must Improve]; R. Bauschke, 'Regulatory Agencies, Pharmaceutical Information and the Internet: A European Perspective,' Health Policy, 104 (2012): 12–18. [hereinafter Bauschke, Regulatory Agencies]
[118] Schwartz and Woloshin, Lost in Transmission, *supra* note 100.
[119] Personal communication from Joel Lexchin to author (Aug. 23, 2013).
[120] Barbui et al., EMA Must Improve, *supra* note 117.

fellow regulators primarily in mind. Several factors support this prioritization. There is no evidence to suggest that clinicians and patients actually seek out and use information about regulatory decision-making. There are clearly important reasons to inform these two user audiences.[121] But given the constraints on physicians' time and the multitude of lay publics that exist, I doubt regulatory decisions, even tightly summarized ones, are the most effective way to inform those audiences. Other tools, such as the "Prescription Drug Facts Boxes" piloted by Schwartz and Woloshin, represent a more promising alternative.[122]

If the purpose of making regulatory decision-making more transparent is to facilitate innovation by reducing waste and improve governance by opening up decisions to more independent scrutiny, then the primary audiences of a jurisprudence of drug regulation should be those critically engaged in developing drugs, interrogating the evidence base, and making regulatory decisions, *i.e.* firms, independent researchers, and fellow regulators. Those are the actors that are most likely to benefit from understanding the reasoning behind a drug's failure, for example; their decision-making is therefore what a jurisprudence of drug regulation should strive first and foremost to inform.

Health Canada describes SBDs as being "written for *all Canadians* interested in the reasons why Health Canada has taken product-specific decisions for drugs and medical devices."[123] Writing SBDs with such a generic audience in mind significantly limits the utility of SBDs to firms, researchers, and regulators alike.

[121] Schwartz and Woloshi, Lost in Transmission, *supra* note 100; Baushke, Regulatory Agencies, *supra* note 117.
[122] L.M. Schwartz, S. Woloshin, H.G. Welch, 'Using a Drug Facts Box to Communicate Drug Benefits and Harms: Two Randomized Trials,' Annals of Internal Medicine, 150 (2009): 516–527.
[123] HC, *Frequently Asked Questions*, *supra* note 103.

INDEPENDENCE: *Decisions should, when necessary for reasons of expertise, be informed by independent advisory committees, and, in any event, authored exclusively by independent officials within a regulator and include dissenting opinions*

There are deep-seated institutional conflicts of interest in drug regulation. A structural conflict of interest derives from the fact that regulatory reviews in the United States, Europe, Canada, and elsewhere have, since the early 1990s, been increasingly funded by "user fees" paid by manufacturers.[124] These fees come with significant strings attached, changing, to some degree, the way regulators operate. Data from Canada and Australia, for example, show that the introduction and subsequent rise in user fees collected by regulators correlate with more and faster new drug approvals.[125] Regulators appear to be "shunting…agency resources into the approval system and away from other regulatory functions, such as postmarketing surveillance,"[126] raising questions about the safety implications of such institutional shifts.[127] According to some sources, user fees appear to be transforming not only regulators' institutional resource allocations, but also the very understanding of their mandate, with industry, rather than the public, becoming the principal client.[128]

Powerful relational conflicts of interest also attend drug regulation. As noted by several researchers, regulators sometimes work in close collaboration with drug

[124] J. Avorn, 'Paying for Drug Approvals — Who's Using Whom?,' N. Engl. J. Med. 356 (2007): 1697–1700 [hereinafter Avorn, Who's Using Whom?]; J. Lexchin, 'Harmony in Drug Regulation, But Who's Calling The Tune? An Examination of Regulatory Harmonization in Health Canada,' International Journal of Health Services, 42 (2012): 119–136; J. Lexchin, 'Drug Approval Times and User Fees,' Pharmaceutical Medicine, 22 (2008): 1-11. [hereinafter Lexchin, Drug Approval Times]

[125] J. Lexchin, 'Relationship between pharmaceutical company user fees and drug approvals in Canada and Australia: a hypothesis-generating study,' Annals of pharmacotherapy, 40 (2006): 2216-2222.

[126] Lexchin, Drug Approval Times, *supra* note 124; United States Government Accountability Office, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, Sep. 17, 2002, available at: < http://www.gao.gov/products/GAO-02-958> (last visited Aug. 12, 2013).

[127] *Id.*; J. Lexchin, 'New Drugs and Safety: What Happened to New Active Substances Approved in Canada Between 1995 and 2010?' JAMA Internal Medicine, 172 (2012): 1680-1681.

