Evidence and Policy in Pharmaceutical Regulation:

The promise of, and barriers to, a system of adaptive licensing

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1. Introduction

In the regulation of pharmaceutical products, there is growing interest in moving to an "adaptive licensing" (AL) model. Eichler et al. (2012) describe "adaptive licensing" as potentially "transformative", shifting pharmaceutical regulation away from a "binary" exercise of evaluating drug safety and effectiveness before and after approval to a more continuous process of "progressive management and reduction of uncertainty" (p. 427). Several jurisdictions have elements of adaptive licensing already in place, such as accelerated regulatory pathways for drugs that address unmet patient needs (e.g. "orphan drugs" for rare diseases). However, according to Eichler et al. (2012), in order for adaptive licensing to be truly transformative, a "comprehensive development and licensing plan" must be "agreed on in advance by the sponsor, regulators, and payers", engendering "more open and timely dialog and cooperation" between the three throughout the process (p. 430) with continuous evidence collection over the drug's life-cycle.

In this presentation we focus on four key elements of the vision articulated by Eichler et al. (2012) -- (1) the preservation of regulatory independence, (2) continuous evidence collection, (3) transparency; and (4) interjurisdictional cooperation – and compare those elements to experience with existing regulatory pathways (and specifically those governing orphan drugs). Focusing on these four elements vis-à-vis existing experience to date highlights four key challenges to adaptive licensing (AL), which those advocating for AL have thus far failed to address.

First, finalizing an agreement in advance of review for safety, efficacy, and cost-effectiveness raises the issue of *regulatory independence*. Under current orphan drug laws, regulators routinely provide "protocol assistance" to manufacturers to meet the challenges of evaluating safety and efficacy in small, rare disease patient populations. Yet binding regulators to a specified licensing plan may reduce their ability rigorously and independently to evaluate the evidence that manufacturers later supply, potentially compromising regulators' assessment of a drug's safety and efficacy. Given the evidentiary limitations associated with many orphan

drug approvals (Kesselheim et al. 2011; Kesselheim and Avorn 2011) this is a compelling concern if protocol assistance becomes the norm across all drug approvals. Thus, in order for AL to succeed without sacrificing patient safety, preserving a degree of independence between regulator and manufacturer is a key challenge to be addressed.

Second, *continuous evidence collection* is integral to AL. Yet experience to date with conditional marketing approvals (which many orphan drugs carry) suggests that industry's compliance with post-marketing study requirements is woeful and regulators' demonstrated capacity to enforce such requirements is, at best, variable. If continuous evidence collection is to occur, proponents of AL must answer concerns about regulators' ability and willingness to enforce evidence collection after market entry and/or develop robust, alternative mechanisms for such evidence collection (for instance, by independent third party research organizations).

Third, the call by Eichler et al. (2012) for open dialogue during the AL process is critical, especially in light of potential shortcomings in the evidence base behind a drug at the time of approval. However, many drug regulators have struggled to make their decision-making processes transparent, and negotiations between manufacturers and payers are uniformly carried out under conditions of strict confidentiality. To maintain public trust as the shift to AL occurs, far *greater transparency* between the sponsor/regulator/payer interface and the public at large will be necessary.

Fourth, building a viable evidence base for AL, especially in federal systems such as the EU, US, or Canada, requires some degree of effective *interjurisdictional collaboration*. The principle of AL is that information about drug effectiveness and safety is collected continually through a compound's life cycle. Where drugs are targeted to specific genetic composition, the subject groups are particularly small, and the need for data to be collected as widely as possible and for as long as possible is especially high. Territorial borders can substantially impede the compilation of this data. Moreover, Eichler et al. (2012) suggest the utility of bringing payers to the table. Involving payers upfront during the R&D process and regulatory review for safety and

efficacy would be a remarkable shift. At present there is a significant gap between the evidence required by regulators for market approval and the evidence required by payers for coverage. (Flood and Dyke 2012) Closing that gap could greatly shorten the R&D process and speed access. However, in federal systems like Europe and Canada, regulatory review for safety and efficacy versus payer review for cost-effectiveness are divided between governmental actors. Achieving AL would therefore require a considerably greater intergovernmental collaboration than presently observed.

The paper is divided into four main parts following this introduction (Part 1). Part 2 is contextual. We set out the scientific and industrial backdrop against which this proposed shift toward AL is occurring. This backdrop includes an increased industry focus on developing so-called “precision medicines” and “orphan drugs” – two intersecting trends that are motivating the shift to AL. We set this alongside an account of the various stakeholders and interests, both aligned and diverging, in play. Part 3 identifies the four key challenges described above in greater detail, drawing in evidence surrounding existing regulatory pathways, especially, orphan drug pathways, that to some extent mirror AL and thus hold valuable lessons for policy-makers looking to make AL the norm rather than the exception. Part 4 synthesizes these key challenges in view of the current Canadian regulatory landscape. Throughout, our primary focus is on the European and Canadian contexts, though, references to the United States’ considerable body of scholarship examining orphan drug regulation in that jurisdictions will also be made.

2. How re-thinking the nature of "evidence" requires a shift in regulatory approaches

2.1 *The era of precision medicine and the growth of orphan drugs*

On January 30, 2015, President Obama recognized a "new era of medicine" by announcing a $215 million Precision Medicine Initiative aimed at revolutionizing the way diseases are diagnosed and treated. Coming in the wake of genomic sequencing, "personalized" or "precision" medicine attempts to match specific treatments to an individual's particular

genetic composition. Each manifestation of breast cancer, for example, may be the result of a very specific combination of variables, both genetic and epigenetic; therefore, the uniform and homogenous treatment options that were common 25 years ago have given way to more targeted or "personalized" therapies.

There are at least three ways that this approach changes the way in which such diseases are addressed. In the first place, precision medicine can utilize various kinds of biological indicators, or "biomarkers", to assess an individual's *potential risk* of experiencing a specific disease (thus permitting effective preventative treatment, as well as early diagnosis). In the second place, these specific biological indicators can *identify responders and nonresponders to specific therapies* before the fact, thus ensuring that patients are matched quickly and accurately with the most effective treatment. And, in the third place, the same kind of data can identify which individuals are more likely to experience *adverse drug reactions*.

