

# THE PROMISE AND PERIL OF ADAPTING THE REGULATORY SYSTEM TO THE PHARMACOGENOMIC CONTEXT

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Pharmacogenomics – the study of the influence that genetic factors have on drug response – presents significant regulatory challenges. Pharmacogenomics products require the approval of both a pharmaceutical drug and a companion diagnostic, a situation which is further complicated by the fact that authority to regulate these two different types of products is fragmented between different levels of government, different provinces, and even different agencies within the same level of government. Although Health Canada reports that they are ramping up efforts to determine the most appropriate means of incorporating pharmacogenomics information into drug evaluation and regulatory decision-making throughout the stages of drug development, Canada continues to

La pharmacogénomique, l'étude de l'influence des facteurs génétiques sur la réponse à un médicament, pose de véritables défis de réglementation. Les produits pharmacogénomiques requièrent à la fois l'autorisation d'un médicament et d'un test diagnostique compagnon. Cette situation est rendue plus complexe par le fait que le pouvoir de réglementer ces deux types de produits est divisé entre deux ordres de gouvernement, différentes provinces, et même différents organismes au sein du même ordre de gouvernement. Bien que Santé Canada annonce qu'il redouble d'efforts afin d'indiquer un moyen approprié d'incorporer l'information pharmacogénomique dans l'évaluation des médicaments et dans les décisions réglementaires à prendre dans toutes les étapes

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lag behind other jurisdictions in adopting substantial reforms. This is in marked contrast to the significant efforts made by the Food and Drug Administration in the US, which has taken a leadership role in proposing new draft guidance on reforms to improve the evaluation and regulation of pharmacogenomic products – documents that provide useful insight into how Canada may more effectively adapt existing regulatory practices to the pharmacogenomic context. Informed both by the literature and by interviews with key Canadian stakeholders, we explore how pharmacogenomic drugs and tests are evaluated and approved within the current Canadian regulatory system and what reforms may be necessary to more effectively evaluate and regulate these emerging health technologies. We begin by looking at, first, the split regulation of companion diagnostics by federal and provincial authorities and, second, how pharmacogenomic products are currently integrated into the drug regulatory system at the federal level. Subsequently, we consider possible reform efforts to better coordinate the review of drug and test components, to offer more flexible approaches to market authorization and to expand regulatory oversight during the post-market phase. Our discussion focuses on the Canadian regulatory system, but our recommendation and discussion are also relevant for other jurisdictions in which pharmacogenomic products are being evaluated.

du développement des produits pharmaceutiques, le Canada continue d'accuser un retard par rapport à d'autres juridictions en ce qui concerne l'adoption de réformes importantes. Cela contraste vivement avec les efforts déployés par la Food and Drug Administration des É-U, qui a assumé un rôle de premier plan en rédigeant des directives préliminaires visant la réforme des pratiques d'évaluation et de réglementation des produits pharmacogénétiques. Ces documents fournissent des perspectives intéressantes relatives à l'adaptation du régime réglementaire présentement en vigueur au Canada dans le contexte pharmacogénétique. Nous basant à la fois sur la littérature et des entrevues avec des intervenants clés au Canada, nous explorons comment les médicaments et les tests pharmacogénomiques sont évalués et approuvés dans le système réglementaire canadien et quelles réformes seraient nécessaires afin de rendre plus efficace l'évaluation et la réglementation de ces technologies de la santé émergentes. Nous examinons d'abord la division du régime réglementaire des tests diagnostiques compagnons entre les autorités fédérales et provinciales du gouvernement ainsi que l'intégration des produits pharmacogénomiques dans le régime de réglementation des médicaments au niveau fédéral. Par la suite, nous considérons des réformes visant plusieurs objectifs, soit une meilleure coordination des régimes de vérification des médicaments et des tests, une approche plus flexible d'autorisation de mise en marché et l'expansion de la surveillance réglementaire après la mise en marché. Bien que notre discussion vise le système réglementaire présentement en vigueur au Canada, nos recommandations et notre discussion restent pertinentes pour toutes les juridictions dans lesquelles les produits pharmacogénomiques sont évalués.

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## INTRODUCTION

In 2003, the completion of the Human Genome Project set the stage for new discoveries on the role of genetics in disease and the development of new therapies tailored to the genetic characteristics of individual patients.<sup>1</sup> One of the touted promises of the further development of genetic research was that health care providers would be able to routinely use an individual's genetic information to select which drugs and drug doses are most likely to benefit a given patient<sup>2</sup> – this being part of the growing field of “personalized medicine.” In basic terms, pharmacogenomics is the study of the influence that genetic factors have on drug response.<sup>3</sup> Depending on each individual's genetic makeup, some drugs may work more or less effectively, or may produce more or fewer side effects. Pharmacogenomics “aims systematically to assess how interacting systems of genes may affect disease susceptibility, pharmacological function, drug disposition and therapeutic

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<sup>1</sup> Ian Kerr, Jennifer Chandler & Timothy Caulfield, “Emerging Health Technologies” in Jocelyn Downie, Timothy Caulfield & Colleen M Flood, eds, *Canadian Health Law and Policy*, 4th ed (Toronto: LexisNexis, 2011) 501 at 504.

<sup>2</sup> National Human Genome Research Institute, “Frequently Asked Questions about Pharmacogenomics”, online: NHGRI <[www.genome.gov/27530645](http://www.genome.gov/27530645)>.

<sup>3</sup> The terms “pharmacogenetics” and “pharmacogenomics” tend to lack a precise definition and they are often used interchangeably: Stuart A Scott, “Personalizing Medicine with Clinical Pharmacogenetics” (2011) 13:12 *Genet Med* 987 at 989-90. In this paper we will use the term “pharmacogenomics,” as it is more commonly used in North America. There is, however, a difference between the two terms. Generally, pharmacogenetics is the study of how an individual's response to drugs is affected by differences in heredity and specific sets of genes: Elliot S Vesell, “Advances in Pharmacogenetics and Pharmacogenomics” (2000) 40:9 *J Clin Pharmacol* 930 at 930. According to the Organisation for Economic Co-operation and Development (OECD), “[i]n simple terms, the discipline aims to identify the best medicine for a specific disease when the disease occurs in a patient population with a particular genotype”: Organisation for Economic Co-operation and Development, *Pharmacogenetics: Opportunities and Challenges for Health Innovation* (2009) at 29, online: OECD <<http://browse.oecdbookshop.org/oecd/pdfs/product/9309081e.pdf>>. In contrast, pharmacogenomics is broader than pharmacogenetics and involves the study of how drugs and disease susceptibility interact with the systems of genes, or the genome. In essence, pharmacogenetics is a subset of pharmacogenomics, the former focusing on the relationship between specific genes and drug response while the latter examines the role of the genome and genetics more generally in drug response: Munir Pirmohamed, “Pharmacogenetics: Past, Present and Future” (2011) 16:19-20 *Drug Discov Today* 852 at 852.

drug response.”<sup>4</sup> By targeting patient subsets with particular genetic biomarkers, pharmacogenomics stratifies broader disease categories into rarer disease genotypes.<sup>5</sup>

Recent years have seen a growing hype around pharmacogenomics and its alleged revolutionary impact on the practice of medicine. The field shows promise for helping to diagnose disease, identify people at risk of disease, and fine-tune treatments. To date, several drugs have been developed that are specifically connected to genetic markers.<sup>6</sup> Some have suggested that pharmacogenomics may even help to jump-start drug development pipelines by identifying new targets for treatment and improving the success of drug development.<sup>7</sup> Consequently, drug companies are developing an interest in increasing the efficacy of their products by developing companion diagnostic tests that can stratify patient populations according to genetic predisposition to respond to drug therapies.<sup>8</sup> However, significant questions remain about the significance and usefulness of some biomarkers in predicting drug response. While there are many statistically significant genetic

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<sup>4</sup> Organisation for Economic Co-operation and Development, *supra* note 3 at 29.

<sup>5</sup> Some members of the scientific community now argue that “stratified” medicine is a more accurate term than “personalized” medicine for describing this new approach, which targets patient subpopulations that are more or less likely to respond to a treatment rather than tailoring the treatment specifically for the individual. See Mark R Trusheim, Ernst R Berndt & Frank L Douglas, “Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers” (2007) 6:4 *Nat Rev Drug Discov* 287 at 287.

<sup>6</sup> Two examples of some of the most successful pharmacogenomic-based treatments are the breast cancer drug Herceptin (trastuzumab) and the leukemia drug Gleevec (imatinib mesylate), both of which have generated billions of dollars in annual sales. See e.g. the discussion in Derek So & Yann Joly, “Commercial Opportunities and Ethical Pitfalls in Personalized Medicine: A Myriad of Reasons to Revisit the Myriad Genetics Saga” (2013) 11:2 *Curr Pharmacogenomics Person Med* 98 at 105-06.

<sup>7</sup> Stuart Hogarth et al, *Regulating Pharmacogenomics: An Overview of Developments in Various Countries and Industry Response to Regulatory Initiatives (A Report for Health Canada)* (2006) at 11, online: King’s College London, Department of Political Economy <[www.kcl.ac.uk/sspp/departments/political-economy/research/biopolitics/publications/RegulatingPharmacogenomicsAreportforHealthCanada.pdf](http://www.kcl.ac.uk/sspp/departments/political-economy/research/biopolitics/publications/RegulatingPharmacogenomicsAreportforHealthCanada.pdf)>.

<sup>8</sup> Ryan Collier, “Bye, Bye Blockbusters, Hello Niche Busters” (2011) 183:11 *Can Med Assoc J* 697 at 698.

associations in drug response, few translate easily at this point into clinical practice.<sup>9</sup> As stated by Fleck, medical researchers have been “uncritically liberal” in identifying biomarkers,<sup>10</sup> and the predictive value of many highly cited biomarkers may be overstated.<sup>11</sup> A detailed review of the difficulties associated with research supporting claims of connections between genetic markers and drug response exceeds the scope of this paper, but it is worth pointing out that there are growing calls for promoting more transparency and accountability in this area, including through a more independent assessment of the pre-clinical evidence supporting drug development.<sup>12</sup>

Pharmacogenomics presents significant challenges for the regulation of both companion diagnostics and pharmaceutical products. The regulation of pharmacogenomic tests is complicated due to, *inter alia*, the technical complexity of the tests, the need to standardize platform technologies, and the need to validate the results of tests that may analyze a large number of biomarkers simultaneously.<sup>13</sup> At the same time, pharmacogenomics also introduces new challenges for drug regulators, who are often less familiar with the diagnostics sector and the challenges of biomarker validation and test evaluation,<sup>14</sup> and who may thus be uncertain of how these technologies impact on drug safety and efficacy. The current regulatory framework, even if it has evolved over time, still largely reflects a very traditional drug development model that dates from before the advent of these new genomic technologies. This creates significant uncertainty around how pharmacogenomics should be dealt with within the existing system.<sup>15</sup>

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<sup>9</sup> Patrick MM Bossuyt, “The Thin Line between Hope and Hype in Biomarker Research” (2011) 305:21 J Am Med Assoc 2229.

<sup>10</sup> Leonard M Fleck, “Pharmacogenomics and Personalized Medicine: Wicked Problems, Ragged Edges and Ethical Precipices” (2012) 29:6 N Biotechnol 757 at 760.

<sup>11</sup> Bossuyt, *supra* note 9.

<sup>12</sup> Jonathan Kimmelman & Alex John London, “Predicting Harms and Benefits in Translational Trials: Ethics, Evidence, and Uncertainty” (2011) 8:3 PLoS Med e1001010.

<sup>13</sup> Hogarth et al, *supra* note 7 at 8.

<sup>14</sup> *Ibid.*

<sup>15</sup> Matthew Avery, “Personalized Medicine and Rescuing ‘Unsafe’ Drugs with Pharmacogenomics: A Regulatory Perspective” (2010) 65:1 Food Drug Law J 37.

In general, pharmacogenomic drugs and companion diagnostics are subject to the same regulatory approval process as conventional pharmaceutical products and diagnostic tests, respectively. However, regulating pharmacogenomics in Canada is complex not only because the treatment requires the approval of both a pharmaceutical drug and a companion diagnostic, but also because the authority to regulate these two different types of products is fragmented between different levels of government, different provinces, and even different agencies within the same level of government. Further, there is currently little coordination between the review of pharmacogenomic drugs and their associated diagnostic tests; both are, in most cases, reviewed independently from one another by different regulatory authorities or health care agencies.

Health Canada has acknowledged that pharmacogenomics is a rapidly evolving field of research, and that “as such, it will take a concerted effort between sponsors and regulators to harness the benefits that it has to offer.”<sup>16</sup> As stated by Hogarth and colleagues, “[i]t is a two-way process with regulators having to adjust their systems to take into account the new technologies being adopted by industry and with the regulatory agencies influencing the adoption of pharmacogenomics through the development of new guidance documents.”<sup>17</sup> Although regulators in various jurisdictions are ramping up efforts to determine the most appropriate means of incorporating pharmacogenomic information into drug evaluation and regulatory decision making throughout the stages of drug development,<sup>18</sup> Canada continues to lag behind other jurisdictions – particularly the US – in adopting significant reforms.

There are no specific provisions in either the *Food and Drugs Act*<sup>19</sup> or its associated regulations that deal specifically with pharmacogenomic treatments. In May 2008, Health Canada issued a guidance document entitled *Submission of Pharmacogenomic Information* to assist manufacturers intending to submit pharmacogenomic information in support of an appli-

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<sup>16</sup> Health Canada, *Submission of Pharmacogenomic Information*, Guidance Document (23 May 2008) at 1, online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/brgtherap/pharmaco\\_guid\\_ld-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/pharmaco_guid_ld-eng.pdf)> [Health Canada, *Pharmacogenomics Guidance*].

<sup>17</sup> Hogarth et al, *supra* note 7 at 8.

<sup>18</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 4.

<sup>19</sup> RSC 1985, c F-27.

cation or submission for drugs, biologics, or medical devices, or as part of ongoing post-market activities.<sup>20</sup> The guidance document helps sponsors navigate the points within the existing regulatory framework where special consideration should be given to pharmacogenomic products. To date, this is the only guidance released by Health Canada that specifically pertains to the pharmacogenomic context. Despite the rapidly evolving nature of new genomic technologies, it has not been updated in content since its release in 2007. This is in marked contrast to the significant efforts made by the Food and Drug Administration (FDA) in the US to clarify the application of existing regulatory procedures to pharmacogenomic products. Moreover, the FDA has been very active in proposing new draft guidance on reforms to improve the evaluation and regulation of pharmacogenomic products – documents that provide useful insight into how Health Canada may more effectively adapt existing regulatory practices to the pharmacogenomic context.

Informed by both the literature and interviews with key Canadian stakeholders,<sup>21</sup> in this paper we explore how pharmacogenomic drugs and tests are evaluated and approved within the current Canadian regulatory system and what reforms may be necessary to more effectively evaluate and regulate these emerging health technologies. We begin by looking at, first, the split regulation of companion diagnostics by federal and provincial authorities and, second, how pharmacogenomic products are currently integrated into the drug regulatory system at the federal level. Subsequently, we

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<sup>20</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16.

<sup>21</sup> While not our central focus, the discussion in certain sections of this paper is informed by interviews conducted as part of a qualitative study on the perspectives of Canadian stakeholders on the legal, ethical, and social implications of pharmacogenomics and drug development. We conducted interviews with 34 key informants representing a wide range of groups, including regulators, drug funders, pharmaceutical industry representatives, scientists, policy experts, and patient advocates. The identities and affiliations of all participants has been kept confidential. In these interviews, many stakeholders expressed concern that the current regulatory framework in Canada is not yet well adapted to the pharmacogenomic context. Of particular concern were the fragmented regulatory responsibility over, and lack of coordination in, the review of the drug and test components, and shortcomings in regulatory oversight during the post-market phase. For more details and study results, see Shannon Gibson, Hamid R Raziee & Trudo Lemmens, “Why the Shift? Taking a Closer Look at the Growing Interest in Niche Markets and Personalized Medicine” (2015) 7:1 *World Med Health Policy* 3.

consider possible reform efforts to better coordinate the review of drug and test components, to offer more flexible approaches to market authorization, and to expand regulatory oversight during the post-market phase.

## I. REGULATION OF COMPANION DIAGNOSTICS

The diagnostic test component of pharmacogenomic products may be subject to regulation by either federal or provincial authorities depending on the manner in which the test is marketed. Specifically, pharmacogenomic tests may be marketed as an *in vitro* diagnostic device or as a laboratory-developed test (LDT). *In vitro* diagnostic devices, similar to pharmaceutical products, fall within the purview of the federal government since consumer protection was originally a matter of criminal law under section 91(27) of the *Constitution Act, 1867*. Conversely, LDTs are considered a type of service offered by laboratories and fall under provincial jurisdiction over civil and property rights under section 92(13) of the *Constitution Act, 1867*, which includes services offered within a province.<sup>22</sup>

### A. Federal regulation of medical devices

The regulation of *in vitro* diagnostic devices is overseen by the Medical Devices Bureau within the Therapeutic Products Directorate at Health Canada. *In vitro* diagnostic devices are defined as medical devices that are intended to be used *in vitro* – that is, in a laboratory vessel or other controlled experimental environment, rather than within a living organism – for the examination of specimens taken from the body.<sup>23</sup> The *Medical Devices*

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<sup>22</sup> *Constitution Act, 1867* (UK), 30 & 31 Vict, c 3, ss 91(27), 92(13), 92(16), reprinted in RSC 1985, App II, No 5 [*Constitution Act, 1867*]. In order for a law or regulation to be valid, that law or regulation must fall under one of the categories of legislative powers belonging to the appropriate level of government.

<sup>23</sup> Health Canada, *Guidance on Supporting Evidence to Be Provided for New and Amended Licence Applications for Class III and Class IV Medical Devices, Not Including In Vitro Diagnostic Devices (IVDDs)*, Guidance Document (5 July 2012), online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/md-im/applic-demande/guide-ld/md\\_gd\\_data\\_im\\_ld\\_donnees\\_ciii\\_civ-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/md-im/applic-demande/guide-ld/md_gd_data_im_ld_donnees_ciii_civ-eng.pdf)>.

*Regulations*<sup>24</sup> under the *Food and Drugs Act* set out a series of measures to assess the safety and effectiveness of medical devices prior to their commercialization.<sup>25</sup>

The regulation of diagnostic devices is based on the principle of risk management: devices that pose greater risk are subject to a higher level of scrutiny.<sup>26</sup> Medical devices are classified from Class I to Class IV based on the probability and magnitude of risk presented to patients through their use, or in the case of diagnostic devices, based on the implications of medical decisions made based on their results. Class III and IV devices present a greater potential for risk, and must undergo in-depth regulatory review before receiving a licence.<sup>27</sup> An *in vitro* diagnostic device which “is intended to be used for genetic testing”<sup>28</sup> is classified as a Class III device, which presents moderate public health risk or high individual risk.<sup>29</sup> The safety and effectiveness of a diagnostic test is impacted by its sensitivity, specificity, and predictive value.<sup>30</sup> In the pharmacogenomic context, false positive

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<sup>24</sup> SOR/98-282.

<sup>25</sup> Élodie Petit, Anne Marie Tassé & Béatrice Godard, “An Empirical Analysis of the Legal Frameworks Governing Genetic Services Labs in Canadian Provinces” (2008) 16:3 Health L Rev 65 at 66.

<sup>26</sup> Hogarth et al, *supra* note 7 at 32.

<sup>27</sup> Class I devices, which present the lowest potential risk, do not require a licence. Class II devices require a declaration by the manufacturer of the safety and effectiveness of the device. See Canadian Agency for Drugs and Technologies in Health, “Medical Device Regulation in Canada: A Primer”, online: CADTH <[www.cadth.ca/products/environmental-scanning/health-technology-update/health-technology-update-issue5/medical-device](http://www.cadth.ca/products/environmental-scanning/health-technology-update/health-technology-update-issue5/medical-device)>.

<sup>28</sup> *Medical Devices Regulations*, *supra* note 24, Schedule 1 (Classification Rules for Medical Devices), Part 2 (*In Vitro* Diagnostic Devices), Rule 4(b).

<sup>29</sup> Patrice Sarrazin, “Regulatory Oversight of Genetic Testing in Canada” (Presentation delivered at 3rd Annual CMOD Canadian Biomarkers and Surrogate Endpoints Meeting, Ottawa, 24-25 May 2011).

<sup>30</sup> Sensitivity refers to the ability of the test to correctly identify those patients with the condition, whereas specificity refers to the ability of the test to correctly identify those patients without the condition. In turn, the positive or negative predictive value is a measure of the value of the test in detecting the condition in actual clinical practice and is dependent on the prevalence of the disease in the population under consideration. See Abdul Ghaaliq Lalkhen & Anthony McCluskey, “Clinical Tests: Sensitivity and Specificity” (2008) 8:6 Continuing

or false negative results can lead to significant harm, since test results can directly influence treatment decisions and dosing levels.<sup>31</sup>

For a Class III medical device to receive a licence, the manufacturer of the genetic test must provide a summary of all studies regarding the safety and efficacy of the test and of investigational testing conducted on the device using human subjects who are representative of the intended users.<sup>32</sup> The Medical Devices Bureau conducts a review of the scientific and medical literature relied upon by the manufacturer of the medical device. Class III devices must also meet the relevant International Organization for Standardization (ISO)<sup>33</sup> design and manufacturing standards.<sup>34</sup> Once the safety and efficacy of the medical device are established, a Class III licence will be granted.