[128] Avorn, Who's Using Whom?, *supra* note 124.

manufacturers during the review process. Manufacturers value these relationships, and the trust engendered between them and individual reviewers, over time. The latest incarnation of the user fee legislation in the United States thus "directs the FDA to allocate user-fee revenue toward efforts such as reducing staff turnover, which industry sees as a barrier to efficient application review."[129] Individual reviewers have been found to have close ties with and, in some cases, a direct financial stake, in manufacturers' holdings.[130] A study published in 2006 by Peter Lurie and colleagues found, in a sample of 221 FDA advisory committee meetings (spanning 16 different committees), that at least one committee member disclosed a conflict of interest in 73% of the meetings yet only 1% of such members were recused from the committee.[131]

To achieve a jurisprudence of drug regulation a greater level of independence amongst decision-makers is required, necessitating a series of organizational changes. The first organizational change relates directly to regulators' use of advisory committees, a practice long entrenched at the FDA and growing elsewhere. The basic motivation behind advisory committees is to add expertise in an ad hoc fashion as therapeutic product submissions test regulators' scientific capacity. In theory, such committees serve as a form of independent scientific review. In practice, however, committee members may be far from disinterested in the products under scrutiny. This threatens the "integrity" of regulatory decision-making.[132] Therefore, while it may not always be possible to fill an advisory committee with non-conflicted experts (although many such

[129] D.B. Kramer and A.S. Kesselheim, 'User Fees and Beyond — The FDA Safety and Innovation Act of 2012,' N. Engl. J. Med. 367 (2012): 1277–1279.
[130] Lurie et al., Financial Conflict of Interest Disclosure, *supra* note 32; Lexchin and O'Donovan, Prohibiting or Managing, *supra* note 33l; GAO, *FDA Advisory Committees*; Sukkar, Sunshine, *supra note 108*; Anon. 'European medicines agency: riddled with conflicts of interest,' Prescrire International, 21 (2012): 278.
[131] Lurie et al., Financial Conflict of Interest Disclosure, *supra* note 32.
[132] Wood and Mador, Uncapping Conflict, *supra* note 63.

experts still seem to exist),[133] that should be regulators' starting objective. A level of disinterestedness should, in other words, be valued equally with expertise. Failing the ability to identify non-conflicted individuals with the requisite expertise, the efforts made to identify such individuals should be documented and made publicly available, as well as the particular conflicts of interests of each serving advisory committee member. In addition, in the event that one or more committee members have an actual or potentially conflicting interest should become a factor to be explicitly weighed by the regulator in making its decision.

Secondly, the actual decision-makers and, insofar as they are different individuals, those who translate them into written decisions for outside scrutiny, must be insulated from officials that are a) sensitive to institutional budgets (of which user fees make up a growing contribution), b) in dialogue with manufacturers, or c) conflicted in other ways. Institutional norms, cultures, and power hierarchies will complicate efforts to insulate decision-makers in this way and ensure some independence. At a minimum, the current practice of vetting decisions (and the reasons to be made publicly available) directly with the manufacturer before they are finalized should stop.

Thirdly, regulatory decisions ought to expand considerably in scope. Above, I noted that the procedural history leading up to both positive and negative regulatory decisions should be transparent. In addition, regulatory decisions need to make room for dissenting opinions and disagreement. In the past, the FDA has shown a tendency to paper over safety-related concerns from internal scientists.[134] These dissenting views, and

[133] *Id*.

[134] This appears to occur most frequently during post-market surveillance. See G. Harris, 'Potentially Incompatible Goals at FDA,' New York Times, Jun. 11, 2007, at A14; Okie, What Ails, *supra* note 76; Willman, New FDA, *supra* note 93; The Adequacy of the FDA to Assure the Safety of the Nation's Drug

the reasons why, in the event of a drug approval or decision not to withdraw a drug, they did not control the outcome, should be transparent. Similarly, to the extent a regulator diverges from an advisory committee recommendation, which regulators are free to do, the diverging views should be explicitly explained in the body of the decision.

Health Canada's SBD project conveys none of these organizational features. Those who author SBDs have no decision-making authority, and the decision is crafted in dialogue with drug manufacturers.[135] Those charged with preparing SBDs are clearly subservient to members of Health Canada's "review team," the very individuals who are in continuous dialogue with manufacturers and also likely to be sensitive to the potential costs (in user fees) of frustrating those relationships. An entirely different infrastructure is needed to achieve a basic level of independence in regulatory decision-making.