In sum, then, the theory is that precision medicine is able to provide better diagnostic accuracy, better treatment efficacy, and better safety in the utilization of medical therapies. It is, however, essential to recognize that precision medicine is still largely aspirational. Massive resource allocations have been made, especially in the US, in the name of advancing precision medicine and a wealth of previously unknown relationships between biomarkers and disease risk, prognosis, and treatment response have been uncovered. But the clinical validity of many of those discovered relationships remains unclear. Whether much of this information helps to explain the underlying mechanism of a given disease is unknown. Meanwhile, researchers and pharmaceutical companies are integrating biomarkers into drug discovery and development, pushing regulators to accommodate new trial designs and measures of safety and efficacy.

This shift in pharmaceutical R&D is particularly visible in the arena of orphan drugs. In general terms, orphan drugs are those that target rare forms of disease. The threshold of rarity varies across jurisdictions with an orphan drug law in place (Herder 2013); in the US, all diseases afflicting 200,000 persons or less are considered rare (US Orphan Drug Act 1983), whereas in

Europe, rare diseases are defined as occurring in 5 or fewer persons per 10,000. (EU Regulation 141/2000) But the list of known rare diseases is far from fixed. In fact, the very insights from biomedical research that help to better characterize the molecular underpinnings of a given disease are also being used to redefine disease categories; in some cases, subdividing diseases previously thought to be common into multiple, rare forms of disease. Thus, from an R&D perspective, progress toward precision medicine can be harnessed through the orphan drug law criteria – something which drug companies are increasingly taking advantage of. Originally, the premise behind orphan drug laws was that extra incentives are needed to encourage drug manufacturers to allocate resources toward developing treatments for diseases that affect small patient populations on the assumption that such treatments will generate lower market returns. However, over time, manufacturers have to come realize that the costs of developing such orphan drugs are often far less than drugs targeting larger populations. As explained next, the costs are less, in significant part, because the volume of evidence (eg, size of studies) required by regulators to secure market approval is generally far less for an orphan drug. Moreover, health care payers have been willing to accept high price points because of the small number of patients involved. Thus, contrary to conventional wisdom, recent estimates suggest orphan drugs hold *greater* profit potential than other drugs (Meekings et al. 2012) and industry has allocated its resources accordingly. Indeed, in 2010 roughly a third of all drugs approved by the US regulator were orphan drugs. (Coté et al 2010)

2.2 *Playing with confounders: how precision medicine changes the way in which we think about - and collect – evidence and disease categories*

The most profound insight of precision medicine - that the more clearly we refine identifiable patient populations, the better we are able to treat them safely and effectively - is, however, the reason that traditional methods for collecting scientific evidence are increasingly inadequate. Traditionally, the "gold standard" of medical research has been the double-blind randomized controlled trial (RCT). The point of RCTs is to ascertain the causal pathways of an effect as clearly and precisely as possible. This requires a large enough number of subjects to make the result statistically significant; a very narrow subset of potential subjects (eg, those

with no additional health issues, only a certain age group, only male subjects, or limited ethnic variability); and a very strict treatment protocol that is carefully monitored. These controlled conditions ensure that the causal relationship under scrutiny is investigated thoroughly, with as little "causal pollution" as possible by confounding variables.

But the problem with RCT evidence is that its very purity diminishes its relevance in the "real world". If the effectiveness of a compound is diminished (or exacerbated) by common confounders, then the existence of (and effects of) such variables is hardly irrelevant, and the neglect of such confounders in RCTs has serious implications for the effect a drug will have in "real-life" circumstances (RCTs, for this reason, often tend to overestimate the size of the treatment effect). Most importantly, as "relevant cohorts" become more and more precisely identified, they also become smaller in size. While major drug trials generally attempt to enrol around 7,000 subjects, those focussing only upon specific biological markers are much more limited (the main trial for the cystic fibrosis drug Kalydeco, for example, involved 161 patients, while the paediatric study enrolled 52. [USFDA: 2013, 40]). Traditional, large RCTs are thus increasingly ill-suited to act as the sole evidence base in the context of precision medicine. Further, where the treatment in question targets a rare disease (perhaps redefined as such by virtue of a new biomarker) large RCTs may be altogether impossible due to small patient numbers.

The nature of evidence-gathering for precision medicine and orphan drugs is thus increasingly more observational than controlled. In observational studies, there is no formal control group, and subjects are aware of the treatments they are receiving. One application of this is the development of single-person trials (N-of-1 trials), in which a large amount of potentially relevant data is collected from one person as frequently as possible. Then, "[b]y looking for commonalities across multiple N-of-1 studies - in which the same types of data are collected using the same procedures - researchers should be able to draw inferences about the effectiveness of an intervention in certain subsets of the population, such as in people sharing particular genetic features, as well as in the whole population" (Schork 2015). A more common

approach is to follow the experiences of patients as they receive treatment in uncontrolled ("real life") environments. Under these conditions, then, the ability effectively to track the effects of drugs in such populations "is critical to the success of personalized medicine" (FDA 2013, 40).

2.3 *Adaptive licensing*

The interest in moving towards a regulatory framework that accommodates these new approaches to evidence-gathering has led to a great deal of discussion on adaptive licensing (AL), also commonly known as "progressive licensing" or "life-cycle" approaches to regulation. Eichler et al. (2012:428) have defined AL as:

> a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainty followed by regulatory evaluation and license adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made.

The key point distinguishing AL from current licensing frameworks is that the latter tend to rest upon a binary presentation of "approved" versus "unapproved" designations (although, as noted below, most systems have also brought in "conditional" categories for market authorization). The problem is that, as more and more active compounds are developed with reference to smaller and smaller populations, the evidence base for these drugs becomes more tenuous, especially in the pre-market entry phase. The principle underlying AL is that this all-or-none process of evaluation is transformed into a long, steady, recursive process of continually collecting and appraising evidence over the entire life-span of the drug. As the efficacy, effectiveness, and safety profiles of drugs become increasingly known, prescribing guidelines can be reconsidered and, if necessary, the compounds can be withdrawn altogether.