### ***B. Provincial regulation of laboratory testing***

Standards of practice for laboratories in Canada are derived from a mixture of regulations enacted by provincial governments and accreditation standards set down by independent and professional organizations. None of the ten provinces in Canada have enacted any specific laws regulating labs offering genetic test services; there is no clear distinction drawn between genetic tests and other biological tests, and therefore genetic tests, including pharmacogenomic tests, fall under general provisions that regulate laboratories in each province.<sup>35</sup> Hogarth and colleagues note that “[g]enetic testing is characterised by a high degree of dependence on tests developed in-house by laboratories.”<sup>36</sup>

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<sup>31</sup> Hogarth et al, *supra* note 7 at 35.

<sup>32</sup> Petit, Tassé & Godard, *supra* note 25 at 66.

<sup>33</sup> The International Organization for Standardization (ISO) is the world’s largest developer of voluntary international standards covering all aspects of technology and business. See “About ISO”, online: ISO <[www.iso.org/iso/home/about.htm](http://www.iso.org/iso/home/about.htm)>.

<sup>34</sup> Canadian Agency for Drugs and Technologies in Health, *supra* note 27.

<sup>35</sup> Petit, Tassé & Godard, *supra* note 25 at 66.

<sup>36</sup> Hogarth et al, *supra* note 7 at 39.

While some provinces have enacted specific legislation to regulate medical labs,<sup>37</sup> other provinces regulate labs through the coverage of diagnostic tests under provincial health insurance plans.<sup>38</sup> In general, laboratories in different provinces are regulated through a combination of measures that may include government-issued licences, peer-delivered accreditation, and internal and external quality control. In provinces that have specific legislation governing medical labs, an operating licence must be obtained from the government before a lab may begin to operate. While each province issues different categories of licences, only two provinces, Ontario and Saskatchewan, require that labs hold a specific category of licence to conduct genetic tests.<sup>39</sup> However, most provinces issue an operating licence with a list of tests that the lab is authorized to perform.<sup>40</sup>

The most widely used mechanism in the regulation of labs is accreditation, which is “the official recognition, by a governing body, of a competent laboratory.”<sup>41</sup> Accreditation may be required under provincial medical laws or as a condition for the issuance of an operating licence. Accreditation generally involves an external assessment of every aspect of a lab’s operations and practices by independent professionals. Out of the ten provinces, five (Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan) have their own respective provincial accreditation bodies.<sup>42</sup> In Ontario, for example, the Ministry of Health and Long-Term Care has mandated

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<sup>37</sup> This is the approach taken in Québec, Ontario, and Saskatchewan. Furthermore, Newfoundland regulates labs through regulations made under its *Health and Community Services Act*, SNL 1995, c P-37.1. See Petit, Tassé & Godard, *supra* note 25 at 66.

<sup>38</sup> This is the approach taken in Manitoba and British Columbia. See Petit, Tassé & Godard, *ibid.*

<sup>39</sup> Ontario has a “cytogenetic” licence category under its lab regulations: see *Laboratories*, RRO 1990, Reg 682, s 2. Saskatchewan requires labs to hold a Category 6 licence (which permits the widest variety of medical tests) before providing “cytogenetic” testing: see *Medical Laboratory Licensing Regulations*, RRS 1995, c M-9.2 Reg 1, s 5(f); Petit, Tassé & Godard, *supra* note 25 at 67.

<sup>40</sup> *Ibid.*

<sup>41</sup> *Ibid.*

<sup>42</sup> Hui Li & Khosrow Adeli, “Laboratory Quality Regulations and Accreditation Standards in Canada” (2009) 42:4 Clin Biochem 249 at 251.

that the Ontario Medical Association be responsible for accreditation and quality assessment of medical laboratories in that province.<sup>43</sup> In the other five provinces (Québec, Nova Scotia, New Brunswick, Prince Edward Island, and Newfoundland), medical laboratories are accredited jointly by Accreditation Canada (formerly the Canadian Council on Health Service Accreditation).<sup>44</sup> Certain accreditation bodies have created specific categories for laboratories wishing to perform genetic tests, and these laboratories must meet requirements specific to such a categorization. For example, both Ontario and British Columbia have specific divisions that conduct accreditations for genetic testing.<sup>45</sup>

In addition to accreditation, quality assurance programs are mandated by law in all provinces to guarantee that data produced by the labs are of the highest quality. Labs are required to both establish internal quality control measures and undertake external quality control through an independent and impartial external review.<sup>46</sup> External quality control programs typically assess the precision and accuracy of test results and the quality of the lab's analyses, as well as promote the standardization of lab practices. While Ontario has an external quality control program dealing specifically with cytogenetics and molecular diagnostics of inherited diseases, most provinces generally require labs to participate in specialized external quality control programs such as the one offered by the College of American Pathologists.<sup>47</sup>

### ***C. Coordinating pharmacogenomic therapies with split jurisdiction***

Currently, there is limited coordination between authorities regarding the approval and regulation of *in vitro* diagnostic tests at the federal level and LDTs at the provincial level. Such fractured jurisdiction over pharmacogenomic products creates the potential for different standards and practices and, consequently, differential access or coverage between provinces. Further, since the companion diagnostic plays an important role in ensuring

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<sup>43</sup> *Ibid* at 253.

<sup>44</sup> *Ibid* at 251. See also Accreditation Canada, "About Us", online: AC <[www.internationalaccreditation.ca/aboutus/history.aspx](http://www.internationalaccreditation.ca/aboutus/history.aspx)>.

<sup>45</sup> Petit, Tassé & Godard, *supra* note 25 at 67.

<sup>46</sup> *Ibid*.

<sup>47</sup> *Ibid*.

the safe and effective use of the drug component, access to the drug may hinge on the availability of the diagnostic test.

As summarized by Petit, Tassé, and Godard,

many procedures and aims are shared among the provinces regarding the use of standard operating procedures, external performance evaluations and staff qualifications which collectively allow an assessment of the quality of the work performed by the labs, as well as the reliability of the scientific tests they offer.<sup>48</sup>

Nonetheless, they note that there is a lack of harmonization between the provinces with respect to the thresholds for reference standards in these aims and procedures.<sup>49</sup> The importance of quality control measures in laboratory testing and the concern about very divergent standards and practices across the country were highlighted by the Commission of Inquiry on Hormone Receptor Testing (the “Cameron Inquiry”) in Newfoundland and Labrador. The Cameron Inquiry investigated whether the Eastern Health Authority had been at fault for erroneous reporting and delayed test results for breast cancer patients from 1997 to 2005.<sup>50</sup> The inquiry report issued in 2009 concluded that Eastern Health had failed hundreds of breast cancer patients through substandard laboratory practices and “practically non-existent” quality controls.<sup>51</sup> The report highlighted not only the importance of effective regulatory oversight, but also the potentially devastating consequences for patients when shoddy laboratory practices prevent the accurate diagnosis of serious and life-threatening diseases. The Cameron Inquiry issued a series of 60 recommendations, including the implementation of proficiency testing in laboratories, improved data collection and adverse-

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<sup>48</sup> *Ibid* at 69.

<sup>49</sup> *Ibid*.

<sup>50</sup> Newfoundland and Labrador, Health and Community Services, News Release, “Government to Undertake Judicial Commission of Inquiry on Estrogen and Progesterone Receptor Testing for Breast Cancer Patients” (22 May 2007), online: Government of Newfoundland and Labrador <[www.releases.gov.nl.ca/releases/2007/health/0522n05.htm](http://www.releases.gov.nl.ca/releases/2007/health/0522n05.htm)>.

<sup>51</sup> “Lab mistakes, poor oversight flagged in N.L. breast cancer inquiry”, *CBC News* (3 March 2009), online: CBC <[www.cbc.ca/news/canada/newfoundland-labrador/lab-mistakes-poor-oversight-flagged-in-n-l-breast-cancer-inquiry-1.793504](http://www.cbc.ca/news/canada/newfoundland-labrador/lab-mistakes-poor-oversight-flagged-in-n-l-breast-cancer-inquiry-1.793504)>.

incident reporting, the creation of standard operating policies and procedures for laboratories, and efforts towards a system of national accreditation.<sup>52</sup>

Another concern is that there is no harmonization between the standards applied by the Medical Devices Bureau of Health Canada in licensing an *in vitro* diagnostic device and those applied by provincial accreditation agencies in evaluating the competency of laboratories performing genetic testing services – other than the fact that both federal and provincial authorities rely to varying degrees on ISO standards. In general, “[w]hile genetic tests are directly targeted by federal regulations, provincial mechanisms aim to ensure the reliability and proper functioning of the labs, rather than the tests *per se*.”<sup>53</sup> Further, while the accreditation bodies in all provinces aim to implement similar elements in their assessment of laboratories and all use the ISO documents to develop their own standards, each accreditation body still establishes its own reference standards.<sup>54</sup> Overall, there clearly is a need for some level of regulatory scrutiny in considering where and how tests are conducted, the level of consistency across testing sites and methods, and whether international guidelines on good clinical and laboratory best practice are followed.<sup>55</sup>

### **1. Variation in the regulatory standards for lab tests versus diagnostic devices**

A related source of concern about the split regulation of diagnostic testing is the potential for discrepancy in the quality standards required in the

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<sup>52</sup> Newfoundland and Labrador, *Commission of Inquiry on Hormone Receptor Testing, Investigation and Findings*, vol 1 (St. John’s: Office of the Queen’s Printer, 2009) at 449-76, online: Government of Newfoundland and Labrador <[www.releases.gov.nl.ca/releases/2009/health/Volume1\\_Investigation\\_and\\_Findings.pdf](http://www.releases.gov.nl.ca/releases/2009/health/Volume1_Investigation_and_Findings.pdf)> [*Cameron Inquiry Report*].

<sup>53</sup> Petit, Tassé & Godard, *supra* note 25 at 69.

<sup>54</sup> Specifically, the accreditation standards in each province are inspired by the ISO 15189 standard and its Canadian version CAN/CSA Z15189-03. See Li & Adeli, *supra* note 42 at 254.

<sup>55</sup> During qualitative interviews, several stakeholders expressed concern about the current lack of coordination in diagnostic testing standards in Canada and how this might impact on access to both the drug and test components of pharmacogenomic products. These same stakeholders highlighted the need for more consistency across the provinces and with Health Canada regarding diagnostic

regulation of LDTs versus those for *in vitro* diagnostic devices (sometimes referred to as kit-based tests). From a regulatory standpoint, if a test is used as a screening tool, its characteristics require scrutiny, including consideration of analytical validity<sup>56</sup> and clinical validity.<sup>57</sup> A particular source of concern is that while kit-based tests are assessed for both analytical and clinical validity, “the regulation of laboratory tests is focused on quality assurance of laboratory procedures and the analytical accuracy of laboratory testing; clinical validation of [laboratory] tests is rarely mandatory.”<sup>58</sup> A similar situation currently exists in the US, where there is even evidence that companies sometimes opt to offer their diagnostic tests through a clinical laboratory in order to get around the more rigorous FDA regulations for *in vitro* diagnostic devices, which include standards of clinical validity.<sup>59</sup> However, it is also worth noting that provincial authorities may engage in an assessment of the clinical validity of diagnostic tests as part of their health technology assessment activities – discussed in more detail below – to determine which health technologies will be funded through the provincial health care system.

Historically in the US, as in Canada, laboratory tests and diagnostic test kits have been subject to different regulatory standards and regimes. Nonetheless, the FDA has a broader mandate in the regulation of medical devices than Health Canada – a mandate which includes oversight over certain aspects of LDTs.<sup>60</sup> In particular, the FDA’s Center for Devices and Radiologic-

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testing standards, as well as more coordination regarding how testing standards impact the assessment of the safety and efficacy of the drug component.

<sup>56</sup> Analytical validity is a “measure of the test’s ability to accurately and reliably detect the genotype of interest” and considers questions related to sensitivity, specificity, and quality control: Mary K Pendergast, “Regulatory Agency Consideration of Pharmacogenomics” (2008) 233:12 *Exp Biol Med* 1498 at 1499.

<sup>57</sup> Clinical validity “relates to whether there is a connection between the measured genotype and a disorder or phenotype of interest.” Relevant questions include sensitivity and specificity, test validation in other populations, and the positive and negative predictive values of the test (*ibid* at 1499).

<sup>58</sup> Hogarth et al, *supra* note 7 at 39.

<sup>59</sup> *Ibid*.

<sup>60</sup> In 1976, the *Medical Device Amendments*, Pub L No 94-295, 90 Stat 539, under the *Food, Drugs and Cosmetics Act* gave the FDA the authority to regulate medical devices intended for use in humans. Under the legislation, the definition of medical devices “applies equally to [*in vitro* diagnostic devices] manu-

al Health has jurisdiction over both kit-based tests and “products used in clinical laboratories and clinical laboratory testing systems, procedures, and reporting.”<sup>61</sup> However, since 1976 when the *Medical Device Amendments* were enacted,<sup>62</sup> the FDA has generally exercised discretion in respect of enforcement of standards for LDTs, leaving most of the regulation of LDTs to the Centers for Medicare and Medicaid Services (CMS), which since 1988 have regulated laboratories under the *Clinical Laboratory Improvement Amendments (CLIA)*.<sup>63</sup> *CLIA* establishes quality standards to ensure the accuracy, reliability, and timeliness of laboratory test results irrespective of where the test is performed.<sup>64</sup> Although the FDA and CMS currently share jurisdiction over diagnostic testing, both regimes are nonetheless organized at the federal level – a somewhat less complicated situation than having lab-based tests devolved to the provincial or state level.

In July 2014, the FDA announced its intention to regulate LDTs as medical devices and released a draft guidance entitled *Framework for Regulatory Oversight of Laboratory-Developed Tests*.<sup>65</sup> This “draft Framework Guidance proposes a risk-based, phased-in framework for oversight of LDTs in a manner that is consistent with FDA’s current regulation of *in*

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factured by conventional device manufacturers and those manufactured by laboratories.” See US, Food and Drug Administration, *Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* (31 July 2014) at 4, online: FDA <[www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf](http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf)> [FDA, *Draft LDT Guidance*].

<sup>61</sup> Pendergast, *supra* note 56 at 1500.

<sup>62</sup> See *supra* note 60.

<sup>63</sup> *Clinical Laboratory Improvement Amendments (CLIA) of 1988*, 42 USC § 263a. In particular, any facility that provides “laboratory testing on specimens derived from humans to give information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health” is subject to *CLIA*: US, Food and Drug Administration, “Clinical Laboratory Improvement Amendments”, online: FDA <[www.fda.gov/medicaldevices/deviceregulation-andguidance/ivdregulatoryassistance/ucm124105.htm](http://www.fda.gov/medicaldevices/deviceregulation-andguidance/ivdregulatoryassistance/ucm124105.htm)>.

<sup>64</sup> US, Centers for Disease Control and Prevention, “CLIA Law and Regulations”, online: CDC <[wwwn.cdc.gov/clia/regulatory/default.aspx](http://wwwn.cdc.gov/clia/regulatory/default.aspx)>.

<sup>65</sup> FDA, *Draft LDT Guidance*, *supra* note 60.

*vitro* diagnostic devices.”<sup>66</sup> In the document, the FDA notes that as a result of evolving technology and business models, LDTs have become increasingly complex and now present potentially greater risks than in the past.<sup>67</sup> They further note a number of gaps in the regulation of LDTs, including the absence of assessment of manufacturing standards, and the lack of requirements for adverse event reporting and for removing unsafe devices from the market.<sup>68</sup> However, one of the FDA’s most serious concerns is that although *CLIA* requires periodic assessment of the analytical validity of LDTs, there is no corresponding assessment of clinical validity which is a critical component in determining the safety and effectiveness of the test.<sup>69</sup> As “personalized medicine,” including pharmacogenomics, becomes more mainstream, the use of diagnostic testing to measure individual patient variables will become increasingly important in informing treatment decisions. Indeed, in the draft guidance, the FDA notes that one of the aspects of modern LDTs that heightens their potential risk is that their results may be used to “direct critical treatment decisions,” and it explicitly lists “prediction of drug response” as an example of such a decision.<sup>70</sup>

Having historically been granted a broad mandate to regulate diagnostic testing, the FDA is well positioned to take on a stronger oversight role for LDTs. Unfortunately, Health Canada has never been granted a similar mandate over laboratory testing, and more importantly, provincial jurisdiction over health care services under the constitutional division of powers would likely make it difficult for the federal government to attempt to regulate laboratory testing. Although the question of jurisdiction over laboratory testing has not been directly addressed by the Canadian courts, similar jurisdictional issues were discussed at length by the Supreme Court of Can-

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<sup>66</sup> Letter from Sally Howard, Deputy Commissioner, Policy, Planning and Legislation, Food and Drug Administration, to Tom Harkin, Chairman, Committee on Health, Education, Labor and Pensions, US Senate (31 July 2014), as appended to FDA, *Draft LDT Guidance*, *supra* note 60.

<sup>67</sup> In particular, the FDA notes that LDTs are “manufactured with components that are not legally marketed for clinical use[,] offered beyond local populations and manufactured in high volume[,] used widely to screen for common diseases rather than rare diseases[,] used to direct critical treatment decisions ... [, and] highly complex”: FDA, *Draft LDT Guidance*, *supra* note 60 at 7.

<sup>68</sup> *Ibid.*

<sup>69</sup> *Ibid* at 7-8.

<sup>70</sup> *Ibid* at 7.

ada in 2010 in the *Reference re Assisted Human Reproduction Act*.<sup>71</sup> In this reference, the Québec government challenged large portions of the federal *Assisted Human Reproduction Act* as violating the constitutional division of powers, including several provisions that established a system whereby certain “controlled activities” involving assistance for human reproduction and related research activities could only be performed in permitted premises by qualified individuals who had received a licence from the federal government.<sup>72</sup> In an unusual 4–4–1 split decision, the Court struck down several provisions in the *Act* that established the licensing system over “controlled activities.” However, whether such a system was unconstitutional was hotly debated and split the court down the middle. In the dissenting decision written by Chief Justice McLachlin, four justices held that although the licensing of controlled activities impacted the regulation of medical research and practice, the impact was incidental to the legislation’s dominant criminal purpose.<sup>73</sup> Conversely, in the majority opinion written by Justice LeBel, four judges ruled that the provisions of the *Act* concerning controlled activities did not fall under the federal criminal law power, but rather belonged to the jurisdiction of the provinces over hospitals, property and civil rights, and matters of a merely local nature.<sup>74</sup> In the tie-breaking decision, Justice Cromwell concurred with the majority and struck down most of the provisions establishing the licensing system on the ground that they were unconstitutional, but was sparse with his reasons. The majority and concurring decisions suggest that any attempt by the federal government to establish similar licensing systems, for example around laboratory testing, may be found to interfere with provincial jurisdiction.<sup>75</sup>

Unifying the regulation of LDTs and *in vitro* diagnostic devices could help to establish consistent and high-quality standards for diagnostic testing, regardless of how the test is performed. In the US, centralizing authority over diagnostic testing in the FDA may be particularly useful for pharmacogenomic products since the FDA also has authority over the drug component. Indeed, well before the FDA released its draft guidance, Pen-

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<sup>71</sup> 2010 SCC 61, [2010] 3 SCR 457, 327 DLR (4th) 257 [*AHRA Reference*].

<sup>72</sup> *Assisted Human Reproduction Act*, SC 2004, c 2, s 13.

<sup>73</sup> *AHRA Reference*, *supra* note 71 at para 26.

<sup>74</sup> *Ibid* at para 227.

<sup>75</sup> For a good discussion of the constitutional implications of the decision, see Ian B Lee, “The *Assisted Human Reproduction Act Reference* and the Federal Criminal Power” (2011) 90:2 Can Bar Rev 471.

dergast predicted that “[i]t is almost inevitable that the FDA will regulate most of the laboratory-based activities used in pharmacogenomic testing.”<sup>76</sup> Unfortunately, Health Canada is not in the same position as the FDA; given the constitutional division of powers in Canada, there is no simple road forward for Health Canada to assert greater regulatory control over LDTs. Therefore, as discussed in the next section, improving the consistency of regulatory standards for diagnostic testing between the provinces and the federal government will likely depend heavily on harmonization efforts between regulatory authorities across jurisdictions.

## 2. Improving consistency across jurisdictions

One potential means to increase the consistency of laboratory testing standards across the country would be to implement a nationalized laboratory accreditation system. In 2009, the Cameron Inquiry concluded that a national program of accreditation would “raise the standard of practice across the country” and “therefore, is the optimum method of accreditation.”<sup>77</sup> The report recommended that the Government of Newfoundland and Labrador “utilize best efforts to work with other provinces towards establishing a national accreditation program.”<sup>78</sup> Such harmonization of accreditation already appears to be taking root. For example, the Standards Council of Canada – a federal Crown corporation with the mandate of promoting efficient and effective standardization in Canada – has a partnership with the Bureau de normalisation du Québec and the Ontario Medical Association to offer a national accreditation program for medical laboratories operating in Canada.<sup>79</sup> Further, in December 2012, Accreditation Canada and the Standards Council of Canada signed a memorandum of understanding “to collaborate on best practices to renew confidence and enhance credibility in medical

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<sup>76</sup> Pendergast, *supra* note 56 at 1500.