Conclusion

The arguments and institutional reforms developed in this paper are motivated by the meagre level of transparency of regulatory decision-making at present and, ironically, the focus of the current policy debate regarding transparency in the drug development process more generally. The focus of the policy debate is on opening up clinical trial data. While greater transparency of clinical trial data is critical, it is unlikely to reveal

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Supply: Hearing Before the H. Subcomm. on Oversight and Investigations, Comm. On Energy and Commerce, 110th Cong. 191 (2007) (statement of Rep. Bart Stupak).

[135] As explained by Health Canada:

> The SBDs will continue to be drafted by Health Canada technical writers, based upon Health Canada's regulatory review reports. The SBD draft will be sent to the Health Canada review team for comment and possible revision, in order to ensure that review conclusions are appropriately reflected and contained within the SBD. The completed SBDs will then be sent to the sponsor/manufacturer for review; feedback will be limited to inaccuracies of data and it is expected that only minor revisions, if any, will be made to the document as a result of industry feedback received.

See HC, Frequently Asked Questions, *supra* note 103.

when regulators made the 'right' or 'wrong' decision except in marginal cases. Regulators' decisions are more often characterized by scientific uncertainty, involve nuanced weighing of not only risks and benefits, but also value judgments about relative patient need and existing therapeutic options, and complicated by extrinsic social, political, and economic factors. The call here for a jurisprudence of drug regulation is, in this sense, meant to out the full complexity of regulators' work; if the four foregoing features of a jurisprudence of drug regulation can be realized, regulatory decision-making should be held in higher esteem. Realizing these four essential features carries obvious costs. Given the potential benefits of greater transparency in regulatory decision-making, in terms of innovation and governance, however, these costs should not justify the status quo.

Table 1. Detailed comparison of regulatory decision-making transparency in Canada, the United States, and Europe during the product lifecycle.

	CANADA	UNITED STATES	EUROPE
PRE-MARKET RESEARCH & DEVELOPMENT			
Investigational Application			
Existence of application	*No*	*No (with limited exceptions)***	*No*
Specifics of application	*No*	*No (with limited exceptions)***	*No*
Decision to hold, terminate, or withdraw	*No*	*No (with limited exceptions)***	*No*
Marketing Authorization Application			
Existence of application	*No*	*No (with limited exceptions)***	*Yes*
Specifics of application	*No*	*No (with limited exceptions)***	*Yes*
Marketing Authorization Application Withdrawal or Abandonment*			
Existence of withdrawal or abandonment	*No*	*No (with limited exceptions)***	*Yes*
Reasons for withdrawal or abandonment	*No*	*No (with limited exceptions)***	*Yes*
MARKET AUTHORIZATION OUTCOME			
Market Authorization Refusal			
Existence of refusal	*No (with limited exceptions)*	*No***	*Yes*
Specifics of refusal	*No (with limited exceptions)*	*No***	*Yes*
Reasons for refusal	*No (with limited exceptions)*	*No***	*Yes*
Market Authorization Approval			
Existence of approval	*Yes (for some products)*	*Yes*	*Yes*
Specifics of approval	*Yes (for some products)*	*Yes*	*Yes*
Reasons for approval	*Yes (for some products)*	*Yes*	*Yes*
Market Authorization Conditional Approval			
Existence of conditional approval	*Yes (for some products)*	*Yes*	*Yes*
Specifics of conditional approval	*Yes (for some products)*	*Yes*	*Yes*
Reasons for conditional approval	*Yes (for some products)*	*Yes*	*Yes*
POST-MARKET SURVEILLANCE			
Suspension of Market Authorization			
Existence of suspension	*No*	*Yes*	*Yes*

	CANADA	UNITED STATES	EUROPE
Specifics of suspension	*No*	*No*	*Yes*
Reasons for suspension	*No*	*No*	*Yes*
Revocation of Market Authorization			
Existence of revocation	*No*	*Yes*	*NA****
Specifics of revocation	*No*	*No*	*NA****
Reasons for revocation	*No*	*No*	*NA****
Withdrawal/Recall of Product			
Existence of withdrawal/recall	*Yes*	*Yes*	*Yes*
Specifics of withdrawal/recall	*Yes*	*Yes*	*Yes*
Reasons for withdrawal/recall	*Yes*	*Yes*	*Yes*

* In the accompanying paper I use the term 'abandoned products' to refer to any products that voluntarily withdrawn or abandoned by the manufacturer before market approval. I reserve the term 'withdrawn drugs' or 'withdrawals' for drugs that are removed from the market after they have receive market authorization from a regulator.

**The FDA published a series of Draft Proposals in 2010, which, if implemented, would make each of these decisions transparent. United States Food and Drug Administration, *Phase II Transparency Report*, May 19, 2010, available at: <http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212110.pdf > (last visited: Aug. 22, 2013).

***The EMA appears to treat withdrawn and revoked products as one and the same.