While AL can be applied to the entire spectrum of regulated drugs, it has received the most attention as a means of addressing the specific requirements of orphan drugs. There are, globally, around 7,000 rare diseases, which affect approximately 350 million people. Yet, of these, only 450 rare diseases have identified treatments (Henderson 2014). As noted above, because of the lower costs involved and added incentives provided by governments and payers, the pharmaceutical industry is increasingly focused on the development of orphan drugs (Herder 2013). By and large regulators have accommodated this shift in industry's focus, with many orphan drugs being approved on the basis of limited evidence albeit while carrying active post-market study obligations. Experience to date with orphan drug approvals thus holds valuable insights for AL more generally, which we will explore below.

2.4 The EU's "Adaptive Pathways" strategy

The process of orphan drug development and licensure is neither simple nor straightforward. While there are specific pieces of legislation in most jurisdictions (such the 1983 Orphan Drug Act in the United States and Regulation 141/2000 in the EU) which set out the legal parameters establishing what orphan drugs *are*, the frameworks governing incentive structures for the development of such compounds, and the limitations on the way they can be authorized, are much more diffuse. The broad orphan drug development framework in the US, for example, involves grants, tax credits, fee waivers, market exclusivity (seven years), and transferable vouchers. Orphan drug submissions are often classified according to the specific application of the compound (eg, tropical diseases, antibacterial, paediatric), and fall under separate regulatory categories (eg, the Gain Act, focussing upon antibacterial or antifungal drugs for serious or life-threatening infections, is under the auspices of Section 801 of the FDA Safety and Innovations Act [FDASIA], while the Breakthrough Therapy Designation falls under Section 902 of the FDASIA.)

Similarly, there are a number of regulatory and developmental pathways available to those producing orphan drugs in the EU. Article 14(7) of Regulation 726/2004, for example, grants *conditional marketing authorization (CMA)* for products with incomplete evidence on the

grounds that applicants will provide comprehensive clinical data within a short time frame. If the product's benefits are deemed to outweigh its immediate risks, it is authorized with specific post-marketing obligations. If these obligations are not met, the product may be withdrawn from the market, or financial penalties may be imposed. Directive 2001/83 permits drugs to be authorized *under exceptional circumstances*. This generally means that the baseline of evidence may be considerably lower if, for example, the disease is so rare that there is little scientific information on its etiology, or if there are reasonable ethical issues precluding the normal collection of evidence. The authorization under these circumstances is assessed every year, to a maximum of five years. Finally, Article 83(2) of Regulation 726/2004 permits the *compassionate use* of drugs currently undergoing clinical trials. Normally, marketing authorization for orphan drugs is determined centrally (ie, must be made by the Committee on Orphan Medicinal Products [COMP] of the EMA). In this instance, however, each drug seeking authorization on the grounds of compassionate use must go through national guidelines established by each member state (eg, the Early Access to Medicines Scheme in the UK). The industrial incentive scheme for orphan drugs within the EU includes protocol assistance and scientific advice, market exclusivity (10 years), fee reductions, EU-level grants, and national-level grants.

Under the EU's federal regulatory structure (drugs can generally be approved either at the EU or national level), the EMA's COMP has begun to work more closely with many national HTA and regulatory agencies, as well as EUnetHTA, in order to harmonize the development and utilization of orphan medicines. The COMP also works closely with the FDA on orphan drug development (in 2012, 62% of the applications submitted to the COMP were also submitted in parallel to the FDA). The COMP is increasingly expanding its interest in collaboration to agencies such as Health Canada and Australia's Therapeutic Goods Administration (Ogbah 2015:9). But the EU's harmonization process focuses not only the coordination of bodies within Europe, and between the EMA and non-European agencies, but also on the coordination of the various regulatory processes already in place.

In March 2014, the EMA announced a pilot project on "adaptive pathways," based upon the principle of a "life-span approach to bring new medicines to patients with clinical drug development, licensing, reimbursement, and utilisation in clinical practice, and monitoring viewed as a continuum" (EMA 2014). By December 2014, the EMA received 34 applications from pharmaceutical companies to consider their products for the pilot project (12 of these drugs were orphan medicines). By April 2015, this had been narrowed to eight products. At this point, the EMA invited industry, HTA agencies, organizations responsible for clinical-treatment guidelines, patient advocacy groups, health care professionals, and academic researchers to discuss "ways of optimizing development pathways". This process has three objectives. The first is to determine an "iterative development plan" outlining the relationship between the ongoing collection of evidence and the changing way in which the drug is utilized. The second is a protocol to engage HTAs and other "downstream" stakeholders (such as patient groups). The third is a careful determination of the relationship between controlled (RCT) and observational evidence: specifically, how is "real life" data to be monitored and collected; and how, precisely, should it be used to supplement RCT data?

2.5 Identifying the interests of key stakeholders

In policy terms, any period when key stakeholders are willing to move away from the status quo is a clear window of opportunity for policy change (Kingdon 2002). That so many stakeholder groups in the EU are interested in the idea of AL is therefore, from a policy perspective, quite significant. Yet God and the devil are in the details and, despite the rhetoric, it is not clear that all groups are willing to move in the same direction. End-users of medicinal products desire timely access to drugs that are both efficacious and safe. The pharmaceutical industry has found in niche drugs a strategic opportunity for economic growth and market expansion. Discrete units within each state hope to provide competitive environments for domestic industries, coordinate public health outcomes with economic investment opportunities, ensure the safety and the effective use of pharmaceuticals, and restrain the cost of new drugs purchased by public health care entities. Each actor sees an advantage in moving

towards a framework of AL in order to achieve their goals; but, at the same time, each actor's set of objectives is quite distinct.