<sup>77</sup> *Cameron Inquiry Report*, *supra* note 52 at 460.

<sup>78</sup> *Ibid.*

<sup>79</sup> Under this program, “laboratories are assessed ... without having to undergo separate assessments by each organization”: Standards Council of Canada, “Medical Laboratory Accreditation”, online: SCC <[www.scc.ca/en/accreditation/laboratories/medical](http://www.scc.ca/en/accreditation/laboratories/medical)>.

testing in Canada” and together to offer accreditation in ISO 15189,<sup>80</sup> the current international standard for quality and competence of medical laboratories.

Petit, Tassé, and Godard argue that due to the importance of the information that genetic tests can reveal, there is a need to establish a formal assessment mechanism at the interprovincial level specifically for genetic tests.<sup>81</sup> One suggestion to encourage harmonization between the standards applied by the provinces in regulating laboratories is to establish an interprovincial agency which would oversee a formal assessment mechanism of genetic tests prior to their first use in clinical laboratories and would ensure harmonization of standards between the provinces.<sup>82</sup> In essence, this agency could play a similar role to that of the Medical Devices Bureau of Health Canada, but instead of regulating *in vitro* diagnostic devices, it would have “licensing” power over new genetic tests that are to be offered in laboratories. Further, an interprovincial agency could coordinate with the Medical Devices Bureau to ensure that similar standards are being applied in the regulation of *in vitro* diagnostic devices at the federal level and laboratory services at the provincial level. Such an agency could also interface with the Therapeutic Products Directorate to ensure that pharmacogenomic products as a whole are properly regulated. Formal assessments connected to a licensing system could be more demanding than those imposed through accreditation. Yet not everyone agrees that genetic testing should be subject to a separate or specialized regulatory regime. In the US, for example, the Centers for Medicare and Medicaid Services have rejected calls to implement “more extensive regulation of genetic testing, essentially rejecting ‘genetic exceptionalism’ as a reason for increasing requirements for genetic tests.”<sup>83</sup>

In 2008, it was reported that the Canadian Coalition for Quality in Laboratory Medicine (CCQLM) had recently been incorporated to serve as an

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<sup>80</sup> Accreditation Canada, Press Release, “SCC and Accreditation Canada Join Forces to Offer Health Care and Medical Laboratory Communities Accreditation to ISO15189” (13 March 2013), online: AC <[www.accreditation.ca/scc-and-accreditation-canada-join-forces-offer-health-care-and-medical-laboratory-communities](http://www.accreditation.ca/scc-and-accreditation-canada-join-forces-offer-health-care-and-medical-laboratory-communities)>.

<sup>81</sup> Petit, Tassé & Godard, *supra* note 25 at 69.

<sup>82</sup> Ingebord Blancquaert et al, “L’encadrement du transfert technologique en génétique moléculaire : un défi à relever” (2001) 2:3 *Isuma Can J Policy Research* 95.

<sup>83</sup> Pendergast, *supra* note 56 at 1500.

educational and coordinating body to provide a national structure for quality management in medical laboratories across Canada. Specifically, the CCQLM was intended to:

promote development and implementation of national and international standards ..., develop models of external quality assessment and accreditation programs, pursue issues of common concern and interest, promote the sharing of educational initiatives ..., and promote communication and collaboration among the member organizations and with other national/international agencies.<sup>84</sup>

The group aimed to link existing provincial accreditation programs and provide a national forum for the review of emerging issues.<sup>85</sup> The CCQLM would have been a positive step forward in coordinating laboratory standards across Canada, but to our knowledge there has been no further discussion of this initiative since then.<sup>86</sup>

Overall, as the number of drugs that are paired with companion diagnostics continues to increase, there is a concurrent need for a national process in Canada that coordinates reviews and achieves a level of uniformity in test review.<sup>87</sup> Despite the rather fractured nature of regulatory oversight for diagnostic tests, there are nonetheless opportunities for both levels of

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<sup>84</sup> Li & Adeli, *supra* note 42 at 252.

<sup>85</sup> Fred B Swaine et al, "Medical labs must meet standards", Letter to the Editor, *Edmonton Journal* (19 July 2008), online: Canada.com <[www.canada.com/story\\_print.html?id=7a4ba51e-985e-41e9-b318-a890567e912b](http://www.canada.com/story_print.html?id=7a4ba51e-985e-41e9-b318-a890567e912b)>.

<sup>86</sup> One potential difficulty that may have been encountered by the CCQLM is that they were a voluntary group without the funding or mandate to undertake extensive oversight. See Swaine et al, *ibid*.

<sup>87</sup> During stakeholder interviews for the qualitative study, several participants highlighted the need for a more national process in the regulation of diagnostic testing. One stakeholder suggested that Health Canada could potentially play a leadership role in designing a standard model for test approval (which could then be adapted based on input from the provinces) and in pushing the agenda for provinces to work together to put the standards into practice. Another stakeholder highlighted the importance of the provinces taking an active role in an agreement towards a more nationalized process, and highlighted the success of the Common Drug Review under the Canadian Associations for Drugs and Technology in Health as a flagship example of cooperation between the provinces. See discussion in Part IV.B, below.

government to work together to agree on the standardization and the accreditation of test performance. For example, if an interprovincial body for quality management in medical laboratories such as the proposed CCQLM were established, it could also serve as the focal point for coordinating the review of pharmacogenomic testing.

## II. REGULATION OF PHARMACOGENOMIC DRUGS

The regulatory review of the pharmaceutical component of a pharmacogenomic product falls entirely within the jurisdiction of the federal government – jurisdiction which is primarily grounded in the federal criminal law power under section 91(27) of the *Constitution Act, 1867*. In particular, the federal government has jurisdiction over all matters in respect of intellectual property rights, drug approval, manufacturing, labelling, pricing, post-market safety and effectiveness, and market competitiveness.<sup>88</sup> The Health Products and Food Branch within Health Canada is responsible for regulating clinical trials and granting market authorization for drugs. Within this branch, the Therapeutic Products Directorate regulates pharmaceutical drugs and medical devices for human use under the authority of the *Food and Drugs Act*<sup>89</sup> and associated regulations.<sup>90</sup>

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<sup>88</sup> Trudo Lemmens & Ron A Bouchard, “Regulation of Pharmaceuticals in Canada” in Jocelyn Downie, Timothy Caulfield & Colleen M Flood, eds, *Canadian Health Law and Policy*, 3d ed (Toronto: LexisNexis, 2007) 311 at 319. Although this paper focuses on the regulatory approval of pharmacogenomic therapies, it is worth noting that while the federal government holds the gatekeeping role of authorizing drugs and *in vitro* diagnostic devices for the Canadian market, the provinces and territories have constitutional responsibility for funding health care services. The provincial and territorial governments are thus responsible for funding most diagnostic testing through provincial health care budgets. Further, pharmaceutical costs that are not borne directly by consumers or private insurance plans are primarily covered by the provinces through hospital funding or public drug programs. Each province and territory maintains its own formulary listing the drugs that are covered under the respective public drug program and mandates its own pricing and cost-containment policies.

<sup>89</sup> *Supra* note 19.

<sup>90</sup> Health Canada, “About Health Canada: Therapeutic Products Directorate” (2 February 2014), online: HC <[www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php](http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php)>.

Pharmacogenomics may impact all stages of drug development, from preclinical research all the way through post-market surveillance. Preclinical development is the stage of research that takes place before clinical trials in humans and during which important data on the safety and usefulness of a product is collected. Preclinical studies are not regulated by either level of government; manufacturers do not require government approval to conduct preclinical trials. Rather, the manufacturer is responsible for gathering and submitting “information and documentation to support the objectives and goals of the proposed clinical trial.”<sup>91</sup>

#### A. *Clinical trials*

Based on data from preclinical studies, a sponsor may submit a Clinical Trial Application (CTA) to the Therapeutic Products Directorate to obtain approval to conduct clinical trials in humans.<sup>92</sup> In particular, the sponsor must satisfy a number of requirements related to safety, dosage, and effectiveness of the drug. Under the regulations, clinical trials are divided into four categories from Phase I to IV.<sup>93</sup> Health Canada approves drugs on the basis of data from Phase I–III trials.<sup>94</sup> The term “Phase IV trial” typically refers to various types of studies conducted after a drug has been approved,

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<sup>91</sup> Health Canada, “Drugs and Health Products” (11 July 2006), online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta\\_background-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_background-eng.php)>.

<sup>92</sup> Like all clinical trials, those involving pharmacogenomic testing are governed by Part C, Division 5 of the *Food and Drug Regulations*, which sets out the rules for the sale and importation of drugs for use in human clinical trials in Canada. See *Food and Drug Regulations*, CRC, c 870, s C.05.001 et seq.

<sup>93</sup> Phase I trials, which are usually the first studies to test a new drug in humans, are typically conducted on a small number of healthy volunteers (20 to 80) to explore the general pharmacological and pharmacokinetic properties of a drug (overall safety, acute side effects, drug metabolism, etc.). Phase II trials are slightly larger (100 to 300 participants) and involve patients who suffer from the condition that the drug under study aims to treat in order to evaluate its efficacy and common short-term side effects. Phase III trials are generally randomized double-blind controlled trials involving a large number of patients (1,000 to 5,000) that may be conducted over many years and allow a more precise study of a drug’s efficacy and safety. Lemmens & Bouchard, *supra* note 88 at 321-25.

<sup>94</sup> *Ibid* at 322-23.

such as trials assessing long-term efficacy and safety of the drug or comparing the drug with other drugs from the same class.<sup>95</sup> However, in some cases, Phase IV (i.e. post-market) trials are little more than a disguised marketing effort intended to accustom physicians and patients to a new drug.<sup>96</sup>

As part of the CTA, sponsors are required to submit pharmacogenomic data “that pertain to the pharmacological or pharmacodynamic aspects, pharmacokinetics, and toxicological effects of the drug if the [pharmacogenomic] data is relevant to, or supports the use of the investigational product in the proposed clinical trial,”<sup>97</sup> including information revealed through previous clinical trials in humans. Pharmacogenomic data must also be submitted as part of the CTA where the data is “being used to support the design of the proposed clinical trial or animal study, to justify testing in humans, or to support the proposed indications or labelling of the drug.”<sup>98</sup> Health Canada encourages sponsors to request consultation meetings with the relevant directorates before submitting a CTA that contains pharmacogenomic information or that makes use of a pharmacogenomic test.<sup>99</sup>

The trial sponsor must obtain written informed consent from every person prior to their participation in the clinical trial.<sup>100</sup> For those trials involving the use of pharmacogenomic testing, the informed consent form should, according to the Health Canada guidance document, specify that pharmacogenomic testing will be conducted, as well as indicate “the research aim, the sample and data coding strategy, and the storage, destruction, and security measures used around sample and data preservation.”<sup>101</sup> Health Canada also mandates that sponsors of clinical trials of drugs and medical devices obtain approval from a research ethics board.

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<sup>95</sup> *Ibid.*

<sup>96</sup> See e.g. Carl Elliott, “The deadly corruption of clinical trials”, *Mother Jones* (September/October 2010), online: MJ <[www.motherjones.com/environment/2010/09/dan-markingson-drug-trial-astrazeneca](http://www.motherjones.com/environment/2010/09/dan-markingson-drug-trial-astrazeneca)>.

<sup>97</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 5.

<sup>98</sup> *Ibid* at 6.

<sup>99</sup> *Ibid* at 11.

<sup>100</sup> *Food and Drug Regulations*, *supra* note 92, s C05.010(h).

<sup>101</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 8-9.

There are several different scenarios under which samples for pharmacogenomic testing may be collected, including as part of the main clinical trial or as part of a sub-study that is indirectly related to the main clinical trial. Samples may also be collected for use in biobanks, where they may be used for future research or in exploratory studies. Where pharmacogenomic testing is part of the main clinical trial, informed consent to testing must be a condition for participation in the clinical trial.<sup>102</sup> However, if the clinical trial sponsor intends to collect samples for exploratory pharmacogenomic testing beyond the scope of the main clinical trial (i.e. for a sub-study or for future use), the guidance document suggests that sponsors must obtain separate informed consent for this purpose in order to enable subjects to decline consent to the collection of samples for exploratory research without impacting their participation in the main trial.<sup>103</sup> In light of the growing recognition of the importance of transparency as a key component of reliable drug development (as discussed further below), Health Canada needs to take greater steps towards requiring that all trials, including studies involving pharmacogenomic-focused data collection, be fully registered in appropriate clinical trial registries and that the results be made publicly available.

## 1. Enrichment strategies

The evidence collected during the preclinical phase is critical to informing the design of clinical trials. Generally, clinical trials are not conducted on a random sample of the general population. Rather, researchers employ a variety of selection procedures to single out a subset of the general population in which the effect of the drug is more likely to be demonstrated.<sup>104</sup> This process of participant selection is known as “enrichment”

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<sup>102</sup> *Ibid* at 8.

<sup>103</sup> *Ibid* at 1. Similar provisions are set out in Canada’s *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, which applies to federally funded research involving human participants, including trials for drugs and medical devices. See Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (December 2014) at 65, online: Panel on Research Ethics <[www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS\\_2\\_FINAL\\_Web.pdf](http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf)>.

<sup>104</sup> US, Food and Drug Administration, *Guidance for Industry Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological*

and can be defined as the “prospective use of any patient characteristic – demographic, pathophysiologic, historical, genetic, and others – to select a study population in which detection of a drug effect ... is more likely than it would be in an unselected population.”<sup>105</sup> While enrichment strategies are used in a wide range of drug development scenarios, genetic biomarkers are an important new tool that can be used to refine the study population, thereby increasing drug efficacy and/or reducing adverse reactions.

The primary reason for enrichment is study efficiency: the drug is more likely to show a result when tested on a selected population (as opposed to the general population). Moreover, testing on selected populations can often be accomplished using smaller sample sizes. Study enrichment also offers the advantage of directing treatment towards patients who are most likely to benefit and thus avoiding potential harm to other patients who would likely not benefit.<sup>106</sup> However, while enrichment increases the power of a study to detect a clinical effect in *some* populations, this study design leaves open two important questions: (1) the generalizability of the results (i.e. whether the drug will work in other populations); and (2) what level of data is needed to establish selection criteria – in particular, the quality of the test and the sensitivity and specificity of the various predictive cut-off points.<sup>107</sup> Further, reducing the size of clinical trials raises concerns about the impact of smaller trial size on the quality and certainty of the resulting research data.<sup>108</sup>

There is some debate surrounding what level and quality of preliminary evidence is required to rationalize undertaking an enriched biomarker study.

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*Products Draft Guidance* (December 2012) at 1, online: FDA <[www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf)> [FDA, *Guidance on Enrichment Strategies*].

<sup>105</sup> *Ibid* at 2.

<sup>106</sup> *Ibid* at 3.

<sup>107</sup> Robert Temple, “Enrichment Strategies” (Presentation delivered at the FDA/DIA Statistics Forum, Bethesda, Md, 25 April 2012), online: FDA <[www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-orgs/documents/document/ucm303485.pdf](http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-orgs/documents/document/ucm303485.pdf)>.

<sup>108</sup> The potential negative impact of smaller clinical trials on the robustness of resulting safety and efficacy data (in comparison to larger-scale clinical trials) was another issue that was highlighted by a number of stakeholders. During qualitative interviews, several stakeholders also expressed concern about how enrichment strategies may result in a lack of data on the safety and efficacy of

On the one hand, where the preclinical evidence clearly demonstrates a correlation between a given biomarker and drug efficacy, including marker-negative patients in the trial may be imprudent if they are unlikely to benefit, if they face a significant risk of negative side effects, or if, as a result, they will potentially miss opportunities to receive more appropriate treatment. On the other hand, where the biomarker and the targeted therapy are poorly correlated or where the preclinical data is uncertain, it will be more difficult to justify the exclusion of biomarker-negative patients where they may have some response or may help refine the marker cut-off.<sup>109</sup> The dilemma of biomarker-based drug development can be situated between two poles: casting the drug development net too narrowly may deprive researchers of valuable information about the potential side-effects or efficacy in other patients, and thus hinder the rational use of new drugs for a significant segment of patients who could potentially benefit; conversely, casting the net too widely may expose patients who are unlikely to benefit to harm in the context of clinical trials, and may also produce misleadingly negative data regarding new products that may in fact work well in a more narrowly defined population.

Before a sponsor can use a pharmacogenomic test for diagnostic purposes or patient management in a clinical trial, the test must either be licensed for sale in Canada or authorized for investigational testing.<sup>110</sup> Health Canada emphasizes that the analytical validity of a pharmacogenomic test must be established “if the test is used to determine subject eligibility, select the dose, assess safety or efficacy of a drug, or otherwise used to manage the health and safety of subjects enrolled in a clinical trial.”<sup>111</sup> In general, the performance characteristics of the test should be validated for every study

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a drug in broader patient populations. See Gibson, Raziee & Lemmens, *supra* note 21.

<sup>109</sup> Temple, *supra* note 107.

<sup>110</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 1. Health Canada classifies all devices intended to be used for genetic testing as Class III medical devices and requires a pre-market scientific assessment of their safety and effectiveness by the Medical Devices Bureau. See *Medical Devices Regulations*, *supra* note 24, ss 32(3)(f), (h)-(i). See also Health Canada, “Guidance for the Risk Based Classification System of *In Vitro* Diagnostic Devices” (17 March 1998) at 13, online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/md-im/ivd-rsk\\_idiv-rsq-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/ivd-rsk_idiv-rsq-eng.pdf)>.

<sup>111</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 7.

based on pharmacogenomic data. However, there is uncertainty around how rigorously regulators consider standards of validation.<sup>112</sup>

In December 2012, the FDA issued a draft guidance document to provide direction to industry on enrichment strategies that can be used in clinical trials and are intended to support effectiveness and safety claims for the approval of new drugs. The guidance describes important enrichment strategies, discusses the advantages and disadvantages of different study design options, and addresses issues related to interpreting the results of enrichment studies.<sup>113</sup> While the FDA notes that the use of enrichment design is largely left to the sponsor of the investigation, regulators have a stake in ensuring the adequacy of the study (“Will it successfully assess effectiveness in a defined population and, in so doing, support marketing approval?”)<sup>114</sup> and the extent to which study findings can be described in drug labelling. Overall, the FDA supports the use of enrichment strategies, but notes that the “extent of data that should be available on the non-enriched subgroup should always be considered”<sup>115</sup> and that “[p]ostmarket commitments or requirements may be requested to better define the full extent of a drug’s effect (including efficacy and safety studies and trials in a broader population).”<sup>116</sup>

To date, Health Canada has not released any specific guidance on the use of enrichment strategies in clinical trials. While enrichment designs are still an emerging strategy, as highlighted in the FDA guidance document, regulators clearly have an interest in ensuring that enriched clinical trials are properly designed. Poorly designed enrichment strategies may limit the quality, and therefore reliability, of the resulting data and inadvertently include non-responders and exclude potential responders. Moreover, even if drugs are approved on the basis of data obtained from a clinical trial focused on a narrow, enriched population in clinical trials, this does not prevent the drug from being prescribed off-label – that is, for conditions or patient populations that were never approved by regulatory authorities – once the drug hits the market. With the expansion of pharmacogenomic drug development and the increasing use of enrichment strategies based on genetic biomarkers,

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<sup>112</sup> Again, during interviews, several stakeholder raised concerns about the uncertainty around how rigorously Health Canada assesses standards of validation.

<sup>113</sup> FDA, *Guidance on Enrichment Strategies*, *supra* note 104.

<sup>114</sup> *Ibid* at 31.

<sup>115</sup> *Ibid* at 32.

<sup>116</sup> *Ibid*.

regulators need to be proactive in addressing the impact of these trends on clinical trial design. While clinical trial sponsors may request a consultation with Health Canada before submitting a proposal to conduct a clinical trial (discussed in more detail below), it is currently unclear what position the agency takes with respect to enrichment strategies. Health Canada should actively engage with industry on this issue and follow the lead of its American counterparts in issuing more detailed guidance to industry on the use of enrichment strategies. Otherwise, enrichment strategies could be used to speed a drug through a shorter and faster clinical trial process, without ensuring that basic safety and efficacy data are gathered.

### **B. Regulatory submissions**

Where data from the requisite Phase I–III clinical trials demonstrate that the potential therapeutic value of a new drug outweighs its risks (adverse events, toxicity), the manufacturer or sponsor may submit a New Drug Submission (NDS) to the Therapeutic Products Directorate to obtain market authorization.<sup>117</sup> The NDS must contain a summary of the data demonstrating the safety, efficacy, and quality of the drug product, including “results of the preclinical and clinical studies, whether done in Canada or elsewhere, details regarding the production of the drug, packaging and labelling details, and information regarding therapeutic claims and side effects.”<sup>118</sup> In addition, where an innovative drug product has already been approved for the Canadian market, a generic sponsor may submit an Abbreviated New Drug Submission (ANDS)<sup>119</sup> – a submission that allows a generic drug to be approved on the basis of being “equivalent” to a brand-name reference product (Canadian Reference Product, or CRP), rather than on the basis of preclinical and clinical trial data.<sup>120</sup> Finally, where a sponsor (usually a

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<sup>117</sup> Lemmens & Bouchard, *supra* note 88 at 325.

<sup>118</sup> Health Canada, “How Drugs Are Reviewed in Canada” (12 February 2015), online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/reviewfs\\_examend-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/reviewfs_examend-eng.php)> [Health Canada, “How Drugs Are Reviewed”]. The NDS must be submitted in compliance with the *Food and Drug Regulations*, *supra* note 92, ss C.08.002, C.08.003, C.08.005.1.

<sup>119</sup> The ANDS must be submitted in accordance with the requirements set out in the *Food and Drug Regulations*, *ibid*, s C.08.002.1.

<sup>120</sup> In particular, the focus of the ANDS is on establishing that the generic version is the pharmaceutical equivalent and “bioequivalent” to the CRP, and has the

brand-name manufacturer) wants to make changes to a drug that has already been approved for the Canadian market, it may submit a Supplemental New Drug Submission (SNDS).<sup>121</sup> In general, an SNDS is made for changes to the dosage form, strength, formulation, method of manufacture, labeling, or recommended route of administration of the drug, or to expand the claims or conditions of use (indications). A generic sponsor may similarly file a Supplemental Abbreviated New Drugs Submission (SANDS) to make changes to a generic product.<sup>122</sup>

According to the Health Canada guidance document, pharmacogenomic data must accompany an NDS, ANDS, or SNDS where: (1) it provides evidence of the safety and/or clinical effectiveness of the new drug in the context of its proposed indications; (2) “it is used to support the proposed dosage of the drug”; (3) it supports “claims to be made for the drug”; or (4) it reveals information “about contraindication and adverse reactions of the drug.”<sup>123</sup> As with CTAs, Health Canada encourages sponsors to request consultation meetings with the relevant directorates before submitting an NDS that contains pharmacogenomic information or that makes use of a pharmacogenomic test.<sup>124</sup>

The Health Products and Food Branch reviews all NDS, ANDS, SNDS, and SANDS submissions to evaluate the safety, efficacy, and quality of the drug product, as well as its potential risks and benefits. If the submission complies with the standards established by the *Food and Drugs Act* and associated regulations, Health Canada will then issue a Notice of Compliance

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same route of administration and conditions of use. Bioequivalence means that “the generic drug product must have the same systemic effects (therapeutic and adverse) as the CRP when administered to patients under the same conditions as the CRP.” Bioequivalence is usually established based on an assessment of pharmaceutical characteristics, bioavailability studies, pharmacodynamic studies, or clinical trials. The ANDS must also contain information on the safety, efficacy, drug manufacturing, packaging, and labelling of the generic product. See Lemmens & Bouchard, *supra* note 88 at 326.

<sup>121</sup> The SNDS must be submitted in accordance with the *Food and Drug Regulations*, *supra* note 92, ss C.08.003, C.08.003.1.

<sup>122</sup> The SANDS must be submitted in accordance with the *Food and Drug Regulations*, *ibid*, s C.08.002.1.

<sup>123</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 9.

<sup>124</sup> *Ibid*.

(NOC),<sup>125</sup> authorizing the manufacturer to begin marketing the pharmaceutical drug for specific use in Canada. With the receipt of the NOC, the manufacturer may also begin applying to list the drug in provincial formularies, which means that the drug will be funded, in full or in part, by the provincial health care plan that oversees that formulary.<sup>126</sup>

Once an initial NOC for a specific indication has been issued, the sponsor may then submit a subsequent SNDS to obtain approval for additional indications. This approach is commonly taken in the approval of many pharmaceutical products. However, because many pharmacogenomic drugs are initially only approved for a very narrow indication, it is common for multiple SNDSs to be submitted over the life cycle of a pharmacogenomic drug product to expand previously approved indications.<sup>127</sup>

## 1. Drug labelling requirements

Manufacturers must submit drug product information such as the name, labels, package leaflets, and product monographs/prescribing information to Health Canada, which are reviewed and approved prior to authorization for sale.<sup>128</sup> Drug labelling communicates important information about the product such as what the drug does, how the drug works, which patients should and should not take the drug, dosing information, and information on adverse drug reactions. The most detailed source of product information is the product monograph, which is “a factual, scientific document on a drug

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<sup>125</sup> An NOC is issued in accordance with the *Food and Drug Regulations*, *supra* note 92, s C.08.004(1)(a). It notifies the manufacturer that they have complied with the requirements necessary for the particular type of submission.

<sup>126</sup> Health Canada, “Drug and Health Products, Progressive Licensing, Introduction to the Current System” (archived 24 June 2013), online: HC <[www.hc-sc.gc.ca/dhp-mps/homologation-licensing/system/intro-eng.php](http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/system/intro-eng.php)> [Health Canada, “Drug and Health Products”]. See also Ontario, Ministry of Health and Long-Term Care, “How Drugs Are Approved” (23 May 2013), online: MHLTC <[www.health.gov.on.ca/en/pro/programs/drugs/how\\_drugs\\_approv/how\\_drugs\\_approv.aspx](http://www.health.gov.on.ca/en/pro/programs/drugs/how_drugs_approv/how_drugs_approv.aspx)>.

<sup>127</sup> See e.g. the multiple NOCs which have been approved for the pharmacogenomic drug Gleevec (imatinib): Health Canada, *Notice of Compliance (NOC) Database*, online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/index-eng.php)>.

<sup>128</sup> Health Canada, “How Drugs Are Reviewed”, *supra* note 118.

product that ... describes the properties, claims, indications, and conditions of use of the drug” and “other information that may be required for the optimal, safe and effective use of the drug.”<sup>129</sup>

Pharmacogenomic drug products are subject to the same labelling requirements as all pharmaceutical products.<sup>130</sup> Health Canada recommends that pharmacogenomic information be included in the product monograph and labelling in a number of different scenarios. For instance, when pharmacogenomic data demonstrate that subgroups of patients are likely to experience higher or lower clinical efficacy, or be at increased or decreased risk for adverse drug reactions, specific labelling should identify and define these population subgroups. Further, drug labelling should indicate any special dosage considerations for specific population subgroups, such as dosage reductions for particular patient subgroups to prevent adverse drug reactions (ADR).<sup>131</sup> Health Canada does not provide a public list of the drugs that include pharmacogenomic information in their labelling, in contrast to the FDA, which maintains a “Table of Pharmacogenomic Biomarkers in Drug Labeling” listing approximately 140 FDA-approved drugs with pharmacogenomic information in their labelling.<sup>132</sup>

Health Canada states that drug labelling should also indicate when pharmacogenomic testing is “recommended or required to optimize the use of the drug,” particularly where testing should be conducted prior to prescribing the drug.<sup>133</sup> However, there is no standardized language or format in the current guidelines regarding where or how pharmacogenomic information should be included in drug labelling. Language indicating whether a test is

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<sup>129</sup> Health Canada, “Frequently Asked Questions: Product Monographs Posted to the Health Canada Website” (11 July 2014), online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm\\_qa\\_mp\\_qr-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_qa_mp_qr-eng.php)>.

<sup>130</sup> Further information on the development of a product monograph is available in Health Canada, *Guidance for Industry: Product Monograph*, Guidance Document (1 June 2014), online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/prodpharma/applic-demande/guide-ld/monograph/pm\\_mp\\_2013-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/monograph/pm_mp_2013-eng.pdf)>.

<sup>131</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 10.

<sup>132</sup> US, Food and Drug Administration, “Table of Pharmacogenomic Biomarkers in Drug Labeling” (August 2014), online: FDA <[www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm](http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm)>.

<sup>133</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 10.

“required” or “recommended” varies widely.<sup>134</sup> Further, information related to diagnostic testing may be included in different sections of the monograph and under different titles: for example, in the case of Herceptin, a drug used to treat breast and gastric cancer, this information is found under the section “Selection of Patients/Diagnostic Tests”,<sup>135</sup> in the case of Tarceva, a drug used to treat skin cancer, it is found under the section “Monitoring and Laboratory Tests.”<sup>136</sup>

While different aspects of pharmacogenomics information will understandably often appear in multiple sections of a product monograph, and the types and extent of pharmacogenomics information may vary widely from product to product, the presentation of this information would nonetheless benefit from a greater level of standardization so that it could be more easily located by health care professionals and other interested parties – a task which may be somewhat daunting given the often very lengthy and detailed product monographs. Once again, this issue has already been addressed by the FDA in a guidance document released in January 2013 (implementing draft guidance that was released in February 2009),<sup>137</sup> which states that:

[i]f applicable, a “Pharmacogenomics” subsection should be included in the CLINICAL PHARMACOLOGY section (e.g.,

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<sup>134</sup> The product monograph for Herceptin, for example, states that the drug “should only be used in patients whose tumours overexpress HER2 as determined by immunohistochemistry”: Roche Canada, “Product Monograph HERCEPTIN®” at 21, online: RC <[www.rochecanada.com/fmfiles/re7234008/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Herceptin/Herceptin\\_PM\\_E.pdf](http://www.rochecanada.com/fmfiles/re7234008/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Herceptin/Herceptin_PM_E.pdf)> [Herceptin Product Monograph]. Other product monographs for pharmacogenomics drugs use stronger language, for example that of Tarceva (erlotinib), which states that “EGFR mutation-positive status must be confirmed prior to starting first-line TARCEVA therapy”: Roche Canada, “Product Monograph TARCEVA®”, online: RC <[www.rochecanada.com/fmfiles/re7234008/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Tarceva/Tarceva\\_PM\\_E.pdf](http://www.rochecanada.com/fmfiles/re7234008/Research/ClinicalTrialsForms/Products/ConsumerInformation/MonographsandPublicAdvisories/Tarceva/Tarceva_PM_E.pdf)> [Tarceva Product Monograph].

<sup>135</sup> Herceptin Product Monograph, *supra* note 134.

<sup>136</sup> Tarceva Product Monograph, *supra* note 134.

<sup>137</sup> US, Food and Drug Administration, *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling*, Guidance for Industry (January 2013), online: FDA <[www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf)>.

as “12.5 Pharmacogenomics”) of the prescribing information (PI) and should include clinically relevant data or information on the effect of genetic variations affecting drug therapy.<sup>138</sup>

While the FDA notes that where pharmacogenomic information has an important impact on the safe and effective use of the drug product, this information should be summarized in other sections of drug labelling with appropriate cross-referencing, they also state that “[d]etailed information about clinically relevant genetic information should be consolidated in the most appropriate labelling section.”<sup>139</sup> They also provide a chart showing the types of pharmacogenomic information that could appear in various sections of labelling.

## 2. Conditions of use

Even after a drug is released on the market, an NOC still places limitations on the use of the drug product. In particular, when an NOC is issued, the drug product is technically only approved for the treatment of specific indications and/or under specific conditions of use, which are set out in the product monograph.<sup>140</sup> One outstanding issue with pharmacogenomic drugs is the extent to which regulators can mandate confirmation of biomarker status or performance of a particular diagnostic test before a patient may be prescribed a pharmacogenomic drug. Although drug products are technically only approved for those specific indications and populations which are covered by the NOC, once a drug is on the market, physicians have the ability to prescribe the drug for any condition that is medically indicated, even those that are not specifically authorized by the product’s labelling – a practice known as “off-label prescribing.” Where drug labelling indicates use in a subpopulation with a particular biomarker, prescription of a product

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<sup>138</sup> *Ibid* at 19.

<sup>139</sup> *Ibid* at 20.

<sup>140</sup> This information is typically set out in the section titled “Indications and Clinical Use” in the product monograph. Product monographs for pharmaceuticals approved by Health Canada can be accessed through the Drug Product Database. See Health Canada, “Drug Product Database Online Query” (25 February 2013), online: HC <<http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>>.

without testing whether the patient falls within the indicated group prior to prescribing the drug should arguably be considered off-label use.<sup>141</sup>

Yvonne Lis and colleagues suggest that in recent years, regulatory authorities in both the US and Europe “have changed emphasis from the reactive collection of safety data to a more proactive risk management approach” and “increased regulatory requirements for postmarketing pharmacovigilance.”<sup>142</sup> Pharmacovigilance is the “process of detecting, assessing, understanding, and preventing adverse reactions or any other problems with drugs.”<sup>143</sup> In the US, for example, the *Food and Drug Administration Amendments Act of 2007*<sup>144</sup> introduced the requirement of Risk Evaluation and Mitigation Strategies (REMS) for certain products with “exceptional circumstances.” REMS can mandate that patients meet safe-use conditions, including diagnostic testing, before a drug is prescribed. In fact, the FDA “gives specific authorization to require the use of modern biomarker screening strategies and [pharmacogenomic] tests”<sup>145</sup> which could be used to assess whether a patient is a suitable candidate for the drug or not. However, while the FDA has been granted the explicit authority to require such measures, they have not yet used REMS to require the performance of diagnostic testing in the pharmacogenomic context.<sup>146</sup>

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<sup>141</sup> When asked, the majority of stakeholders interviewed during the qualitative study indicated that a failure to conduct diagnostic testing prior to prescribing a pharmacogenomic drug should be considered off-label prescribing.

<sup>142</sup> Yvonne Lis et al, “Comparisons of Food and Drug Administration and European Medicines Agency Risk Management Implementation for Recent Pharmaceutical Approvals: Report of the International Society for Pharmacoeconomics and Outcomes Research Risk Benefit Management Working Group” (2012) 15:8 *Value Health* 1108.

<sup>143</sup> Health Canada, “Drug and Health Products: Life-Cycle Management” (11 April 2007), online: HC <[www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/life-cycle-vie-eng.php](http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/life-cycle-vie-eng.php)>.

<sup>144</sup> *Food and Drug Administration Amendments Act of 2007*, Pub L No 110-85, 121 Stat 823.

<sup>145</sup> Barbara J Evans, “Seven Pillars of a New Evidentiary Paradigm: The Food, Drug and Cosmetic Act Enters the Genomic Era” (2010) 85:2 *Notre Dame L Rev* 419 [Evans, “Seven Pillars”].

<sup>146</sup> As reported in 2012 in Barbara J Evans, “Legal Trends Driving the Clinical Translation of Pharmacogenomics” in Russ B Altman, David Flockhart &

Canada has also been moving towards increasing risk management planning. In 2009, Health Canada issued a notice regarding the two-year interim implementation of a risk management planning initiative, which would expand “the use of regulatory tools to support and enhance health product vigilance review activities for pre- and post-authorization of health products.”<sup>147</sup> Yet at the time, Health Canada conceded that it did not have the regulatory authority to compel manufacturers to submit to a risk management plan, and instead requested that manufacturers submit such plans on a voluntary basis.<sup>148</sup> This, however, recently changed when new drug safety legislation received royal assent in November 2014: Bill C-17 or the *Protecting Canadians from Unsafe Drugs Act* (“*Vanessa’s Law*”) contains provisions that grant the government the power to pass regulations authorizing the Minister of Health to impose terms and conditions on market authorizations.<sup>149</sup> While *Vanessa’s Law* does not provide any details on what form such terms and conditions may take, presumably they could be similar to the REMS currently available under the US system. It clearly provides a wide-ranging statutory basis for further regulations that would strengthen Health Canada’s powers to impose active risk management after a drug hits the market. While the FDA is not yet using REMS to require the performance of diagnostic testing in the pharmacogenomic context, as these technologies continue to advance and more pharmacogenomic therapies hit the market, such measures could play an important role in preventing the inappropriate use of pharmacogenomic products.

### C. *Alternative approval mechanisms*

Drug regulators often face a difficult task in balancing demands for robust evidence on safety and efficacy and with those for timely access

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David B Goldstein, eds, *Principles of Pharmacogenetics and Pharmacogenomics* (New York: Cambridge University Press, 2013) 81 at 90.

<sup>147</sup> Health Canada, “Questions and Answers Regarding the Implementation of Risk Management Planning” (12 February 2009), online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/qa\\_rmp\\_qr\\_pgr-eng.php#q7](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/qa_rmp_qr_pgr-eng.php#q7)>.

<sup>148</sup> *Ibid.*

<sup>149</sup> Bill C-17, *An Act to amend the Food and Drugs Act*, 2nd Sess, 41st Parl, 2013, cl 6(1) (assented to 6 November 2014). The bill has now passed into law as SC 2014, c 24 [*Vanessa’s Law*]. The new provision referred to here has been enacted as section 30(1.2)(b) of the *Food and Drugs Act*, *supra* note 19.

to promising new therapies. In recent decades, many patients have been demanding more autonomy in drug treatment decisions, including determining acceptable levels of risk.<sup>150</sup> Particularly in the wake of HIV/AIDS advocacy for faster access to potentially life-saving drugs, regulators have introduced programs for compassionate access to drugs and early access to promising new therapies.<sup>151</sup> In an attempt to provide more flexible access to new drugs in exigent circumstances, Health Canada offers three alternative mechanisms that can potentially provide earlier access to drug products: the Special Access Program (SAP), the Priority Review Policy, and the Notice of Compliance with Conditions (NOC/c).

Since pharmacogenomic therapies are often used in the treatment of serious or life-threatening diseases or diseases for which there are few, if any, other treatment options, access to these therapies is often initially provided through these alternative approval mechanisms. While not actually a form of market authorization, the SAP allows practitioners to request access to drugs that have not been approved for the Canadian market.<sup>152</sup> As the name indicates, it is an exceptional program under which “access is limited to patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable,

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<sup>150</sup> See, for example, a 2012 study by Chewning and colleagues which identified a general trend towards patients wanting to play a more active role in treatment decisions, rather than delegating treatment decisions to a physician: Betty Chewning et al, “Patient Preferences for Shared Decisions: A Systematic Review” (2012) 86:1 Patient Educ Couns 9 at 15.

<sup>151</sup> For an interesting discussion of the impact of HIV/AIDS on the drug regulatory process focusing on the US FDA, see Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton, NJ: Princeton University Press, 2010) at 428-61. It is worth noting here, however, that it is perhaps also particularly in the context of serious and life-threatening diseases such as HIV/AIDS that the pressure to fast-track promising drugs may compromise reliable data gathering. The saga of the approval of AZT is a case in point.

<sup>152</sup> The SAP is supported by the *Food and Drug Regulations*, *supra* note 92, ss C.08.010-C.08.011. See also Health Canada, *Guidance Document for Industry and Practitioners: Special Access Programme for Drugs* (14 January 2008, as amended 19 December 2013), online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/acces/sapg3\\_pasg3-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/acces/sapg3_pasg3-eng.pdf)> [Health Canada, *SAP Guidance Document*].

or are unavailable.”<sup>153</sup> It may involve drugs that will never be submitted for drug regulatory approval (e.g., when it relates to a disease that only very rarely affects Canadians) or drugs that have not yet gone through the regulatory process in Canada but have been approved elsewhere and where granting compassionate access on an individual basis seems appropriate. Health Canada does not conduct a comprehensive evaluation of the validity of drug information or of the manufacturer’s claims on the safety, efficacy, and quality of the drug; Health Canada makes no representations that a drug is safe, efficacious, or of high quality.<sup>154</sup> There has been concern about the potential misuse of the program to get unapproved drugs into the country without going through the lengthy and costly approval procedures.

Turning to the second mechanism, the Priority Review Policy allows for the “fast-tracking” of eligible NDS and SNDS submissions “intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions.”<sup>155</sup> Importantly, drugs evaluated under the Priority Review Policy are subject to the same safety, efficacy, and quality criteria as standard drug submissions, but receive an accelerated review time: target review times for Priority Review are 180 days, versus 300

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<sup>153</sup> Health Canada, “Special Access Programme – Drugs” (15 August 2005), online: HC <[www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapfs\\_pasfd\\_2002-eng.php](http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapfs_pasfd_2002-eng.php)>. Most drugs accessed through the SAP are used to treat serious or life-threatening conditions such as “intractable depression, epilepsy, transplant rejection, hemophilia and other blood disorders, terminal cancer, and AIDS”; decisions under the SAP are made on a patient-by-patient basis (*ibid*).

<sup>154</sup> Health Canada emphasizes that marketed alternatives should always be considered before resorting to the use of non-marketed drugs and, further, that alternative mechanisms to provide emergency access, such as clinical trials, should be attempted before requesting a drug through the SAP. When an SAP request is granted, the practitioner must agree to provide a report on the result of the use of the drug, including any ADRs, to Health Canada. See Health Canada, *SAP Guidance Document*, *supra* note 152 at 10.

<sup>155</sup> Health Canada, *Guidance for Industry: Priority Review of Drug Submissions* (8 December 2008) at 1, online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/priordr-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/priordr-eng.pdf)> [Health Canada, *Priority Review*]. Further, to qualify for Priority Review, there must be substantial clinical evidence that the drug either: (1) “treat[s], prevent[s] or diagnos[es] ... a disease or condition for which no drug is presently marketed in Canada” or (2) “[provides] a significant increase in efficacy and/or significant decrease in the risk” of treating the disease or condition, in comparison to currently available drugs (*ibid* at 2).

days for non-priority submissions.<sup>156</sup> Essentially, Priority Review allows drug manufacturers to jump the queue ahead of other drug submissions.