Patient organizations representing those with rare diseases (including EURORDIS in the EU and CORD in Canada) have become very active in lobbying for adaptive licensing. An obvious reason for this is that AL promises to provide access to therapeutic drugs in a more expedited manner than under standard approval processes. As noted above, however, current regulatory systems in the EU, US, and Canada already have rapid-approval processes added into standard approval processes. What is novel in the adaptive pathways process is that the recursive process upon which it is based would permit patients themselves to become actively involved in the regulatory process, rather than remaining passive objects of study. At each stage of authorization in an AL system, the feedback of targeted populations using the drugs (regarding, eg, new formulations, new routes of administration, treatment modality, assessment of quality of life, and prevalence of adverse events) would be required before further marketing authorizations were granted (Ogbah 2015). There is a pilot project underway in Canada wherein feedback from patients (through CORD) is to be integrated directly into the regulatory review of two new rare disease treatments. The intention of AL is to make such patient involvement the norm.

Pharmaceutical companies generally support the adaptive pathways initiative for five interrelated reasons: first, "rare disease" drugs are an expanding market for companies whose mass-market products are coming off-patent. Orphan drug sales between 2005 and 2011, for example, increased at a rate of almost ten per cent per year (almost twice as much as the industry as a whole), for a total of US$86 billion globally (Bennett 2013), and they are expected to grow at a compound annual rate of 5.67 per cent between 2013 and 2018 (Henderson 2014). "The unmet need in the orphan-disease space," stated one pharmaceutical executive, "is enormous" (Bennett 2014). Second, the adaptive pathways process, despite its iterative, multi-stage design, simplifies and accelerates the procedure for getting drugs to market. The EMA, through discussions with national regulators and health technology agencies (HTAs), is

attempting to harmonize evidentiary standards across European jurisdictions. Having effective systems of parallel scientific advice and protocol assistance in place would mean that pharmaceutical producers could spend less time meeting varying requirements for each European state. Third, as discussed above, a system of adaptive licensing provides greater flexibility for companies in gathering appropriate evidence. The quid pro quo introduced by AL permits authorization based upon less rigorous evidence balanced by a more limited market authorization. Fourth, by engaging in early dialogue with nation states to ascertain states' perceived needs regarding pharmaceutical treatments, drug developers can more efficiently cultivate strategic "pipelines" by focussing on the development of drugs which authorities perceive are in the interest of public health (such as new antibiotics or vaccines). Finally, the adaptive pathways initiative has the potential to increase the volume of drugs purchased across Europe. Currently, new drugs for orphan diseases command exceptionally high prices. This has led austerity-minded European states to negotiate stringent pricing deals with the producers of these drugs (such as Ireland's refusal to purchase Kalydeco, and the Netherlands' refusal to pay for drugs targeting Fabre and Pompe diseases, unless the price was brought down to "acceptable levels"). The European Federation of Pharmaceutical Industries (EFPIA) hopes that the EU's adaptive pathways program, focusing on a European-wide collaboration of the assessment of the relative value drugs provide, may result in increased use of such drugs across Europe. In this way, the diminished returns resulting from lower negotiated per unit prices would be balanced by a higher volume of sales (Bennett 2013).

The interests of **states** in the adaptive pathways process are more complex. This is because the modern state is comprised of units with discrete responsibilities and mandates; the process of governing is thus the playing out of conflicts between these units (Miliband 1969). Adaptive pathways are relevant to at least four separate public functions. In the first place, the *public health* function of governments imposes an obligation for public authorities to identify and nurture promising compounds and technologies, which may substantially improve public health. The development of the hepatitis C drug Sovaldi, for example, meant a response rate of 90 per cent compared to a rate of 50 per cent with the standard treatment with drugs such as

ribavirin and interferon (Nordrum 2015). There has, for this reason, been increasing interest by governments in "horizon scanning" practices, in which emerging health advances are identified, monitored, and even nurtured by governments who have an interest in getting new compounds into the public sphere. The mandate for "early dialogue" between state and industry in the adaptive pathways program is designed to have the same effect. On this particular front, there is a clear convergence of interests between government, industry, and patient advocacy groups. In the second place, the pharmaceutical sector is an important part of Europe's industrial strategy. For the EU as a whole, the pharmaceutical industry is worth €220 *billion* annually, and accounts for approximately 800,000 jobs. Given that the world market for medical products is expected to reach US$1.17 *trillion* by 2017, DG-Enterprise (the arm of the European Commission responsible for the development of trade and industry, now merged with DG-Internal Market) has focused upon the pharmaceutical sector as a key long-term growth market (EC, n.d.;EC 2014). The function of the state here is to act as *a protector and incubator of commercial growth*. To this end, the EU, in partnership with EFPIA, established a €2 billion partnership, the Innovative Medicines Initiative, to "enhance the competitiveness of the pharmaceutical sector in Europe" (Goldman 2012). This is now being superseded by the second phase of the initiative (IMI2). Here, again, the interests of state and industry clearly converge, although the focus on pharmaceutical growth as a function of industrial policy is more pronounced in some states than in others. The third and fourth functions of the state, however, do not align as comfortably with the interests of pharmaceutical producers. The *regulatory function* of the state is to provide for the safety and well-being of citizens by monitoring the risks of pharmaceutical products, to determine when the benefit-risk ratio of such compounds is unacceptable, and to ensure that producers are following proper protocol and releasing all relevant data. This function can conflict quite sharply with the objectives of commercial interests to market their products as quickly as possible, and to keep the profile of adverse events as limited as possible (Light, Lexchin and Darrow 2013; Davis and Abraham 2014). Finally, the *economic sustainability* function of the state is to ensure that authorized pharmaceutical products are affordable, cost-effective, and accessible to those in need. When the state itself is primarily responsible for paying for the cost of drugs (in contrast to private

insurance systems) the motivation to negotiate advantageous contracts with the pharmaceutical sector becomes pronounced. In this context, again, the interests of both the state and the pharmaceutical industry are clearly juxtaposed.

3. Four key challenges to the success of adaptive licensing

The recent experiences with the regulation of orphan drugs across jurisdictions highlights four specific challenges in implementing AL more widely: (1) preserving regulatory independence in the midst of an even closer relationship with industry and patient groups; (2) actively collecting high quality evidence about drug safety and effectiveness across drug life cycles; (3) fostering transparency in the evidence base and regulatory process; and, (4) institutionalizing cooperation amongst different governmental bodies. We detail each in turn in this Part.