Finally, the NOC/c is a special type of authorization issued by Health Canada that allows the sponsor to market a drug in Canada on the condition that they undertake additional studies to confirm the clinical benefit of the product.<sup>157</sup> Evidentiary requirements under the NOC/c policy are less onerous in comparison to the two controlled trials demonstrating safety and efficacy that are typically required to obtain an NOC without conditions. Before an NOC/c may be granted, the sponsor must agree: (1) to carry out additional clinical trials to verify the clinical benefit of the drug; (2) to undertake increased monitoring of the drug and reporting to Health Canada; (3) to provide educational material, including the nature of the conditions of use, to health care practitioners and patients; and (4) to adhere to certain restrictions on advertising and labelling.<sup>158</sup> Once all of the conditions set out in the NOC/c have been met and the sponsor is able to provide Health Canada with satisfactory evidence of the drug's clinical effectiveness, the drug is granted a full NOC without any associated conditions.<sup>159</sup>

## 1. NOC/c and niche markets

The NOC/c policy is the “early access” mechanism that seems best suited to pharmacogenomic products because it is designed for drugs that show promising clinical effectiveness but still require additional clinical trials to verify their clinical benefit.<sup>160</sup> As noted earlier, since pharmacogenomic drugs are often narrowly targeted towards patient subpopulations with a specific genetic marker, the population base on which to conduct clinical trials may be inherently limited. Pharmacogenomic drugs, like other drugs for rare diseases, may need to rely on post-market (Phase IV) studies and

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<sup>156</sup> Ron A Bouchard & Monika Sawicka, “The Mud and the Blood and the Beer: Canada’s Progressive Licensing Framework for Drug Approval” (2009) 3:1 McGill JL & Health 49 at 59.

<sup>157</sup> Health Canada, “Notice of Compliance with Conditions – NOC/c (Therapeutic Products)” (6 June 2007), online: HC <[www.hc-sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/noccfcs\\_accfd-eng.php](http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/activit/fs-fi/noccfcs_accfd-eng.php)> [Health Canada, “NOC/c Fact Sheet”].

<sup>158</sup> *Ibid.*

<sup>159</sup> *Ibid.*

<sup>160</sup> *Ibid.*

data to more fully establish their safety and efficacy.<sup>161</sup> Avery, for example, has supported the use of “conditional” approval for pharmacogenomic products, writing that, “[i]f Phase III trials conclude and the sponsor must rely on data from a probably valid [pharmacogenomic] biomarker to show safety and/or efficacy, [regulators should] ‘conditionally approve’ the drug with a limited labeling and a requirement for a Phase IV study to validate the biomarker.”<sup>162</sup> Indeed, a number of pharmacogenomic drugs have already received initial approval through the NOC/c policy, including Tassigna (nilotinib), Gleevec (imatinib), Vectibix (panitumumab), Iressa (gefitinib), and Sprycel (dasatinib).<sup>163</sup> Avery also cautions, however, about the potential risk to patients that could arise from relying on invalidated biomarkers. He therefore suggests that conditional approval may only be acceptable where the possible harm to the patient is restricted to simply receiving an ineffective treatment.<sup>164</sup>

Several conditions have to be fulfilled to use an NOC/c. First, as with Priority Review, the new drug must be intended “for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions.”<sup>165</sup> In addition, it must involve a product for which there is currently no alternative therapy available on the Canadian market, or which potentially represents “a significant improvement in the benefit/risk profile over existing products.”<sup>166</sup> Further, the drugs must have demonstrated promising clinical effectiveness and have an acceptable benefit–risk profile.<sup>167</sup>

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<sup>161</sup> In contrast, since the Priority Review policy still requires the same safety, efficacy and quality criteria as standard drug submissions, this policy is of little use for pharmacogenomic drugs that may still lack sufficient evidence of their clinical benefit. See Health Canada, *Priority Review*, *supra* note 155.

<sup>162</sup> Avery, *supra* note 15 at 60.

<sup>163</sup> See the register of NOC/c at Health Canada, *Notice of Compliance with Conditions (NOC/c)* (2 July 2013), online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php)> [Health Canada, *NOC/c Register*].

<sup>164</sup> Avery, *supra* note 15.

<sup>165</sup> Health Canada, “NOC/c Fact Sheet”, *supra* note 157.

<sup>166</sup> *Ibid.*

<sup>167</sup> Under the NOC/c policy, the sponsor is required to demonstrate that the drug in question “has the potential to provide a statistically significant and clinically relevant improvement in benefit/risk profile” over therapies currently

Once Health Canada has determined that a drug qualifies under the NOC/c policy, it issues a Qualifying Notice,<sup>168</sup> which sets out the agreed terms between Health Canada and the sponsor regarding additional clinical evidence to be provided by the sponsor in confirmatory trials and the sponsor's post-market surveillance responsibilities.<sup>169</sup> However, Law notes that "while the [Qualifying Notice] outlines the conditions proposed by Health Canada, the final conditions agreed to by the manufacturer and Health Canada in the [Letter of Undertaking] may be different and are kept confidential."<sup>170</sup> The sponsor's outline for confirmatory trials must include timeframes for initiation and completion.<sup>171</sup> Key revisions to the policy in 2011 included the addition of annual progress reports on ongoing confirmatory trials.<sup>172</sup>

The approval program most similar to the NOC/c offered by the FDA in the US is the Accelerated Approval mechanism, which allows drugs targeting serious conditions that address an unmet medical need to be approved more quickly on the basis of a "surrogate endpoint," i.e., a metric that is

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available in Canada. Such potential can be demonstrated through: (1) trials with surrogate markers requiring validation; (2) Phase II trials requiring confirmation with Phase III trials; or (3) Phase III trials requiring an additional trial confirming the safety or efficacy of the drug in question. See Health Canada, *Notice of Compliance with Conditions*, Guidance Document (30 June 2011), online: HC <[www.hc-sc.gc.ca/dhp-mpps/alt\\_formats/pdf/prodpharma/applic-demande/guide-ld/compli-conform/noccg\\_accd-eng.pdf](http://www.hc-sc.gc.ca/dhp-mpps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/compli-conform/noccg_accd-eng.pdf)> [Health Canada, *NOC/c Guidance Document*].

<sup>168</sup> *Ibid* at 17. Finally, the sponsor must provide a letter indicating agreement with the terms in the Qualifying Notice and a Letter of Undertaking. The sponsor's Letter of Undertaking must contain a provision committing the sponsor to informing the Therapeutic Products Directorate in writing of significant changes (or no changes) to the risk-benefit profile of the drug on an annual basis. In some instances, the sponsor may also be required to undertake active surveillance responsibilities to monitor drug safety (*ibid* at 25-26). "Examples of active surveillance include targeted safety monitoring trials (in hospitals and health facilities), prescription event monitoring, registries, or sentinel sites" (*ibid* at 24).

<sup>169</sup> *Ibid* at 16.

<sup>170</sup> Michael Law, "The Characteristics and Fulfillment of Conditional Prescription Drug Approvals in Canada" (2014) 116:2-3 *Health Policy* 154.

<sup>171</sup> Health Canada, *NOC/c Guidance Document*, *supra* note 167 at 19.

<sup>172</sup> *Ibid* at 20.

believed to *predict* clinical benefit without directly measuring it.<sup>173</sup> While the Accelerated Approval program, like the NOC/c, requires the drug sponsor to conduct Phase IV confirmatory trials, it previously differed from the NOC/c in that it was initially limited to drugs approved solely on the basis of surrogate endpoints.<sup>174</sup> However, the *FDA Safety and Innovation Act of 2012* recently expanded the scope of the Accelerated Approval process to allow approval on the basis of both surrogate and intermediate clinical endpoints.<sup>175</sup> Yet the increasing approval of drug products based on surrogate and intermediate endpoints raises concerns. Surrogate endpoints are what the term suggests: they are surrogate measures, and as such may or may not reliably reflect whether and to what extent a product really provides a tangible benefit to patients' health.<sup>176</sup> It is worth noting here that there are strong financial interests associated with the use of surrogate endpoints rather than clear clinical outcomes. Since trials with surrogate endpoints are shorter and involve fewer patients. But once a drug is approved on that basis, companies have no direct incentive to conduct further studies ensuring that the surrogate endpoints are really meaningfully reflecting clinical outcomes. In fact, the opposite is often true.<sup>177</sup> This makes follow-up studies and confirmatory trials essential. There are also increasing apprehensions about whether regulatory authorities are effectively enforcing requirements for confirmatory trials and increased monitoring. In 2009, for example, the

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<sup>173</sup> See US, Food and Drug Administration, "Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review" (18 September 2014), online: FDA <[www.fda.gov/ForPatients/Approvals/Fast/default.htm](http://www.fda.gov/ForPatients/Approvals/Fast/default.htm)>. For a more detailed discussion of surrogate endpoints, see Thomas R Fleming & John H Powers, "Biomarkers and Surrogate Endpoints in Clinical Trials" (2012) 31:25 *Stat Med* 2973 at 2974-75.

<sup>174</sup> While a surrogate endpoint is an indirect measure of clinical effectiveness, a clinically meaningful endpoint directly measures how a patient "feels, functions or survives" (Fleming & Powers, *ibid* at 2979). In general, "[v]alidating a surrogate endpoint requires providing an evidence based justification, often from randomized controlled clinical trials, that achievement of substantial effects on the surrogate endpoint reliably predicts achievement of clinically important effects on a clinically meaningful endpoint" (*ibid* at 2974).

<sup>175</sup> Pub L No 112-144, 126 Stat 993.

<sup>176</sup> For a detailed discussion on the use of surrogate endpoints in accelerated approval procedures, see Thomas R Fleming, "Surrogate Endpoints and FDA's Accelerated Approval Process" (2005) 24:1 *Health Aff (Millwood)* 67.

<sup>177</sup> Staffan Svensson, David B Menkes & Joel Lexchin, "Surrogate Outcomes in Clinical Trials: A Cautionary Tale" (2013) 173:8 *JAMA Intern Med* 611.

US Government Accountability Office released a report that raised a number of concerns with the Accelerated Approval program and recommended that the FDA improve its oversight of drugs approved on the basis of surrogate endpoints.<sup>178</sup>

## 2. Improving the transparency of the NOC/c process

While the NOC/c policy may, in certain circumstances, benefit patients by providing earlier access to promising new therapies, there are nonetheless a number of problems with the existing process. First, allowing earlier market entry for some products likely increases the chance of having to later withdraw a drug from the market for safety reasons.<sup>179</sup> Further, there is a lack of transparency in the existing NOC/c policy, particularly with respect to how the conditions are monitored and enforced: many NOC/c remain unfulfilled for many years with no indication of what work is currently being done to meet the conditions.<sup>180</sup> An NOC/c could potentially be used by a drug manufacturer hoping to launch a drug quickly without having to go through the lengthy, more cumbersome, and more costly regular approval process. The consequences are potentially serious since drugs that go through the NOC/c process may rapidly become widely available. While the Qualifying Notice provides details on the confirmatory trials to be undertaken, and sponsors are required to submit annual progress reports, little or no information is made public between the posting of the Qualifying Notice and the notification that the conditions of the NOC/c have been fulfilled, which usually occurs many years later. As stated by Joel Lexchin, “these drugs remain in a state of uncertainty regarding clinical efficacy for prolonged periods of time and the requirements to remove them from that state are a secret.”<sup>181</sup>

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<sup>178</sup> US, Government Accountability Office, News Release, “FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints” (23 September 2009), online: GAO <[www.gao.gov/products/GAO-09-866](http://www.gao.gov/products/GAO-09-866)>.

<sup>179</sup> During qualitative interviews, one stakeholder reported that in the US, there has been a reluctance to venture into conditional approval partly because it is difficult to withdraw approvals later.

<sup>180</sup> Joel Lexchin, “Notice of Compliance with Conditions: A Policy in Limbo” (2007) 2:4 *Healthc Policy* 114.

<sup>181</sup> *Ibid* at 120-21.

A 2014 study conducted by Law revealed that of the 70 NOC/c approvals granted by Health Canada to that point, 29 (41%) had fulfilled their conditions and received a full NOC, 34 (49%) were still outstanding, and 7 (10%) subsequently had either the indication or the drug itself withdrawn.<sup>182</sup> Most drug products initially approved through an NOC/c meet the conditions associated with the authorization within five or so years of the initial issuance.<sup>183</sup> However, some NOC/c remain outstanding for much longer than that; according to Law, “[t]he top 10 longest wait times for drugs ranged from 6 years to over 11 years.”<sup>184</sup> While drug companies are not necessarily intentionally violating the terms of an NOC/c, it is often hard to know what is going on behind the scenes due to the lack of transparency. It is also clear that there are few market incentives to really fulfill the NOC/c once a drug is on the market. Law rightly argues that “Health Canada should make the conditions of approval under a NOC/c more explicit and time-limited.”<sup>185</sup>

In Europe, the European Medicines Agency (EMA) offers a conditional approval mechanism similar to Health Canada’s NOC/c policy known as a Conditional Marketing Authorization (CMA).<sup>186</sup> In comparison to the NOC/c policy, the review and reporting requirements demanded by the EMA are more transparent, and arguably more rigorous, than those demanded by Health Canada. As with the NOC/c, CMA holders are required to complete

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<sup>182</sup> Law, *supra* note 170 at 157.

<sup>183</sup> The study by Law found that the median time for fulfilling the NOC/c requirements was 1828 days, or just over five years, though there was significant variation in the timeframes. *Ibid* at 157-58.

<sup>184</sup> *Ibid* at 157.

<sup>185</sup> *Ibid* at 159.

<sup>186</sup> EC, *Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council*, [2006] OJ, L 92/6 at 8, art 4 [*EU Conditional Marketing Policy*]. The CMA allows for the approval of a drug in the absence of comprehensive clinical data referring to the drug’s safety and efficacy – provided that several requirements are met: the risk–benefit balance of the drug is positive; it is likely that the applicant will be able to provide comprehensive clinical data; the drug fulfills an unmet medical need; and the public health benefits of making the drug immediately available outweigh the risks inherent in the fact that additional data are still needed. Once the holder has met its specific obligations, the Committee for Medicinal Products for Human Use may issue a recommendation for the CMA to be replaced with a formal marketing authorization.

ongoing studies or to conduct new studies with the aim of providing the clinical data missing from the original application and confirming the drug's positive risk–benefit balance,<sup>187</sup> and may also be obligated to collect additional pharmacovigilance data.<sup>188</sup> However, unlike an NOC/c, CMAs are subject to renewal on an annual basis<sup>189</sup> and as part of the renewal process, the holder is required to submit interim reports on its progress in fulfilling its specific obligations.<sup>190</sup> Additionally, the holder must submit periodic safety update reports at least every six months following the granting or renewal of its CMA.<sup>191</sup> Perhaps most significantly, the results of these interim assessments are made publicly available on the EMA website.<sup>192</sup>

Currently, the NOC/c policy is not set out in any legislation; rather, NOC/c are issued under the general licensing provisions of the *Food and Drug Regulations*.<sup>193</sup> Drugs granted an NOC/c are subject to the enforcement provisions outlined in the *Food and Drug Regulations* for NOCs. For example, the Therapeutic Products Directorate has the discretion to request a manufacturer to stop selling a drug product if the sponsor fails to undertake or complete a confirmatory trial, or fails to provide results of a confirmatory trial by a specified date.<sup>194</sup> The Minister of Health can also suspend an

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<sup>187</sup> *Ibid*, art 5(1).

<sup>188</sup> *Ibid*.

<sup>189</sup> *Ibid*, art 6.

<sup>190</sup> *Ibid*, art 6(2).

<sup>191</sup> *Ibid*, art 9.

<sup>192</sup> See e.g. the numerous documents under the assessment history of Tyverb (lapatinib): European Medicines Agency, “Tyverb”, online: EMA <[www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000795/human\\_med\\_001120.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000795/human_med_001120.jsp)>.

<sup>193</sup> Licences are granted under the authority of C.08.004(1), and “conditions of use” are provided for under C.08.002(2), particularly subsections (g) and (h). See *Food and Drug Regulations*, *supra* note 92, ss C.08.002(2), C.08.004(1).

<sup>194</sup> Section C.01.013(1) of the *Food and Drug Regulations*, *ibid*, provides that “[w]here the manufacturer of a drug is requested in writing by the Director to submit on or before a specified day evidence with respect to a drug, the manufacturer shall make no further sales of that drug after that day unless he has submitted the evidence requested.”

NOC/c if confirmatory trials raise safety concerns<sup>195</sup> or fail to demonstrate clinical benefit.<sup>196</sup> However, withdrawing the licence for drugs that fail to meet the conditions of the NOC/c is a rather blunt and drastic sanction. Politically, it can be a very hard sell, both to industry and to patients. Patients may feel – rightly or wrongly – that the government’s intervention is depriving them of an important new medication. A licence withdrawal may also create problems for patients who found the treatment to be effective. It therefore seems doubtful that industry will improve its compliance record and that the regulators will have the stamina to take the most drastic actions. Another firm regulatory stick is needed. Law suggests that adding financial penalties to the NOC/c regime would help to encourage the fulfillment of conditions without the harsh measure of removing the drug from the market.<sup>197</sup> This would be in line with the conditional approval regimes offered by the FDA and the EMA, which give regulatory authorities the ability to levy financial penalties on sponsors who fail to fulfill their conditions.

The NOC/c policy may, in certain circumstances, fill an important gap by granting earlier market access to potentially life-saving drugs. The movement towards pharmacogenomics will likely increase the use of conditional licensing. For example, Pignatti and colleagues note that “matching targeted drugs with better patient selection in the exploratory phases of development will lead to a wider use of early approval mechanisms, with drugs increasingly being approved initially for small subgroups of patients with great unmet needs.”<sup>198</sup> However, for doctors and patients to be able to make informed treatment decisions about drugs approved under the NOC/c policy, they need to have access to the most up-to-date study information. Law observes that “[t]here has not been any investigation into whether these conditions or having received a NOC/c is considered by physicians in their prescribing decisions.”<sup>199</sup> Although the most recent version of the NOC/c policy released in 2011 included more rigorous monitoring and report-

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<sup>195</sup> *Ibid*, s C.08.006(2)(a).

<sup>196</sup> *Ibid*, s C.08.006(2)(b).

<sup>197</sup> Law, *supra* note 170 at 160.

<sup>198</sup> Francesco Pignatti et al, “The European Medicines Agency: An Overview of its Mission, Responsibilities, and Recent Initiatives in Cancer Drug Regulation” (2011) 17:16 *Clin Cancer Res* 5220 at 5225.

<sup>199</sup> Law, *supra* note 170 at 155.

ing requirements,<sup>200</sup> there has been little or no movement towards making the results of interim reporting publicly accessible. Law recommends that Health Canada create an online public database of drugs approved through the NOC/c process that includes the conditions attached to the approval, as is currently done in the US and Europe.<sup>201</sup> At the very least, Health Canada should provide periodic summary reports updating the current status of drugs under the NOC/c policy so that health care professionals and patients are not completely in the dark during the period between the granting of an NOC/c and the fulfillment of conditions – a period which may last many years, as indicated above. Important questions also remain about how to discuss the provisional nature of the NOC/c approval with patients who are taking the drug.<sup>202</sup> In addition, it also seems important that Health Canada ensure ongoing, independent evidence gathering on the real-world use of these drugs. While this is important for all approved products, it is clearly even more important for drugs approved under the NOC/c regime.

### III. COORDINATING REVIEW AND MONITORING

For many pharmacogenomic therapies, the companion diagnostic is an essential component in ensuring the safe and effective use of the drug product. For example, pharmacogenomics can help to identify the optimum dosage for each patient based on underlying metabolizer phenotypes (i.e., based on pharmacokinetic variability), thereby reducing the risk of a drug overdose.<sup>203</sup> Consequently, significant problems may arise if there is varia-

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<sup>200</sup> In particular, “key revisions include changes to post-market surveillance reporting, labelling requirements and the addition of the annual confirmatory trial progress reports”: Health Canada, “Release of the Final Guidance Document: Notice of Compliance with Conditions (NOC/c)” (30 June 2011), online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/compli-conform/noccg\\_accd-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/compli-conform/noccg_accd-eng.php)>.

<sup>201</sup> *Ibid* at 60.

<sup>202</sup> This particular concern was raised by a stakeholder during qualitative interviews.

<sup>203</sup> One such example is the role of pharmacogenomics in dosing the anticoagulant warfarin. Although warfarin is a widely prescribed drug, it is unusual in that the dosage typically needs to be individualized for each patient. The biomarkers CYP2C9 and VKORC1 have been shown to be important predictors of stable warfarin dose requirements. Proper dosing of warfarin is very important since “[o]vercoagulation places the patient at risk of potentially fatal

tion in the availability of diagnostic tests or in the standards that are applied in their assessment.<sup>204</sup> As noted above, there is a need to ensure a consistent level and quality of testing methodology regardless of the type of test or who is responsible for its regulation.

Similarly, the interdependence of the drug and test components for the safe and effective use of pharmacogenomic products highlights the need for more coordination in the approval of the two components where they are developed concurrently; if the drug and test components are reviewed separately, then regulators may have an incomplete picture of the safety and efficacy of the drug product.<sup>205</sup> An outstanding question is whether, or to what extent, the drug and test components of pharmacogenomic therapies can and should be reviewed together. As noted by Pendergast, “[t]he clinical validity and utility of pharmacogenomics lie at the intersection of testing and drug use.”<sup>206</sup> Accordingly, if there is a coordinated effort to review drug and test components in relation to one another, this may help to establish their interdependence and increase the likelihood that both the drug and the companion diagnostic will be made available and funded together. As stated by the Cancer Quality Council of Ontario, “[t]o be safe and effective, these services need to be harmonized, evidence-based and efficiently coordinated ... so ideally they should be evaluated together.”<sup>207</sup>

The extent to which the review of drug and test components can be coordinated depends on when and how these components are developed.