3.1 *Maintaining regulatory independence while providing protocol assistance*

Regulators regularly provide scientific advice to drug companies during the pre-market phase of drug development. The lag between submission and approval can consume several years; in the intervening period, regulators have grown accustomed to conferencing with company representatives and documenting their concerns and suggestions to satisfy safety and efficacy standards. Orphan drug laws in the US, Japan, Australia and Europe each formalize this iterative advice process in the form of "protocol assistance", which regulators *must* provide in an effort to define, in contractual terms, what safety and efficacy endpoints will suffice for regulatory approval. (Herder 2013) Reducing the uncertainties involved in the regulatory process from the perspective of companies, protocol assistance is regarded as one of the key tools to encourage orphan drug R&D.

Drug companies are keenly aware not just of the value of scientific advice or protocol assistance in terms of designing studies, but also the value of being seen by the regulator to respond to it. Companies are increasingly seeking scientific advice from regulators for the specific purpose of using alternative trial designs (ElsaBer et al. 2014), and one study suggests

that one of the strongest predictors of regulatory approval is a company's compliance with regulators' advice. (Regnstrom et al. 2010)

However, the increasing exchange of advice and assistance between regulators and the regulated has occurred at the same time as the independence and rigor of regulators has fallen into serious question. Numerous cases, including the antiarrhythmic drugs of the 1980s, Vioxx in the late 1990s, Paxil in the early 2000s, and others, have revealed regulatory failure and industry capture. (Healy 2012, Abraham and Davis 2013, Gøtzsche 2013) Several commentators suggest that legislative reforms that have tied regulatory performance to industry-paid user fees have engendered a structural conflict of interest, compromising regulatory science and in turn patient safety. But it is also possible that the institutionalized provision of advice and assistance, not just decisions, has contributed to the close-knit relationship that has evolved between regulators and industry. By advising or, in the case of protocol assistance, helping to define a set of evidentiary milestones to be met for market approval, it is plausible that regulatory officials consciously or unconsciously develop a shared stake in a given drug application.(Herder 2014) Therefore, if the onset of adaptive licensing marks the onset of regulatory advice and assistance to drug companies across the board, for all drugs, additional measures and institutional processes to maintain regulatory independence and rigor will be essential.

There are strategies to mitigate this problem. For instance, regulators could establish firewalls between those officials that are in dialogue with drug companies and those who make the ultimate decision about market entry. Both sets of officials could, moreover, be insulated from those in the institution who have budgetary responsibilities and thus at risk of influencing the review process in order to recoup maximum user fees. However, thus far, such strategies have not been part of the policy conversation about moving towards AL.

3.2 *Curating continuous evidence collection despite post-market disincentives*

Several regulators already require ongoing evidence collection after a drug enters the market. The FDA's Accelerated Approval pathway, the EMA's Exceptional Circumstances and Conditional Marketing Authorisation pathways, and Health Canada's Notice of Compliance "with conditions" (NOC/c) pathway are each predicated upon making regulatory approval contingent upon subsequent evidence collection, whether through active surveillance or so-called "phase 4" clinical trials. (Law 2014)

Companies' compliance with these post-market evidence collection conditions has generally been moderate to poor. In Canada, for example, a recent study found that the evidence collection requirements for only 41% (or 29 out of 70) drugs approved on the basis of an NOC/c had been met. Further, when met, on average, those requirements took upwards of five years to fulfill. (Law 2014; see also Lexchin 2007) These findings map onto the findings of a larger study conducted by the US Government Accountability Office (2009) regarding the FDA's Accelerated Approval (AA) pathway. Like Health Canada's NOC/c pathway, the post-market conditions attached to most drugs approved through the FDA's AA were not met; when they were, it was only after exceptional delays. (GAO 2009) Similarly, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) recently noted that "a review of the actual post authorisation study requests conducted by HTA bodies reveals that many of the requested studies are never conducted. Among those which are started, many do not come to an end because of enrolment or other feasibility issues. Among those which come to an end, many are considered 'unreliable' because they have been conducted by the MAH [market authorization holder]" (ENCePP 2013).

Further, regulators have not shown the will to enforce evidence collection requirements, either to ensure they are met within a reasonable period of time or to remove the drug from the market when the requirements are not met or instead reveal greater safety and efficacy shortcomings than anticipated at the time of regulatory approval. (Law 2014) The first reported example of a regulator (the FDA) removing a drug from the market because the

company in question had failed to meet its post-market obligations was in 2010, and that action occurred 14 years after the drug was approved. (Law 2014)

Given these shortfalls in compliance and enforcement of post-market requirements to collect evidence under existing regulatory pathways, an even greater reliance upon ongoing evidence collection as part and parcel of AL poses unequivocal risks to patient safety. It also raises sustainability or value for performance concerns for health care payers to the extent that studies of a drug's cost-effectiveness are only agreed upon in principle, but never actually completed.

It is an inescapable reality that drug companies have a significant disincentive to evaluate a drug's safety and effectiveness once it is on the market: the results of that research may, if carried out appropriately and rigorously, undermine the companies' sales or even result in the drug's withdrawal. For this reason, even putting aside issues of compliance and enforcement, many suggest that independent post-market evaluation of drug safety and effectiveness is preferable. (Wiktorowicz et al. 2012) Several jurisdictions have established entities to conduct such evaluation, including the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance and Canada's Drug Safety and Effectiveness Network (see discussion below). Funding for these entities remains unstable, however, rendering post-market drug evaluation efforts more sporadic than systematic. If AL ushers in conditional licensing across the board on the theory that real world drug use should inform assessments of safety and effectiveness, these independent post market research models have to become more robust.

3.3 *Fostering openness in evidence production and assessment in the face of market competition*

AL has been envisioned by Eichler et al. (2012) as an open dialogue amongst drug companies, regulators, payers, and patients. It is not clear whether they envision a dialogue that is open amongst only those named parties, or one that is open to others and thus

supportive of a public dialogue as well. If it is the latter for at least some of what Eichler et al. (2012) imagine under the banner of AL, then it is useful to situate that call for openness amidst parallel efforts to foster greater transparency in pharmaceutical R&D and regulation more generally.

Calls to increase the transparency of the evidence base behind, and regulatory decisions made in respect of, drugs go back decades. (Dickersin and Rennie 2012; FDA 2010) And awareness of the risks posed by a lack of transparency to patient safety and the practice of evidence-based medicine alike is now acute. Several jurisdictions and international institutions have promulgated laws and policies in an effort to encourage researchers, drug companies, and regulators to register clinical trials, publish their results, and make their decision-making transparent. Progress has been piecemeal. Even in jurisdictions where clinical trial registration and results reporting is legally required and subject to financial penalties, compliance has been meagre to date. (Prayle et al. 2012; Law et al. 2011) Regulatory openness is even less in hand. (Herder 2014) Canada, for example, only publishes a limited subset of its regulatory decisions and many of the conditions attached to many drug approvals – a key instrument in the context of AL – are not publicly available. (Law 2014) Nevertheless, meaningful commitments have been made nationally and internationally and there is a sense that the principal remaining challenge is not so much a question of rule change, but rather the harder and slower work of norm change. (IOM 2015)

The one area where transparency is not the stated aspiration concerns pharmaceutical pricing. Several commentators have called for greater transparency in order to ensure fairness and performance-based pricing. (Roberts et al. 2015; Morgan et al. 2013; Simoens 2011; Roos et al. 2010) But these calls have not received purchase at governmental levels, much less with industry. The conventional view is that such negotiations and the information exchanged during coverage negotiations are private and proprietary to the company involved. That is, companies are seen as having a legitimate interest in keeping pricing information, including cost-effectiveness data, confidential given the highly competitive nature of the industry. Health care

payers also frequently sign confidentiality agreements, precluding disclosure of the agreed upon drug price, which companies game to their advantage in negotiations with other payers.(Morgan et al. 2013) Thus, to the extent Eichler et al. (2012) imagine AL will open up such confidential conversations, they will have to contend with industry's proprietary claims to the contrary. Conversely, if present norms surrounding pricing negotiations prevailed in AL, there is a risk that industry may contend other aspects of the dialogue, for example, concerning the safety and effectiveness of drugs, must be treated as confidential as well in the interest of facilitating frank discussion with regulators, payers, and patients. AL may thus become a foil to ongoing efforts to institutionalize transparency in the name of patient safety. This hidden tradeoff merits far greater attention from proponents of AL.

3.4 *Establishing greater collaboration between federal units*

The call for the participation of payers in the AL process presents another problematic dynamic beyond that of transparency. This is the issue of whether, and how, to coordinate policy-making by autonomous jurisdictions across a federal system. In the case of orphan drugs in the EU, the market authorization is determined centrally by the EMA, while the pricing of these drugs remains a national responsibility. Eichler et al. (2012) call for payers to become engaged in the process of AL. Yet they do not explain why this is necessary. Certainly the collaboration of purchasers of pharmaceutical products would be an effective means of lowering drug prices, especially for smaller states with less purchasing power. At the same time, pharmaceutical industries have an interest in being able to gauge the interest in, and the demand for, specific kinds of compounds by those who pay for them. Ideally, there would a constructive trade-off between the affordability won by the payers, and the predictability and stability of knowing demand, achieved by the sellers.

Interestingly, there is some evidence that European collaboration on drug pricing is slowly and sporadically beginning to coalesce. In June 2014, for example, the EU implemented a Joint Procurement Agreement, a purely voluntary collaborative endeavour which was initially established to ensure equitable and efficient access to pandemic vaccines, but which may be expanded to negotiate the procurement of other pharmaceutical products. Then, in April 2015,

Belgium and the Netherlands announced a pilot program in which the two states would work together to negotiate better prices for orphan drugs. Significantly, the Netherlands will ascend to the Presidency of the EU in January 2016, and will use its position to encourage European cooperation on drug pricing (O'Donnell 2015a).

At the same time, however, there are many obstacles to a strategy of collaborative purchasing. In the first place, different jurisdictions have different requirements regarding the same drug (viz., states generally have specifications for particular volumes, formulations, and even delivery conditions, which require individual contracts tailored to specific markets). Second, larger states with more technical capacity are often able to negotiate favorable terms by themselves, and they are generally disinterested in any coordinated activity on pricing. (A similar dynamic plays out amongst larger and smaller provinces in Canada: see Morgan et al. 2013). Third, states with a strong domestic pharmaceutical sector may simply choose not to support such a pricing strategy. And fourth, the EU is a federation established primarily to ensure the free flow of goods and services; therefore, substantial joint-purchasing strategies may potentially run afoul of European anti-competition law.

Yet the attempt to bring payers to the table in a pan-European system of AL may, in the end, be unnecessary. At present there is a significant gap between the evidence required by regulators for market approval and the evidence required by payers for coverage, although this varies by jurisdiction. But this gap is shrinking. States are increasingly purchasing drugs based on how well they work. And, to do so, they require the same quality of data used by regulators. To this end, ensuring effective collaboration between payers and regulators/HTAs may be sufficient. Once good-quality data are available, payers should be more able to make effective value-based drug purchases independently. How does this work?

The "official list price" set by pharmaceutical companies is largely symbolic; in reality, the actual prices paid depends upon the ability and willingness of payers to negotiate these prices. In states with poorly-developed HTAs, payers must rely upon a system of external reference pricing, in which prices are set with reference to what other specified states are paying. This method is highly inefficient, for a number of reasons (Husereau and Cameron 2011, Kavanos et al. 2011). But states with greater HTA capacity are able to move toward a system of

cost-effectiveness pricing, in which prices are set depending upon whether new compounds are more effective, or as effective, as existing compounds; by the degree of greater effectiveness; and by the type of effectiveness: eg, greater longevity versus better quality of life (Danzon, Towse, and Mulcahy 2011). A similar alternative is *value-based pricing*, which incorporates multiple criteria in the decision-making, including not only the effectiveness of the drug per se, but also the potential general socioeconomic impact of access to the drug (see, eg, McGuire, Raikou, and Kanavos 2008). An even more sophisticated form of pricing is that of *risk-sharing agreements* and *managed-entry agreements*, in which pricing is dependent upon factors that play out over time. For example, conditional coverage permits prices to be set temporarily; failure to achieve specified clinical targets means that prices may fall, or coverage may be discontinued. Outcome guarantees, or payment by result, require pharmaceutical companies to provide rebates if specified outcomes are not met. Similarly, price and volume agreements require companies to pay a penalty (or to supply more product gratis) if the drug overshoots preset budgets (see Adamski et al. 2010, Ferrario and Kanavos 2013, and Mahjoub,Odegaard, and Zaric 2013).