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hemorrhage whereas undercoagulation means that the patient does not benefit from the drug.” See Ann K Daly, “Pharmacogenomics of Warfarin” in Sandosh Padmanabhan, ed, *Handbook of Pharmacogenomics and Stratified Medicine* (London, UK: Elsevier, 2014) 497 at 497.

<sup>204</sup> During qualitative interviews, both the drug and test components were commonly viewed as being essential to the safety and efficacy of the product as a whole.

<sup>205</sup> During qualitative interviews, numerous stakeholders highlighted the importance of assessing the drug and test components of the pharmacogenomic product in tandem, whenever possible.

<sup>206</sup> Pendergast, *supra* note 56 at 1500.

<sup>207</sup> Cancer Quality Council of Ontario, *Mapping a Way through the Double Helix: Making Sense of Personalized Medicine for Ontario's Cancer System; Signature Event Report: Recommendations and Proceedings* (May 2011) at 2, online: CQCO <[www.cqco.ca/common/pages/UserFile.aspx?fileId=98415](http://www.cqco.ca/common/pages/UserFile.aspx?fileId=98415)>.

There are generally three different scenarios for the discovery of a targeted therapy: (1) prospective co-development of a drug and a test, where a companion test is put on a co-development path with the drug from early-phase clinical studies; (2) discovery of a targeting strategy late in clinical trials; and (3) post-market discovery of a target, when the results are stratified based on genomic information.<sup>208</sup> Ideally, the FDA recommends the first scenario, but in reality, biomarkers are often not identified until late-stage clinical trials. As noted by Avery, “[w]hile parallel development is clearly optimal in theory, it is difficult to execute in practice, and very few pioneers have successfully coordinated the development of a drug product and its companion diagnostic.”<sup>209</sup>

Regulatory procedures may vary somewhat depending on when and how biomarker identification and test development occur. Where the drug and test components are developed concurrently, reform efforts will likely need to focus on how to better coordinate the review of these two components in tandem, such as through a combination of the procedures described in the next section. However, where biomarker identification and test development occur later in the development life cycle, reform efforts will likely need to focus on improving systems of post-market surveillance and evidence generation such that the conditions of use and labelling for pharmacogenomic products are continually revised and reflect the evolving evidence.

#### ***A. Synchronizing the review of federally regulated drugs and tests***

To recap, for pharmacogenomic treatments that are comprised of a genetic test in the form of an *in vitro* diagnostic device and a pharmaceutical drug, the federal level of government has complete regulatory control. Sponsors of such a pharmacogenomic product must submit two separate applications: an NDS to the Therapeutic Products Directorate and an application to the Medical Devices Bureau for a licence for the *in vitro* diagnostic device.

Health Canada indicates that where a sponsor requests a consultation with the relevant directorate prior to submitting a CTA or NDS, they should

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<sup>208</sup> Barbara J Evans, “What Will It Take to Reap the Clinical Benefits of Pharmacogenomics?” (2006) 61:4 Food Drug Law J 753 [Evans, “What Will It Take?”].

<sup>209</sup> Avery, *supra* note 15 at 57.

indicate whether an associated application for an investigational pharmacogenomic test has also been submitted to the Medical Devices Bureau. In such cases, representatives from the Bureau will attend the consultation meeting “where applicable.”<sup>210</sup> However, all pre-submission meetings, including those for pharmacogenomic products, are conducted under the general process outlined for all drug products.<sup>211</sup> We could not find more specific details on whether, or how, Health Canada would coordinate the review of associated pharmacogenomic drug and test components between directorates.

In the US, the FDA also utilizes consultation meetings to facilitate the review of pharmacogenomic products, and provides public details on how such reviews may be conducted. In 2011, the FDA released a draft guidance document clarifying the pre-submission program for therapeutic products intended for use with an *in vitro* companion diagnostic device; it was issued in final form in August 2014.<sup>212</sup> The document emphasizes that the FDA’s review of pharmacogenomics products is carried out collaboratively by the relevant FDA subsidiaries.<sup>213</sup> The guidance advises sponsors developing either one of the products to request a meeting with the relevant device or drug review division early in the development process.<sup>214</sup> It further recom-

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<sup>210</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 11.

<sup>211</sup> See the description of pre-submission meetings in Health Canada, “Guidance for Industry – Management of Drug Submission” (20 December 2013) at 4-5, online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/prodpharma/applic-demande/guide-ld/mgmt-gest/mands\\_gespd-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.pdf)>.

<sup>212</sup> For the final issued version, see US, Food and Drug Administration, *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff* (6 August 2014), online: FDA <[www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf)> [FDA, *Guidance on In Vitro Companion Diagnostic Devices*]. To obtain approval, an *in vitro* companion diagnostic device requires a pre-market application or a 510(k) clearance. On the therapeutics side, a sponsor must demonstrate that the drug is safe and effective through the submission of a New Drug Application. See *Federal Food, Drug, and Cosmetic Act*, 21 USC §§ 301 et seq, § 505.

<sup>213</sup> FDA, *Guidance on In Vitro Companion Diagnostic Devices*, *supra* note 212 at 8.

<sup>214</sup> *Ibid* at 5. Both sponsors are encouraged to submit information about the proposed *in vitro* companion diagnostic device in a “preIDE” to their respective diagnostic review centers so that officials can plan for contemporaneous

mends parallel development of the drug and companion diagnostic, noting that “[i]deally, ... the clinical performance and clinical significance of the IVD companion diagnostic device [will be] established using data from the clinical development program of the corresponding therapeutic product.”<sup>215</sup> However, the document also acknowledges that parallel development is often unrealistic and describes scenarios where the FDA will proceed with approving a therapeutic product when its companion diagnostic is not being cleared contemporaneously.<sup>216</sup>

### 1. Regulating pharmacogenomic therapies as combination products

Once again, Canada may look to the US for guidance on combining the regulatory pathways for *in vitro* diagnostic devices and pharmaceutical products. In the same guidance document referenced in the preceding paragraph, the FDA indicates that certain *in vitro* diagnostic devices and their paired therapeutic products may be classified as “combination products”<sup>217</sup> and regulated by a specialized agency, the Office of Combination Products (OCP). The FDA’s definition of a combination product includes not only two or more regulated products that are sold as a single entity or packaged together, but also “[a]ny investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect”<sup>218</sup> – a definition which may encompass pharmacogenomic drugs and tests.

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drug and companion diagnostic device approval. A pre-Investigational Device Exemption (preIDE) is a consultative submission intended to ensure that appropriate validation studies are planned and carried out. See US, Food and Drug Administration, “IDE Approval Process”, online: FDA <[www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm)>.

<sup>215</sup> FDA, *Guidance on In Vitro Companion Diagnostic Devices*, *supra* note 212 at 7.

<sup>216</sup> *Ibid* at 8-9.

<sup>217</sup> *Ibid* at 6.

<sup>218</sup> Combination products are defined in the US federal regulations at 21 CFR § 3.2(e).

The OCP was established to ensure the prompt assignment of combination products to agency centres so that they undergo timely and effective review.<sup>219</sup> The OCP does not itself review pre-market applications for combination products, but assigns each combination product to an Agency Center<sup>220</sup> or alternative organizational component that will have primary jurisdiction for the product's pre-market review and regulation based on a determination of the "primary mode of action."<sup>221</sup> If the primary mode of action of a combination product is that of a drug, then the Center for Drug Evaluation and Research has primary jurisdiction, and if the primary mode of action of a combination product is that of a device, the Center for Devices and Radiological Health has primary jurisdiction.<sup>222</sup> Where the jurisdiction of a combination or non-combination product is unclear, a formal request for designation may be submitted to the OCP.<sup>223</sup> While conducting a review, the lead Agency Center may consult or coordinate with another Agency Center. Primary research responsibilities can be shared between reviewers from two or more Agency Centers for a defined portion of the submission. More frequently, a reviewer in one Agency Center will consult with another reviewer from a second Center on a specific issue raised in the submission. Generally, sponsors of a combination product will submit a single investigational application containing information on all constituent parts of the combination product in the format expected by the lead Agency Center.<sup>224</sup> There are, however, occasions when separate marketing applications for the drug and device components of a combination product are required.<sup>225</sup>

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<sup>219</sup> *Federal Food, Drug, and Cosmetic Act*, *supra* note 212, § 353(g)(4)(A)-(B).

<sup>220</sup> The Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).

<sup>221</sup> US, Food and Drug Administration, "Frequently Asked Questions about Combination Products", online: FDA <[www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm](http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm)> [FDA, "Combination Product FAQs"].

<sup>222</sup> *Federal Food, Drug, and Cosmetic Act*, *supra* note 212, § 353(g).

<sup>223</sup> FDA, "Combination Product FAQs", *supra* note 221.

<sup>224</sup> *Ibid.* For example, if the device is the combination product's primary mode of action, the investigation would be under an Investigational Device Exemption that includes the drug information.

<sup>225</sup> *Ibid.* One such example is when one constituent part is already approved for another use and its labelling will need to be altered to reflect its new intended

Overall, the OCP “serve[s] as a focal point for combination product issues for agency reviewers and industry” and helps to clarify regulatory responsibility when jurisdiction is unclear or in dispute, to coordinate reviews involving more than one Agency Center, and to ensure consistency and appropriateness of post-market regulation.<sup>226</sup> However, the proposal to review pharmacogenomic products through the OCP has not openly evolved since its initial discussion in a 2005 FDA concept paper<sup>227</sup> and it is unclear to what extent pharmacogenomic tests are currently being reviewed under this process.

## 2. Health Canada’s policy on combination products

In 1997, Health Canada released a policy statement on drug/medical device combination products to allow such products to be reviewed through a single regulatory pathway, rather than requiring the combination product to satisfy the requirements of two sets of regulations (i.e., those for both drugs and medical devices). However, the current policy is not applicable to pharmacogenomic tests and drugs since they do not fit under Health Canada’s current definition of a combination product, a definition that is much narrower than the one adopted by the FDA and requires that combination products consist of a single entity.<sup>228</sup> The policy explicitly states that it “does

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use in the combination product. A sponsor may also elect to submit multiple applications in order to receive some benefit that accrues only from approval under a particular type of application, such as orphan status or new drug product exclusivity. The OCP is developing a guidance document addressing the factors the FDA expects to consider in determining how many marketing applications should be submitted for a combination product.

<sup>226</sup> *Ibid.*

<sup>227</sup> US, Food and Drug Administration, *Drug-Diagnostic Co-Development Concept Paper: Draft – Not for Implementation* (April 2005), online: FDA <[www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf](http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf)>.

<sup>228</sup> Specifically, Health Canada defines a combination product as “a therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is integrated in a singular product.” See Health Canada, *Drug/Medical Device Combination Products* (1 March 2006), online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/prod-pharma/applic-demande/pol/combo\\_mixte\\_pol\\_2006-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prod-pharma/applic-demande/pol/combo_mixte_pol_2006-eng.pdf)> [Health Canada, *Combination Products*].

not apply to combinations of drugs and medical devices where the drug component and the device component can be used separately.”<sup>229</sup> Pharmacogenomic therapies clearly do not fall under this definition, as they consist of two separate components – a drug and a diagnostic test – each of which can be used independently of the other (although this may significantly hinder their individual effectiveness), and each of which may be developed by a different manufacturer.

Moreover, even if the pharmacogenomic drug/test pair were considered to be a combination product, the existing policy simply states that Health Canada will classify the drug/device combination product according to “the principal mechanism of action by which the claimed effect or purpose of the product is achieved.”<sup>230</sup> Consequently, the entire product will be regulated under the *Food and Drug Regulations* if classified as a drug, and under the *Medical Devices Regulations* if classified as a device.<sup>231</sup> There is no coordinating body similar to the OCP in the US that would act to streamline the application; the policy is simply intended to clarify which regulatory pathway different combination products will follow. The policy thus does not appear to lead to any coordinated review.

Health Canada acknowledges that the combination product policy document is only an “interim” mechanism to address a gap in the current regulatory schemes for drugs and medical devices, and that ultimately, the regulatory framework for new and emerging therapeutic products will need to be amended to properly address combination products that are difficult to define under current frameworks.<sup>232</sup> However, the policy has undergone

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<sup>229</sup> *Ibid.*

<sup>230</sup> *Ibid.*

<sup>231</sup> Examples of combination products that have been classified as drugs include, among others, “prefilled syringes[,] ... patches for transdermal drug delivery [, and] ... implants whose primary purpose is to release a drug.” Conversely, examples of combination products that have been classified as devices include “drug coated devices such as catheters, shunt sensors, or pacemaker leads ... [and] wound dressings and surgical barriers containing an antimicrobial agent.” See Health Canada, *Policy on Drug/Medical Device Combination Products – Decisions* (21 July 2014), online: HC <[www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/combo\\_mixte\\_dec\\_pol-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/combo_mixte_dec_pol-eng.php)>.

<sup>232</sup> Health Canada, *Combination Products*, *supra* note 228 at 1.

only limited reforms in the 17 years it has been in place.<sup>233</sup> Given the recent expansion of pharmacogenomic therapies and other combination products, it seems to be time for Health Canada to revisit its current policy on combination products to make it more relevant to the current health technology development paradigm.

### ***B. Post-market surveillance***

Although the current regulatory system focuses on pre-market activities, manufacturers must nonetheless adhere to a number of obligations once their drug or test enters the market. Like all pharmaceutical products, pharmacogenomic drugs are subject to post-market obligations, including informing Health Canada of any reported serious adverse drug reactions, complying with advertising restrictions, updating safety information pertaining to their products, maintaining the quality of their drug to the appropriate standard, and applying for further authorization from Health Canada for significant changes to their product.<sup>234</sup> In addition, the *Medical Devices Regulations* set out the requirement for mandatory problem reporting for medical devices, including pharmacogenomic tests (Class III devices).<sup>235</sup> At the provincial level, ongoing quality control initiatives may also be considered as a sort of post-market monitoring for lab-based tests, although once again, these evaluations focus on individual lab performance rather than on the tests themselves.

Prior to the passage of *Vanessa's Law*, Health Canada's regulatory authority became significantly diminished once a drug entered the market.<sup>236</sup>

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<sup>233</sup> The current version of the policy has not undergone any changes since March 2006, when the current policy replaced the previous policy from May 1999. See *ibid.*

<sup>234</sup> See Canada, Standing Senate Committee on Social Affairs, Science and Technology, *Prescription Pharmaceuticals in Canada: Post-approval Monitoring of Safety and Effectiveness* (Ottawa: Canadian Senate, 2013) at 5-15, online: Parliament of Canada <[www.parl.gc.ca/Content/SEN/Committee/411/soci/rep/rep20mar13-e.pdf](http://www.parl.gc.ca/Content/SEN/Committee/411/soci/rep/rep20mar13-e.pdf)>.

<sup>235</sup> See *Medical Devices Regulations*, *supra* note 24, ss 59-61.

<sup>236</sup> For a detailed discussion of post-marketing surveillance in the Canadian context, see Trudo Lemmens & Shannon Gibson, "Decreasing the Data Deficit: Improving Post-Market Surveillance in Pharmaceutical Regulation" (2014) 59:4 McGill LJ 943, especially at 958.

The regulatory agency itself noted that following drug approval, products largely disappeared from the radar screen unless significant adverse reports were reported.<sup>237</sup> Unless the drug was authorized under an NOC/c, regulators lacked the authority to compel manufacturers to conduct additional studies on safety and efficacy or on therapeutic effectiveness.<sup>238</sup> Although drug manufacturers were expected to conduct such further studies and to comply with various other post-market commitments, they often neglected to do so.<sup>239</sup> This can be viewed as a direct result of regulatory authorities' failure to adequately enforce existing post-market surveillance commitments.<sup>240</sup>

Recent amendments in both the US and Europe have granted regulatory authorities expanded power to demand post-market studies. In the US, for example, the *Food and Drug Administration Amendments Act of 2007* expanded the FDA's authority to require manufacturers to conduct post-market studies after market approval if new safety information comes to light.<sup>241</sup> In addition, following the passage of new pharmacovigilance legislation in 2010, European regulatory authorities now also have the authority to require manufacturers to conduct post-market studies within the framework of a "Risk Management Plan."<sup>242</sup>

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<sup>237</sup> Health Canada, "Brief History of Drug Regulation in Canada" (11 April 2007), online: HC <[www.hc-sc.gc.ca/dhp-mps/homologation-licensing/info-reseign/hist-eng.php](http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/info-reseign/hist-eng.php)> [Health Canada, "Brief History"].

<sup>238</sup> Health Canada, for example, previously stated that it lacked the regulatory authority to explicitly require post-marketing studies as a condition for further sales of a pharmaceutical product. See Health Canada, "Authority to Require Post-Market Studies" (2011), online: Wayback Machine Internet Archive <<https://web.archive.org/web/20130111131841/www.hc-sc.gc.ca/dhp-mps/homologation-licensing/docs/pma-aac/pma-aac04-eng.php>>.

<sup>239</sup> For example, a study by Avorn revealed that more than half of the open commitments for post-market studies requested by the FDA had not yet been started, were behind schedule, or had been terminated before completion. See Jerry Avorn, "Paying for Drug Approvals – Who's Using Whom?" (2007) 356:17 *New Eng J Med* 1697 at 1698.

<sup>240</sup> Lorraine E Ferris & Trudo Lemmens, "Governance of Conflicts of Interest in Postmarketing Surveillance Research and the Canadian Drug Effectiveness Network" (2010) 4:2 *Open Med* E123.

<sup>241</sup> Evans, "Seven Pillars", *supra* note 145.

<sup>242</sup> Patrick Waller, "Getting to Grips with the New European Union Pharmacovigilance Legislation" (2011) 20:5 *Pharmacoepidemiol Drug Saf* 544.

Fortunately, Canada has now also embarked on some major reforms in this context. As noted above, in 2014, the Federal Government passed new drug safety legislation, *Vanessa's Law*,<sup>243</sup> aimed at improving Health Canada's regulatory authority in the post-market phase. One of the most important reforms in the new law is the ability for Health Canada to require pharmaceutical companies to "compile information, conduct tests or studies," monitor drug use after a drug has entered the market, and provide the Minister of Health with the results.<sup>244</sup> The grounds on which such additional evidence may be required under *Vanessa's Law* appear to be very broad: there are no preconditions specified in the legislation that must be met before additional information or assessments may be demanded from the authorization holder, other than that the assessment or information request be in respect of the therapeutic product in question.<sup>245</sup> Specific conditions will have to be set out in future regulations. *Vanessa's Law* appears to grant more expansive authority to demand post-market evidence generation than is granted to the FDA under the *Food and Drug Administration Amendments Act of 2007*, which requires that a new safety concern be revealed before additional studies may be demanded.<sup>246</sup> Health Canada is also working on a proposed Health Product Vigilance Framework, which "conceptually describes Canada's future integrated product vigilance system."<sup>247</sup>

Another important component of *Vanessa's Law* is the substantial increase in fines and penalties for contraventions of the *Food and Drugs Act* and associated regulations. While the previous maximum fine was \$5,000 for both summary conviction and conviction on indictment, the new legislation increases the maximum fine to \$5 million for an indictable offence

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<sup>243</sup> *Supra* note 149. The bill is named after Vanessa, the daughter of MP Terence Young, who died at the age of 15 as a result of the side-effects of Ortho-Jansen's controversial reflux drug Propulsid, which was subsequently removed from the market. See Terence H Young, *Death by Prescription* (Oakville, Ont: Mosaic Press, 2013).

<sup>244</sup> *Vanessa's Law*, *supra* note 149, s 4, amending *Food and Drugs Act*, *supra* note 19, s 21.32.

<sup>245</sup> *Ibid.*

<sup>246</sup> *Supra* note 144 at 923 (§ 901), amending 21 USC § 355(o)(2)(C); see also Evans, "Seven Pillars", *supra* note 145.

<sup>247</sup> HealthCanada, *HealthProductVigilanceFramework* (12 September 2012) at 1, online: HC <[www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/pubs/medeff/fs-if/2012-hpvf-cvps/dhpfv-ecvps-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/pubs/medeff/fs-if/2012-hpvf-cvps/dhpfv-ecvps-eng.pdf)> [Health Canada, *Vigilance Framework*].

– a thousandfold increase over the previous maximum.<sup>248</sup> Further, if an offence is found to have been committed or continued over multiple days, the maximum available fine is multiplied by that number of days, increasing substantially the potential upper limit of fines for a contravention. Finally, under a new provision, where a person knowingly or recklessly causes risk of injury to human health in the commission of an indictable offence, there is no maximum fine: the person is liable for “a fine the amount of which is at the discretion of the court.”<sup>249</sup> These increased penalties are significant and certainly necessary: in the US, substantial fines and criminal settlements have been imposed in the context of pharmaceutical industry misconduct, particularly for the illegal promotion of off-label use of drugs, yet have still not succeeded in rooting out the problems.<sup>250</sup>

Overall, the expansion of post-market regulatory oversight and the significant increases in penalty provisions created by *Vanessa’s Law* are an important step forward in ensuring the continued safety and efficacy of drugs approved for the Canadian market. However, the new law does not go far enough to promote transparency in the clinical trial process. In particular, there are no provisions mandating clinical trial registration and results reporting, which are already required in both the US and Europe. The success of the new legislation in improving post-market evidence generation will also ultimately depend on Health Canada actively exercising their new authority and enforcing contraventions of the *Food and Drugs Act* and regulations.

## 1. Pharmacogenomics and evolving evidence

Post-market data may be obtained from a variety of sources, including post-market studies, results from independent research,<sup>251</sup> and “information

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<sup>248</sup> The maximum fines for a summary conviction are increased to \$250,000 for a first offence and \$500,000 for subsequent offences. *Vanessa’s Law*, *supra* note 149, s 9, amending *Food and Drugs Act*, *supra* note 19, s 31.2(b).

<sup>249</sup> *Vanessa’s Law*, *supra* note 149, s 9, amending *Food and Drugs Act*, *supra* note 19, s 31.4(a).

<sup>250</sup> Many of these settlements have been in the range of hundreds of millions of dollars, with settlements increasingly exceeding the billion-dollar mark. See David Evans, “Big Pharma’s crime spree”, *Bloomberg Markets* (2 December 2009) 72.

<sup>251</sup> There are a number of independent researchers, organizations, and networks that are working to improve the knowledge base around pharmacogenomics.

from spontaneous ADR reports.”<sup>252</sup> There are a number of reasons why post-market evidence generation may be particularly important in the context of pharmacogenomic therapies. First, as noted above, genetic biomarkers may be used to enrich clinical trials for pharmacogenomic products, a fact that increases the imperative to conduct follow-up studies in the post-market phase to verify the safety and efficacy of the drug in broader populations. An associated concern is the potential shortcomings of the evidence produced in smaller-scale clinical trials, as compared to that of larger trials. Some gene–drug interactions may be rare and may only be revealed after a drug is taken by a large number of people after market approval.<sup>253</sup> Further, many new pharmacogenomic products are used in the treatment of critical conditions – most notably cancer – and so regulators often face intense pressure to provide earlier access to these therapies, even in the face of uncertain evidence. Such drugs may be fast-tracked through the approval process, increasing the risk that the review process may miss important safety issues, and therefore also increasing the need to more closely monitor the use of these products after market entry.<sup>254</sup> As noted above, some drugs for which there is great medical need may be approved through the NOC/c on the basis of surrogate endpoints, which are intended as – but may not in fact be – predictive of clinical endpoints; post-market monitoring is essential to determining whether such drugs deliver true clinical benefit.

Health Canada has recognized that pharmacogenomics “may enhance the ability to identify safety and efficacy issues associated with therapeutic products in the post-market setting, particularly in products with variable pharmacokinetic/pharmacodynamic properties and narrow therapeutic

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For example, the Clinical Pharmacogenetics Implementation Consortium is a project that produces “freely available, peer-reviewed, updateable, and detailed gene/drug clinical practice guidelines” in order to reduce the barriers to implementing pharmacogenomic tests into clinical practice. Such research initiatives may be an important source of evolving information about the role of genetic factors in drug response. See PharmGKB, “CPIC: Clinical Pharmacogenetics Implementation Consortium”, online: PharmGKB <[www.pharmgkb.org/page/cpic](http://www.pharmgkb.org/page/cpic)>.

<sup>252</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 11.

<sup>253</sup> Evans, “What Will It Take?”, *supra* note 208.

<sup>254</sup> Joel Lexchin, “New Drugs and Safety: What Happened to New Active Substances Approved between 1985 and 2010?” (2012) 172:21 *Arch Intern Med* 1680.

indices.<sup>255</sup> For example, post-market data may suggest “reduced or no efficacy of a [pharmacogenomic] product in specific subpopulations,” or pharmacogenomic-derived data may “identify certain subpopulations that are vulnerable to certain ADRs” (or classes of ADRs).<sup>256</sup> Moreover, as discussed above, the increasing use of enriched clinical trial design raises concerns about the lack of evidence on the safety and efficacy of pharmacogenomic drugs outside of the particular biomarker group studied in pre-market clinical trials, and may warrant further studies of the drug in the broader population in the post-market phase.

Pharmacogenomic information relating to safety and efficacy that is obtained during the post-market phase may also necessitate amendments to the labelling of the product in question.<sup>257</sup> The evolution of diagnostic testing technology, for example, should be reflected in drug labelling: if a new test proves to be more reliable or more effective, this new information should be captured in a timely manner.<sup>258</sup> Even drugs that were initially approved without a companion diagnostic may benefit from the subsequent development of a test that can provide more detailed information to guide prescribing.<sup>259</sup> It is worth noting that *Vanessa’s Law* includes provisions that expand the ability of Health Canada to demand changes to product labelling. In particular, the new section 21.2 of the *Food and Drugs Act* created by *Vanessa’s Law* gives the Minister the power to order a manufacturer “to modify the product’s label or to modify or replace its package” where “he

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<sup>255</sup> Health Canada, *Pharmacogenomics Guidance*, *supra* note 16 at 11.

<sup>256</sup> *Ibid* at 11-12.

<sup>257</sup> Health Canada notes that for the analysis of post-market safety/efficacy issues arising from pharmacogenomics, it requires at a minimum the following information: the ADR in question (including lack of efficacy), the suspected single nucleotide polymorphism (SNP)/halotype involved, and validation information on the pharmacogenomic test used. See *ibid* at 12.

<sup>258</sup> During qualitative interviews, a couple of stakeholders stressed the importance of updating labelling information to reflect the most recent diagnostic technologies.

<sup>259</sup> For example, subsequently developed pharmacogenomic tests have allowed for safer prescribing of older drugs such as codeine and warfarin. See Joseph P Kitzmiller et al, “Pharmacogenomic Testing: Relevance in Medical Practice” (2011) 78:4 *Cleve Clin J Med* 243.

or she believes that doing so is necessary to prevent injury to health.”<sup>260</sup> Such expanded regulatory authority seems very important in ensuring that product labelling reflects the most up-to-date product information.

Pharmacogenomic research may improve our understanding of drug response on a more individual level. The FDA, for example, has acknowledged that if “new science enables us to determine that the adverse events are restricted to a small, identifiable segment of the population, public health could be improved by making the drug available to others who could benefit without undue risk.”<sup>261</sup> For example, diagnostic testing may identify those subpopulations that may not experience the same increased risk, and perhaps in limited circumstances could thus even allow drugs to stay on or return to the market under more restricted terms. Ideally, improved pharmacovigilance systems and more rigorous post-market studies may allow for increasingly responsive tailoring of prescribing guidelines and the incremental expansion and tightening of approved drug indications based on evolving post-market evidence. *Vanessa’s Law* also adds strength to the regulatory framework in this context: it has introduced new requirements for prescribed health care institutions – namely hospitals – to report adverse drug reactions or medical device incidents to the federal government.<sup>262</sup> Such mandatory adverse-event reporting for health institutions may help improve the frequency and consistency of reporting, which is an important means of flagging potential safety concerns with therapeutic products.

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<sup>260</sup> *Vanessa’s Law*, *supra* note 149, s 3, amending *Food and Drugs Act*, *supra* note 19, s 21.2.

<sup>261</sup> US, Food and Drug Administration, *The Future of Drug Safety – Promoting and Protecting the Health of the Public: FDA’s Response to the Institute of Medicine’s 2006 Report* (January 2007) at 3, online: FDA <[www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm171627.pdf](http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm171627.pdf)> [FDA, *Future of Drug Safety*].

<sup>262</sup> *Vanessa’s Law*, *supra* note 149, s 5, amending *Food and Drugs Act*, *supra* note 19, s 21.8. The details of the adverse event reporting requirements will be set out in future regulations, which the Minister of Health is empowered to enact under the new section 30(1.2) of the *Food and Drugs Act* (created by section 6 of *Vanessa’s Law*).

#### IV. MOVING EVIDENCE GENERATION BEYOND THE PRE-MARKET PHASE

##### A. *The life-cycle approach*

Health Canada notes that in the real world, the use of health products changes over time as our understanding of their benefits and risks evolves; unfortunately, they acknowledge, “current regulatory tools are blunt instruments because they are not designed to easily respond to increasing knowledge of the real-world use of the product, such as, by changing the terms and conditions of market authorization.”<sup>263</sup> In 2005, Health Canada launched the Progressive Licensing Project to explore reform proposals for “the entire federal drug licensing system, from early clinical trials to market authorization, and then the monitoring of drugs once they are on the market.”<sup>264</sup> The Project included proposals to adopt a “lifecycle approach” to drug approval that does away with the distinction between pre-market and post-market stages and instead calls for the initial and ongoing collection, evaluation, and communication of evidence at all stages of drug development.<sup>265</sup>

The Progressive Licensing framework proposed changes to the standards for market authorization, based on a tiered approach to the evidence. While Health Canada has committed to retaining the demonstration of efficacy, safety, and quality for the proposed conditions of use as the baseline requirement for initial market authorization, it has indicated that in certain circumstances, there may be compelling reasons for a manufacturer to depart from these baseline requirements. In such cases, a more flexible approach could allow the initial requirements for substantial evidence of efficacy and safety to be counterbalanced against other contextual benefit–

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<sup>263</sup> Health Canada, *Vigilance Framework*, *supra* note 247 at 7.

<sup>264</sup> Health Canada, “Drug and Health Products: Background” (11 April 2007), online: HC <[www.hc-sc.gc.ca/dhp-mps/homologation-licensing/info-renseign/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/info-renseign/index-eng.php)>. See also Health Canada, *Blueprint for Renewal: Transforming Canada’s Approach to Regulating Health Products and Food* (October 2006), online: Government of Canada Publications (archived) <[http://publications.gc.ca/collections/collection\\_2014/sc-hc/H164-173-2006-eng.pdf](http://publications.gc.ca/collections/collection_2014/sc-hc/H164-173-2006-eng.pdf)>.

<sup>265</sup> Health Canada, “Health Products & Food Regulatory Modernization: Initial Development” (30 May 2012), online: HC <[www.hc-sc.gc.ca/ahc-asc/activit/strateg/mod/ini/index-eng.php](http://www.hc-sc.gc.ca/ahc-asc/activit/strateg/mod/ini/index-eng.php)>. Similarly, the FDA has acknowledged that the science of safety spans the entire life cycle of a product and that “safety signals generated at any point in the process will robustly inform regulatory decision making”: FDA, *Future of Drug Safety*, *supra* note 261 at 3.

risk considerations.<sup>266</sup> Essentially, under this flexible approach, initial authorization would require a favourable evidence-based benefit–risk profile for the drug’s use under the proposed conditions. Subsequently, in order to maintain market authorization, the drug product would have to continue to show a favourable benefit–risk profile for the authorized conditions of use through the product’s life cycle.<sup>267</sup> The flexible approach under the progressive licensing framework is in many ways an expansion and codification of the existing NOC/c policy, which would likely itself become obsolete if the proposed reforms were adopted.<sup>268</sup>

The life-cycle approach gives regulators the flexibility to allow some level of access to drugs that may be severely needed, but for which the evidence may not be very robust. In an ideal world, shifting more focus towards post-market surveillance and evidence generation may mitigate the risks that often go along with granting earlier access to drugs that have reduced evidence profiles.<sup>269</sup> There are many different ways to stratify rights associated with phased approval and provide manufacturers with incentive to conduct further research. The ability to impose the obligation to conduct further studies on the drug is particularly important, especially where there has been significant variation in treatment response.

When drugs are approved based on a reduced evidence profile, the expansion of pharmacovigilance is in our view an essential element to counterbalancing the increased uncertainty around the safety and efficacy of the drug after market entry. Pharmacovigilance has traditionally only been implemented after a drug has entered the market, and usually only after

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<sup>266</sup> Health Canada, “Benefit–Risk Evaluation: A Tiered Approach to an Enhanced Scope for Safety, Efficacy, and Quality Evidence” (archived 24 June 2014), online: HC <[www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/evaluation-eng.php#bm01](http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/evaluation-eng.php#bm01)> [Health Canada, “Benefit–Risk Evaluation”].

<sup>267</sup> *Ibid.*

<sup>268</sup> This observation was made by one of the stakeholders during qualitative interviews.

<sup>269</sup> During qualitative interviews, several stakeholders looked favourably upon the ability to impose more post-market obligations on pharmaceutical companies under the proposed progressive licensing framework. This was seen as an advantage over the current focus of the drug regulatory system on pre-market activities and relatively weak regulatory oversight during the post-market phase.

safety concerns have been identified.<sup>270</sup> It also has traditionally received less attention and less funding in the drug regulatory system, which has so far invested more heavily in pre-market review and approval. However, under the life-cycle model, pharmacovigilance may be incorporated at an early stage in drug development to improve risk management and allow for the earlier detection of adverse reactions.<sup>271</sup> The process of ongoing assessment also provides a mechanism for ensuring that drug labelling is up to date.

Health Canada notes that the life-cycle approach may be particularly well suited to the development of drugs for niche markets, such as drugs that treat rare diseases or potential breakthrough drugs for the treatment of cancers. Since such special drugs are developed to meet extraordinary needs, “[b]y their very nature, limited or no human clinical information may have been generated for these drugs.”<sup>272</sup> Consequently, the benefits and risks of such drugs may need to be assessed through the collection and analysis of data obtained from their use in the real world (i.e., outside of clinical trials); evolving information is important to their regulation.<sup>273</sup> Further, where there is an extraordinary need for a drug, a manufacturer may opt for the more flexible approach to initial authorization since “the potential benefits of bringing the drug to market are deemed to outweigh the relatively increased uncertainty regarding the safety and efficacy.”<sup>274</sup>

Pharmacogenomic therapies, in particular, may appear to be a natural fit for the life-cycle approach since genetic diagnostic testing could be used to identify those specific patient populations that are most likely to respond to a drug and are consequently the best candidates to receive initial access to it. Subsequent pharmacogenomic data collected during the post-market phase

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<sup>270</sup> Historically, the drug regulatory system has focused on pre-market activities. Further regulatory review or action by Health Canada during the post-market phase has typically only been triggered once safety concerns have arisen about a particular drug product. See Health Canada, “Brief History”, *supra* note 237.

<sup>271</sup> For example, beginning at the pre-market development stage, the information required for a new Clinical Trial Application could be expanded to include the manufacturer’s complete plan for development of the drug. See Health Canada, “Life-Cycle Management” (11 April 2007), online: HC <[www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/life-cycle-vie-eng.php](http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/life-cycle-vie-eng.php)>.

<sup>272</sup> *Ibid.*

<sup>273</sup> *Ibid.*

<sup>274</sup> Health Canada, “Benefit–Risk Evaluation”, *supra* note 266.

can help refine our understanding of drug response; as more evidence is generated about which specific patient populations may benefit from drug treatment or which may be at particular risk, the approved population base may be incrementally expanded or restricted. This strategy may also work well for the validation of companion diagnostics, as the clinical utility of a new test is generally not fully established until employed in wide clinical use.<sup>275</sup>

While the life-cycle approach offers a number of important improvements to the drug approval system, perhaps most importantly with regard to improving post-marketing surveillance and reporting obligations, certain aspects of the framework remain controversial. This framework will, after all, be implemented in a specific economic, social, and regulatory context in which there are huge financial pressures to get pharmaceutical products quickly onto the market, in which patient vulnerabilities can easily be exploited, and in which government agencies are relatively underfunded and subject to various political and economic pressures. There is still significant debate around what level of evidence should be required before allowing a drug to enter the market and whether the risk of allowing earlier access to important drugs can be counterbalanced by enhanced post-market obligations. A serious concern is that enhancing surveillance and evidence generation during the post-market phase may come at the expense of sufficient evidence generation during pre-market clinical trials. This increased focus on the post-market phase may be perceived to reduce the robustness of pre-market evaluations, with the exploration of important questions about drug safety and efficacy delayed until after the drug enters the market.<sup>276</sup> Bouchard and Sawicka, for example, caution that the focus of the life-cycle approach “will be on industrial development rather than public protection, including a continued preference for access, faster review times, private

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<sup>275</sup> Requiring diagnostic test developers to demonstrate clinical utility may be cost-prohibitive unless there is more certainty around intellectual property protection and reimbursement for the diagnostic test. Evans suggests that tests could be initially approved based on their analytical validity, while their clinical validity and clinical utility could be further established through post-market studies. See Evans, “What Will It Take?”, *supra* note 208.

<sup>276</sup> Again, a common area of concern expressed by stakeholders during qualitative interviews was the potential for progressive licensing to lead to an erosion of safety and efficacy standards at the point of market entry. The general consensus was that expanded post-market commitment should not be introduced at the expense of rigorous pre-market evaluation.

[intellectual property] rights, and minimal post-marketing obligations.<sup>277</sup> Further, earlier market entry increases the risk of later having to withdraw the drug from the market. Even when only a few patients may have benefited (or at least believe themselves to have benefited), withdrawal tends to be psychologically and politically more problematic than delaying the entry of a new drug into the market in the first place.<sup>278</sup> The significant political and financial power of the pharmaceutical industry must be taken into consideration when assessing the likelihood that regulators will be able to act decisively in this context. Another important question is how to fully disclose to patients the level of uncertainty and the risks involved when a drug is approved under the flexible approach.<sup>279</sup>

Given Health Canada's current lack of enforcement efforts for existing post-market requirements, relying more heavily on post-market surveillance will be problematic without truly significant reforms to the way that post-market monitoring is conducted and without significant and ongoing political commitment to strengthen and invest in the regulatory system. If Health Canada does not have the resources or political will to enforce the existing, more limited post-marketing commitments, this raises serious questions about whether they will be able to properly administer and enforce the more expansive post-marketing commitments under the life cycle approach. Such problems are already evident under Health Canada's existing NOC/c process, where required conditions can take many years to be fulfilled and there is a lack of transparency. Another potential hurdle is setting up the procedures and infrastructure for data collection, including determining how data will be collected and used and by which parties. Any efforts to increase the level of post-market evidence generation under the life-cycle approach must be coupled with effective systems to quickly and accurately communicate the results of such surveillance, in order to stimulate proper use of the drug and allow the regulator to modify drug labelling or restrict use, when necessary.<sup>280</sup>

Whether or not the pharmaceutical industry looks favourably upon a shift towards the life-cycle approach will likely turn on how such a regu-

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<sup>277</sup> Bouchard & Sawicka, *supra* note 156 at 80.

<sup>278</sup> FDA, *Future of Drug Safety*, *supra* note 261 at 3.

<sup>279</sup> This observation was made by a stakeholder during qualitative interviews.

<sup>280</sup> Another shared area of concern among many stakeholders related to enforcement under a progressive licensing framework. Significant concerns were

latory framework is structured – in particular, on the balance of the advantages that can potentially be gained from earlier market access versus the greater obligations that may be imposed on sponsors as a condition of market approval. On the one hand, industry is likely to be in favour of any regulatory reforms that offer a way to get new drugs to market faster.<sup>281</sup> The life-cycle approach also offers the practical advantage of allowing an initial licence based on the evidence available at the time of approval, with amendments made as experience with the drug is gained.<sup>282</sup> Many sponsors already voluntarily choose to submit certain drugs for approval under the existing NOC/c process (and similar conditional approval procedures in other jurisdictions). In these cases, the sponsor obviously considers the earlier market access gained through these alternative approval methods to be worth undertaking the additional obligations that are imposed as a condition of the licence.

On the other hand, industry will likely be wary of a shift towards the life-cycle approach if they view approvals under the new system as being too provisional or coming with too many strings attached. Industry may also use its political clout to oppose extending regulatory oversight into the post-market phase, which may be seen as drawing out the already lengthy approval process.<sup>283</sup> Pharmaceutical companies will likely advocate for the

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raised, in particular, about the lack of infrastructure for post-market surveillance, a lack of transparency during post-market activities, and a lack of resources and political will to enforce new post-market regulations. As one stakeholder noted, effective post-market surveillance requires not only more monitoring, but also effective policing to ensure that surveillance commitments are being met and that when problems are flagged in the system, there is a fast and effective response to send out warnings and, when necessary, withdraw drugs from the market.

<sup>281</sup> This observation was made by a stakeholder during qualitative interviews.

<sup>282</sup> One industry stakeholder, in particular, was very much in favour of progressive licensing and commented that until we start using the drug in the real world, we cannot truly know what it actually does.

<sup>283</sup> One industry stakeholder expressed concern that a progressive licensing framework would result in primarily placing further restrictions on a drug, rather than providing a framework for expanding the use of a product. For manufacturers, the progressive licensing framework requires greater commitments and investment in post-market monitoring and clinical studies. This stakeholder stressed the importance of ensuring that post-market surveillance activities collect effectiveness data in the same rigorous manner in which safety data is col-

need for more regulatory certainty before making significant investments in the development of new drug products.<sup>284</sup> Approving drugs on less certain pre-market data could also potentially open the pharmaceutical industry up to more liability: the more uncertain the safety and efficacy of the drug at market entry, the more likely that patients may be injured by the drug and seek legal action against the manufacturer;<sup>285</sup> the likelihood is also higher in such a case that a drug may later need to be withdrawn from the market.