What this means is that payers increasingly depend upon a solid, extensive rubric of health technology assessment in order to finance effective treatments and to negotiate sustainable contracts with suppliers. The adaptive pathways pilot project has actively attempted to draw together national health assessment agencies, as well as some national regulators, via the EMA (and through EUnetHTA), in an effort to streamline assessment methodologies and benchmarks, establish a shared set of IT tools, expand the pool of relevant registries, and integrate HTA capacities. This endeavour, moreover, has a solid treaty base under Article 15 of the 2011 Cross-Border Directive. Thus, to the extent that individual national pricing decisions are increasingly reliant upon solid and extensive HTA data, and to the extent that this HTA data is becoming increasingly integrated, payers themselves do not have to be directly involved at the table because the information that they are using to negotiate sustainable pricing schema is already becoming increasingly consolidated.

4. Is Canada ready for AL?

AL is not altogether foreign to the Canadian context. In 2006 and 2007, Health Canada issued two "Blueprints for Renewal," in which a life-cycle approach to regulation (generally referred to as "progressive licensing") was introduced. This approach was incorporated into Bill C-51, which died on the order paper in 2008 when an election was called and Parliament was adjourned. Despite expectations that this legislation would soon be reintroduced when the incumbent government was reelected (Jepson 2009), it was not. When the Food and Drug Act was finally updated by the passage of Vanessa's Law in November 2014, AL was not an explicit focus of the legislation. However, various provisions in the Act could facilitate the development of new regulatory frameworks, which could support a shift to AL in the future.

But is Canada ready for AL? Or, to be more precise, what kinds of adaptations would be necessary to AL to work effectively in the Canadian context? The reasons underscoring the desirability of AL are even more pronounced now than they were in 2008. The recursive approach to evidence that characterizes AL is especially important with the growing emphasis on precision medicine. This is because "precision medicine" focuses upon how well particular compounds work upon very specific subpopulations of individuals. And, with an emphasis on treating smaller and smaller populations more appropriately, the way we think about the collection and interpretation of evidence shifts dramatically. This is now quite evident with the way in which orphan drugs are evaluated; but the point is that, under a rigorous system of precision medicine, most drugs will essentially become "orphan drugs."

The contribution of Eichler et al. (2012) is useful here; it brings AL-related processes and standards into sharp relief. Eichler et al. (2012) clearly explain the technical composition, and advantages, of AL. Nonetheless, this account does not carefully attend to the competing pressures(from diverse interests) to remake drug regulation in the interests of competitive industrial policy, to provide faster and cheaper access to drugs, to generate better evidence and more informed decision-making, and so on. The challenges we have identified attempt to think about how those diverse interests and sources of pressure affect the actual operationalization of AL. At the same time, while these challenges transcend individual regulatory systems, each system may need to respond to AL differently in view of local constraints and considerations,

especially available institutional resources and intergovernmental dynamics. Canada's regulatory context provides a case in point.

As noted above, aspects of Canada's regulatory system mirror some of AL. Since 1998 a conditional marketing approval program (the NOC/c regulatory pathway) has been in place. More recently, the regulatory has secured a variety of new legal powers that are intended to improve its ability to regulate drugs across the life-cycle. Amendments to Canada's Food and Drug Act in 2014 give Health Canada the power to recall drugs from the market; compel drug companies as well as health care institutions to provide information about drugs; enforce post-market study obligations (a power it lacked despite the NOC/c pathway); compel changes to drug labels; and, make a variety of information about the safety and effectiveness of drugs publicly available. (Bill C-17) But, as noted in the discussion in section three, challenges remain:

4.1 . Regulatory independence

Despite these new legal tools, Health Canada's demonstrated culture and practices will undercut its capacity to move to AL and successfully address the key challenges we have identified. To begin, Health Canada's regulatory independence is limited. Repeated studies of Health Canada have characterized its culture and practices as one of "mutual dependence" with industry. (Wiktorowicz 2003) Lacking the resources and clout of a larger regulatory agency like the US FDA, Health Canada has an extensive history of fostering direct cooperation with industry in many facets of regulatory functions, from developing drug standards to working out safety concerns informally rather than imposing sanctions. (Herder 2015) This deep cooperative relationship with the regulated industry also likely lies behind the lack of enforcement of NOC/c post-market study obligations observed to date (Lexchin 2009), and is the fundamental driver of Health Canada's continuing opacity.

4.2. Curating continuous evidence collection

As noted above, AL requires a framework in which drug monitoring at all stages in a compound's life cycle can be maintained over time and across jurisdictions. Through the

establishment of such bodies as the EMA (in 1995), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, in 2006) and the European Network for HTA (EUnetHTA, in 2010), the EU has been able to establish a reasonable framework upon which AL can be developed. Yet even these structures remain tenuous and vulnerable to political pressure. The EUnetHTA, for example, formally enjoys limited-term status as a Joint Action facilitated by the European Commission. There is hope that it may be given a more permanent status as a body operating under the aegis of the EMA, but as yet this has not materialized. ENCePP has no legislative mandate nor public funding, and depends upon industry funding to carry out its studies. Even the EMA itself is susceptible to political dynamics: in September 2014 it was transferred from the EU's Health Directorate to the newly-merged directorate for Internal Market, Industry, Entrepreneurship, and Small and Medium-sized Enterprises (and it was returned back to the Health Directorate a month later due to a very public outcry).

The capacity for the ongoing monitoring of pharmaceuticals in Canada is even more limited and tenuous. The Drug Safety and Effectiveness Network (DSEN) was established in 2009 and, under its aegis, the Canadian Network for Observational Drug Effect Studies (CNODES) was launched in 2011. But the mandate of these bodies is strictly limited. Studies can only be undertaken in response to a formal query submitted by Health Canada, provincial health plans, or the Canadian Agency for Drugs and Technologies in Health (CADTH). Privacy legislation enacted by each province has posed a particular barrier to the collaborative collection of health data. Moreover, the long-term funding prospects for these networks is uncertain. Cochrane Canada, for example, the Canadian arm of the international network providing systematic research reviews, will no longer be funded after 2015. Finally, there is no national database of patient registries. Registries are generally run by the pharmaceutical industry, which collects and interprets the data; and Health Canada has no mandate to monitor these industries and the way they gather or disseminate information collected from their registries (HCC 2010). Any attempt to implement a system of AL in Canada would thus require a more extensive, independent, and proactive framework with the capacity to monitor a very large number of medical products over a much longer period of time.

4.3. *Fostering transparency in evidence production*

Health Canada lags far behind the EMA and other regulators in terms of transparency. The practice of treating information about the safety and effectiveness of drugs as company property goes back decades (Herder 2015). Unlike Europe, the US, and elsewhere, no legal requirement to register clinical trials or report trial results presently exists in Canada. (Herder et al. 2014) The enactment of Bill C-17 in late 2014 finally granted the Minister of Health and in turn Health Canada several new transparency related powers, including the discretion to disclose drug safety and effectiveness data (assuming it is characterized as confidential business information under the law) in order to prevent serious injury to human health or to persons that carry out functions related to the "protection or promotion of human health", which will ideally extend to independent researchers and physicians. There is also a provision that would impose a requirement upon drug manufacturers to disclose certain "prescribed information", which could be used to make clinical trial registration and results reporting mandatory. However, given Health Canada's entrenched culture of keeping manufacturers' data confidential, it remains to be seen whether the Minister of Health will exercise her discretion to disclose more data to independent researchers and physicians, nor that Health Canada will move quickly to draft regulations to "prescribe" what information must be made transparent. Seven months and counting since the passage of Bill C-17, and the necessary implementing regulations have yet to be published.

Assuming these critical transparency regulations are eventually developed, enforcement will also present considerable challenges. Better-resourced regulators such as the US FDA and the EMA have, to date, largely failed to enforce clinical trial registration and results reporting requirements. (Anderson et al. 2015) Thus, while transparency is essential to AL, it is not clear that Health Canada has the institutional capacity or resources to meaningfully improve the transparency of the evidence it reviews.

4.4. Establishing greater collaboration between federal units

A major principle of the EU's adaptive pathways approach is "close collaboration among key constituencies" (O'Donnell 2015b). The EU, as a federal system with relatively little centralized influence built upon spending power, has effectively developed a system facilitating coordinated policy-making between member states through collaborative devices as Joint Actions. (Fierlbeck 2014) The European Network on Health Technology Assessment is one outcome of this process. But Canadian provinces remain stymied by the failure to build potent collaborative networks, even as more costs and responsibilities are placed upon the provinces by Ottawa's refusal to become involved in what it perceives to be a provincial responsibility (including, notably, the dismantling of the Health Council of Canada). One difficult dynamic in the attempt to establish more collaborative ventures is that larger provinces have the capacity to undertake complicated and expensive tasks, like drug effectiveness evaluation, which others do not. Six provinces, for example, have Quality Control councils (British Columbia, Alberta, Saskatchewan, Ontario, Quebec, and New Brunswick); four (Manitoba, Nova Scotia, Prince Edward Island, and Newfoundland) do not. The functions undertaken by these quality control centres varies tremendously as well. Ontario, for example, funds an Evidence Development and Standards Branch; smaller provinces like New Brunswick tend to focus on the health status on their respective populations.

In the area of joint purchasing, the Council of the Federation's Health Care Innovation Working Group has, between 2012 and 2015, been able to make progress on reducing the prices for 10 generic and 14 brand-name drugs, but only through bulk purchasing, rather than through the establishment of comprehensive value-based pricing. Intriguingly, the Canadian Partnership Against Cancer (CPAC) has been able to establish a very effective model of pan-Canadian collaborative research in the field of cancer, including a national coordinating centre for Canadian clinical trials in cancer, a synoptic reporting initiative, and a quality implementation initiative to determine best practices in treatment. Because oncologics are amongst the fastest-growing (and expensive) category of drugs (partly due to their capacity to gain "orphan drug" status), such coordinated monitoring and benchmarking is a promising start to building HTA capacity in this field. The challenge, of course, will be to integrate this data into an AL system.

5. Conclusion

The existing regulatory framework for pharmaceuticals is being increasingly challenged around the world. One key shift is in the development of "precision medicine," or the attempt to ground diagnostic and treatment modalities upon specific biogenetic markers. The focus upon precision medicine, in turn, requires us to rethink the way in which evidence about the effectiveness of pharmaceuticals is gathered and evaluated. Specifically, smaller and smaller target populations mean that the traditional large-scale RCT is increasingly ill-suited to assess the effectiveness and safety of compounds. Real-world experience in this kind of evidence-gathering has been developing in the attempt by various jurisdictions to address the specific regulatory issues thrown up by "orphan drugs." In a sense, the discussion over the regulation of orphan drugs is a useful pilot project to think about the challenges of adopting a wider and more thoroughgoing framework of AL. AL is certainly better adapted to the regulatory issues presented by medicine's interest in the interplay between drugs, genetics, and epigenetics. But regulatory frameworks are created within very specific environments that are replete with institutional, economic, technical, and political barriers. The undertaking to establish AL systems in any jurisdiction must recognize these obstacles and think through very carefully how to address them. Any attempt to set up regulatory reforms without a clear and realistic appreciation of the tensions and dynamics underlying the regulation of pharmaceutical products threatens to reinforce the very problems that weaken the current regulatory regime.

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