In April 2008, many of the proposed amendments to the *Food and Drugs Act* outlined in the Progressive Licensing Project were tabled as Bill C-51 in the House of Commons.<sup>286</sup> Bill C-51 also introduced a number of amendments to other aspects of the regulatory system, including the creation of new offences, substantial increases in available penalties, the expansion of the power of inspectors, new administrative and enforcement measures, and changes to the regulation of natural health products. In the weeks following the introduction of Bill C-51, significant concerns about the scope and intent of the bill were raised in Parliament, in the media, and by many outspoken members of the public.<sup>287</sup> Ultimately, Bill C-51 never passed second reading and died on the order sheet when Parliament was dissolved in September 2008 prior to the federal election in October. Although reform efforts are ongoing, the amendments proposed in Bill C-51 in 2008 have not yet been

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lected. (The stakeholder stated, “If we have a commitment for increased investment, there has to be an opportunity for increased payback.”) In other words, in this stakeholder’s opinion, if post-market surveillance is to accurately reflect the risk–benefit ratio of the drug product, equal attention has to be paid to collecting both safety and effectiveness data.

<sup>284</sup> This observation was made by a stakeholder during qualitative interviews.

<sup>285</sup> However, as noted by one stakeholder, the strength of this effect will likely be less pronounced in Canada than in the US due to the significantly lower level of pharmaceutical liability and class action cases in the former.

<sup>286</sup> Bill C-51, *An Act to amend the Food and Drugs Act and to make consequential amendment to other Acts*, 2nd Sess, 39th Parl, 2008.

<sup>287</sup> One of the most hotly contested aspects of Bill C-51 was in fact the proposed changes to the regulation of natural health products, which many people believed would result in natural health products being subject to the same licensing requirements as pharmaceutical drugs – an allegation that the federal government denied. Other concerns about the bill included the beliefs that the search and seizure powers included in the bill were too broad and that the increased penalties for violating the *Act* or its regulations were excessive. See *ibid.*

reintroduced in Parliament.<sup>288</sup> However, the pharmacovigilance framework released by Health Canada in September 2012 emphasized the agency's efforts to move towards a "proactive, lifecycle approach" to regulating all health products.<sup>289</sup> The document indicated that "Health Canada has initiated discussions with stakeholders on new legislative and regulatory instruments with the aim of providing more flexibility, consistency, continuity and accountability in the approach to regulating [health] products."<sup>290</sup> As noted above, the expansion of post-market regulatory authority and the increased penalty provisions set out in *Vanessa's Law* are also important elements of ongoing regulatory reform.

In December 2012, the Canadian government released an *Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework*. In this document, the Government outlined their plans to develop a policy to incentivize research into drugs for the treatment of rare diseases, sometimes referred to as "orphan drugs" because these markets have historically been neglected by drug developers. Many of the principles of the life-cycle approach originally outlined in the Progressive Licensing Project are reflected in the orphan drug framework: the stated objective of the proposal is to "manage the benefits, harms and uncertainties by considering the nature, intended use and exposure of orphan drugs throughout the life-cycle."<sup>291</sup> Moreover, the framework explicitly states that "the life-cycle concepts first introduced in this regulatory framework will drive all other modernization efforts for drugs and medical devices that will follow."<sup>292</sup> Overall, Health Canada views orphan drug markets as a good starting point for introducing the life-cycle approach due to "the limited information that may be

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<sup>288</sup> One regulatory stakeholder indicated that Health Canada has moved away from the "progressive licensing" terminology since the death of Bill C-51.

<sup>289</sup> Health Canada, *Vigilance Framework*, *supra* note 247 at 3.

<sup>290</sup> *Ibid* at 8.

<sup>291</sup> Health Canada, Office of Legislative and Regulatory Modernization, *Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework* (13 December 2012) at 6, online: Orpha.net <[www.orpha.net/national/data/CA-EN/www/uploads/Initial-Draft-Discussion-Document-for-A-Canadian-Orphan-Drug--Regulatory-Framework.doc](http://www.orpha.net/national/data/CA-EN/www/uploads/Initial-Draft-Discussion-Document-for-A-Canadian-Orphan-Drug--Regulatory-Framework.doc)>.

<sup>292</sup> The draft orphan drug framework is described as an early deliverable of Health Canada's modernization effort entitled *Regulatory Roadmap for Health Product and Food*, which builds on earlier initiatives including the Progressive Licensing Project. See *ibid* at 6.

available and the need to retrieve more once the drug is on the market.”<sup>293</sup> As many pharmacogenomic drugs have already been granted orphan drug status under the American and European orphan drug policies, the introduction of the life-cycle approach under the proposed Canadian framework will likely have an important impact on the way that many pharmacogenomic products are approved.

### ***B. The role of health technology assessment***

As a final point, it is worth noting that gaining market authorization for new health technologies is only the first step towards market adoption. Following regulatory approval, health technologies must go through evidence-based and economic analysis to demonstrate that the technology meets the needs of the health care system – a process known broadly as health technology assessment (HTA). Conventionally, drug products and diagnostic devices have undergone separate HTA processes. As with regulatory decisions, the pharmacogenomic context may complicate HTA because the therapy requires consideration of both a drug and a test component. Pharmacogenomic products may thus pose a challenge to HTA bodies that must attempt to join the evidence from these two different processes into an overall recommendation.

As each of the provincial and territorial governments is responsible for funding a substantial portion of prescription drugs through hospital funding and public drug programs, each jurisdiction has its own assessment procedures for determining which drugs will be funded through the public system.<sup>294</sup> Further, each of the provinces maintains its own formulary of health technologies that are funded under the public system, and therefore coverage decisions may vary between provinces, which may lead to unequal access

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<sup>293</sup> *Ibid* at 4.

<sup>294</sup> Nearly half of prescription drug expenditures in Canada are covered by the public sector, the vast majority of which come from provincial and territorial governments. In particular, the Canadian Institute for Health Information estimates that in 2012, private sector sources accounted for 55.5% of prescription drug expenditures in Canada, while public sector funding accounted for the remaining 44.5%. See Canadian Institute for Health Information, *Drug Expenditure in Canada, 1985 to 2012* (2013) at iii, online: Government of Canada <[http://publications.gc.ca/collections/collection\\_2013/icis-cihi/H115-27-2012-eng.pdf](http://publications.gc.ca/collections/collection_2013/icis-cihi/H115-27-2012-eng.pdf)>.

across Canada.<sup>295</sup> While funders vary in their evaluation and coverage decisions between jurisdictions, a common trend across provinces has been an increasing reliance on provincial HTA units or independent HTA organizations to inform coverage decisions. The largest producer of HTA in Canada is the Canadian Agency for Drugs and Technology in Health (CADTH), a national, independent body funded by the provincial, territorial, and federal governments that carries out assessments on health technologies deemed to be of national interest, including medical devices, systems, and drugs.<sup>296</sup>

On the pharmaceutical side, there has been a strong movement to improve the efficiency and consistency of HTA for drug products across Canada. Most significantly, the Common Drug Review (CDR) program administered by CADTH was established as “a pan-Canadian process for conducting objective, rigorous reviews of the clinical effectiveness and cost-effectiveness, as well as reviews of patient input for drugs and providing formulary listing recommendations to Canada’s publicly funded drug plans, excluding that of Québec.”<sup>297</sup> The CDR aims to “reduce duplication of reviews by jurisdictions[,] provide equal access to timely, evidence-based information and expert advice[, and] consolidate the submission filing process for pharmaceutical manufacturers.”<sup>298</sup> However, although the information and recommendations provided by the CDR hold significant influence with health care decision makers, the decision to list a given drug or not ultimate-

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<sup>295</sup> During qualitative interviews, the potential for disparity in coverage decisions between provinces represented a concern for several stakeholders, as it may lead to a sense of inequality. One stakeholder noted that on one hand, the decision by one province to reimburse a particular health technology or to offer broader conditions of coverage may increase pressure on other provinces to extend coverage as well. However, in other cases, provinces may instead bide their time and wait to see the results of funding decisions in other provinces before making their own coverage decisions.

<sup>296</sup> Devidas Menon & Tania Stafinski, “Health Technology Assessment in Canada: 20 Years Strong?” (2009) 12:S2 Value Health S14 at S14. A couple of stakeholders interviewed for the qualitative study argued that in comparison to government bodies, independent HTA organizations are arguably freer from political considerations and thus better able to make neutral and objective health technology funding decisions.

<sup>297</sup> See Canadian Association for Drugs and Technology in Health, “About the Common Drug Review”, online: CADTH <[www.cadth.ca/en/products/cdr/cdr-overview](http://www.cadth.ca/en/products/cdr/cdr-overview)>.

<sup>298</sup> *Ibid.*

ly lies with each provincial drug plan and may be influenced by other factors such as the plan's mandate, the jurisdictional priorities, and financial resources. In addition, since many pharmacogenomic drugs currently approved for the Canadian market are used for the treatment of cancer, many of these drugs are subject to a separate interprovincial review process through the pan-Canadian Oncology Drug Review (pCODR), which is a partner organization of CADTH.<sup>299</sup>

For the pharmaceutical component, the CDR and pCODR serve as flagship examples of provincial cooperation in HTA. Indeed, the concordance between CDR recommendations and provincial formulary uptake is quite high.<sup>300</sup> However, on the non-drug side, HTA initiatives have been much more fragmented between the provinces. In the majority of cases, the analysis of evidence for non-drug technologies is performed in each province, and the standards for test approval differ among them.<sup>301</sup> Some provinces have invested much more heavily in HTA than others; in particular, Alberta, Ontario, and Québec have made considerable investments in HTA initiatives

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<sup>299</sup> pCODR was established in 2010 by Canada's provincial and territorial Ministries of Health (except Québec) to assess cancer drug therapies and make recommendations to guide drug coverage decisions. pCODR aims to streamline the national cancer review process through evidence-based decision making. Pan-Canadian Oncology Drug Review, "About pCODR", online: pCODR <[www.pcodr.ca/wcpc/portal/Home/AboutCODR/GuidingPrinciples](http://www.pcodr.ca/wcpc/portal/Home/AboutCODR/GuidingPrinciples)>.

<sup>300</sup> According to CADTH, the participating drug plans across Canada conform with CDR recommendations about 90% of the time. However, a 2011 study by Attaran and colleagues concluded that the actual rate of agreement with CDR recommendations was 65%. See Amir Attaran, Rosario Cartagena & Andree Taylor, "The Effectiveness of the Common Drug Review in Canada's National Drug Strategy", *Atlantic Institute for Market Studies* (December 2011) at 1, online: AIMS <[www.aims.ca/site/media/aims/Final%20-%20The%20Effectiveness%20of%20the%20Common%20Drug%20Review%20in%20Canada's%20National%20Drug%20Strategy.pdf](http://www.aims.ca/site/media/aims/Final%20-%20The%20Effectiveness%20of%20the%20Common%20Drug%20Review%20in%20Canada's%20National%20Drug%20Strategy.pdf)>.

<sup>301</sup> This observation was made by two stakeholders during qualitative interviews. One stakeholder further noted that one reason for redundant HTA in each province is that unlike drugs, non-drug technologies are much more dependent on health care infrastructure, which is different in each province; while a drug may only require a prescription to be dispensed, non-drug technologies may involve, for example, hospital infrastructure, operating room or emergency room time, physician reimbursement, or human resource implications or training. Consequently, the provinces are nervous about non-drug technologies being approved by another jurisdiction or at the national level.

designed to meet their specific needs.<sup>302</sup> Further, some provinces have been more active than others in assessing pharmacogenomic tests. For example, the Ontario Health Technology Advisory Committee (OHTAC)<sup>303</sup> has been active in establishing “a preliminary list of emerging pharmacogenomic tests and scan[ning] the pharmacogenetic horizon to recommend priorities for health technology assessment.”<sup>304</sup> The OHTAC assessments contribute valuable evaluations of pharmacogenomic tests, but since OHTAC is specifically an Ontario initiative, its evaluations do not lead to any standardization across provinces. This uneven investment in HTA may create the potential for greater divergence in review of non-drug technologies between Canadian jurisdictions.

While CADTH is also involved in assessing non-drug technologies, only select technologies are reviewed; the process is much less comprehensive than drug evaluations under the CDR and pCODR. Within CADTH, the Health Technology Expert Review Panel is tasked with developing “guidance and/or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system,”<sup>305</sup> which

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<sup>302</sup> Menon & Stafinski, *supra* note 296 at S15.

<sup>303</sup> In Ontario, the OHTAC is an arms-length expert committee that performs health technology assessments and makes recommendations to the Ministry of Health and Long-Term Care and other health care system authorities on a wide range of clinical procedures, devices, and equipment, including diagnostic medical devices and laboratory tests. See Health Quality Ontario, “Ontario Health Technology Advisory Committee Information Sheet” [nd], online: HQO <[www.hqontario.ca/en/ohtac/pdf/ohtac\\_info\\_sheet.pdf](http://www.hqontario.ca/en/ohtac/pdf/ohtac_info_sheet.pdf)>.

<sup>304</sup> See Ontario Health Technology Advisory Committee, “OHTAC Recommendation: Emerging Pharmacogenomic Tests” (June 2011), online: Health Quality Ontario <[www.hqontario.ca/Portals/0/Documents/eds/recommendation-horizon-scan-110620.pdf](http://www.hqontario.ca/Portals/0/Documents/eds/recommendation-horizon-scan-110620.pdf)>.

<sup>305</sup> CADTH notes that:

[t]he approach of the Panel is evidence based and uses a multi-criteria framework that considers the strength and quality of available clinical evidence, the strength and quality of available economic information, current practices and resource utilization patterns, and other factors including, but not limited to, patient input and practical, ethical, environmental, and psychosocial considerations.”

Canadian Association for Drugs and Technology in Health, “Health Technology Expert Review Panel”, online: CADTH <[www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel](http://www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel)>.

includes the review of diagnostic tests and medical devices. However, due to the sheer volume of health care technologies, CADTH only reviews those technologies that are identified as being the highest priority from a national perspective. Thus, only a handful of non-drug technologies undergo formal review.<sup>306</sup>

Ultimately, access to a pharmacogenomic product depends on funding authorities providing reimbursement for both the drug and test components; the inability to access the diagnostic test may prevent a patient from being offered the associated drug product. As with regulatory review, to properly assess pharmacogenomic products, there needs to be a coordinated effort by HTA bodies to consider both the drug and the test together.<sup>307</sup> However, at present, HTA for the drug and test components may be split between CADTH, pCODR, and provincial HTA bodies. While CADTH may not currently have the capacity to comprehensively evaluate all non-drug technologies, companion diagnostic tests for pharmacogenomic products should be considered as part of review of the drug component under the CDR or pCODR. A positive development on this front is that CADTH recently launched an environmental scan to gain more insight into the impact of companion diagnostics in guiding clinical use of pharmaceutical products. The objective of the project is “to provide an overview of the current and projected use of companion diagnostic tests required for the prescription of targeted drug therapies, as well as the regulatory and reimbursement processes for these devices and drugs, both nationally and internationally.”<sup>308</sup> Ultimately, given the success of pCODR and the CDR in unifying HTA review for drug products, if this HTA process is expanded to include an assessment of companion diagnostics for pharmacogenomic therapies, the interprovincial drug review process could serve as an additional mechanism to ensure that the combination of the pharmacogenomic drug and companion diagnostic is safe and effective.

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<sup>306</sup> Menon & Stafinski, *supra* note 296 at S14. In contrast, all new drugs (i.e., those recently approved by Health Canada that are not yet funded under public drug plans) are reviewed under the CDR, which brings about a high degree of concordance among provinces in their drug coverage decisions.

<sup>307</sup> This observation was made by several stakeholders during qualitative interviews. Having separate bodies assess the drug and test components of the pharmacogenomic product was viewed by these stakeholders as problematic.

<sup>308</sup> Canadian Association for Drugs and Technology in Health, “Pharmaceuticals Requiring Companion Diagnostics”, online: Wayback Machine Internet Archive <<https://web.archive.org/web/20141017224206/www.cadth.ca/products/environmental-scanning/environmental-scans/es0289>>.

## V. RECOMMENDATIONS

As noted earlier, the adoption of pharmacogenomics depends on a two-way process in which regulators adapt the regulatory system in response to new technologies and industry adapts its development and evidence-generation models based on guidance from regulators. To date, Canadian regulatory authorities have not played a very active role in this process. Rather, most of this exchange has occurred south of the border, where the FDA has taken a strong leadership role in shaping the adoption of pharmacogenomics. While Health Canada has released only a single guidance document on the treatment of pharmacogenomic products within the existing regulatory system, in contrast, the FDA has engaged extensively with industry on how to adapt regulatory processes to incorporate pharmacogenomic information, issuing numerous guidance documents (both in final and draft form) to outline their current and proposed approaches to addressing the evolving pharmacogenomic context.<sup>309</sup>

Nonetheless, it is important to recognize the differing mandates and resource constraints of Health Canada and the FDA. Naturally, given the population differences between the US and Canada, the FDA is a much larger organization – with a correspondingly larger budget and resource base – than Health Canada. The FDA has committed significant resources to pioneering the field of pharmacogenomics, whereas Health Canada has not. Health Canada may also be restricted by the scope of its mandate since legislators have been slow to modernize the Canadian drug regulatory system and grant Health Canada more powers of oversight, particularly over post-market activities. For example, while the FDA has had the ability to require manufacturers to conduct post-market studies since 2007, similar powers have only just been granted to Health Canada with the passage of *Vanessa's Law* in November 2014. In the absence of a clear mandate prior to this point, Health Canada may have been reluctant to issue clear guidance in areas that require post-marketing surveillance authority.

Properly addressing the new opportunities and challenges of the pharmacogenomic context will require deeper, more concrete reforms to the regulatory system than those that Health Canada has promoted to date. Following

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<sup>309</sup> The FDA has compiled a list of 22 guidance documents that relate to various aspects of personalized medicine. See US, Food and Drug Administration, “Select FDA Guidance Documents that Relate to Personalized Medicine” (31 July 2014), online: FDA <[www.fda.gov/ScienceResearch/SpecialTopics/PersonalizedMedicine/ucm372544.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/PersonalizedMedicine/ucm372544.htm)>.

the lead of the FDA, further guidance and policy development is particularly needed to clarify uncertainty around the coordination in the review of drugs and companion diagnostics, ensure the quality and robustness of evidence used to support the approval of pharmacogenomic therapies, improve post-market surveillance and risk-management planning, and make the regulatory system more responsive to evolving information about the safety and efficacy of pharmacogenomic therapies. However, Health Canada cannot work alone: the cooperation of provincial authorities will be required to help harmonize the standards for diagnostic testing and to ensure that drugs and companion diagnostics are effectively reviewed through HTA procedures once the drug product and companion diagnostic are approved for the Canadian market. As a result of the distribution of jurisdictional power in the context of health care-related regulations and the risk of constitutional challenges, there can be a tendency in the Canadian context to leave a lot of room for “soft governance” or industry self-regulation.<sup>310</sup> With respect to pharmacogenomics, strict standard setting and enforcement for both the drugs and the diagnostic tests appears essential to ensure product safety and effectiveness. Both federal and provincial agencies have to engage in the development of appropriate regulatory tools, identifying clear requirements and introducing firm regulatory tools to ensure compliance.

#### ***A. Better harmonization of diagnostic testing standards***

While the lack of harmonization of diagnostic testing standards is a broad issue, it warrants specific consideration in the pharmacogenomic context because, first, proper assessment of the safety and efficacy of the drug component depends on the quality and accuracy of the diagnostic test and, second, access to the drug component may hinge on the availability of the companion diagnostic in a given jurisdiction. Whereas the FDA recently announced that it will soon be enforcing its jurisdiction over LDTs, Health Canada will continue to be restricted in its authority over diagnostic testing due to the constitutional division of powers that grants the provinces authority over most aspects of laboratory testing. This makes it much more challenging to ensure consistent standards for the regulation of diagnostic testing across Canada.

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<sup>310</sup> A good example related to drug regulation is the variable levels of provincial regulation related to research ethics review, with some provinces relying largely on institutional and industry self-regulation, other provinces using the powers of professional medical colleges to regulate research in the private sector, and still other provinces enacting a legislative framework.

Even with this jurisdictional split, there are opportunities for harmonization, such as through a more nationalized accreditation system or an interprovincial organization to coordinate reference standards. A particular point of concern is the lack of requirements around clinical validity in laboratory testing. Improving the coordination of diagnostic testing standards could lead to more consistency in the quality and availability of diagnostic testing across Canada, including requiring all diagnostic tests to meet standards of clinical validity regardless of how they are performed. Moreover, interjurisdictional coordination would help ensure that stakeholders in all jurisdictions, including federal drug regulatory authorities, have access to the best and most recent data on pharmacogenomic testing. As mentioned above, any soft-law-based mechanism of coordination has to be accompanied by provincial regulatory powers that enable strict enforcement of standards.

### ***B. Better coordination in the review of drug and test components***

As noted throughout this paper, the companion diagnostic test is essential for the safe and effective use of the drug component, and thus a proper assessment of the pharmacogenomic therapy depends on the two components being assessed in relation to one another. As such, regulatory authorities should put in place procedures that allow for some level of coordination between those responsible for the approval of the diagnostic test and those responsible for the approval of the pharmaceutical component. At the federal level, it is currently unclear to what extent the Medical Devices Bureau and the Therapeutic Products Directorate consult with one another when assessing an associated drug and *in vitro* diagnostic device for a pharmacogenomic product, other than the fact that representatives from both departments may be present at a pre-submission consultation. Although co-development of the drug product and companion diagnostic occurs only in a minority of cases, regulatory processes should facilitate this development route whenever possible. A coordinating body similar to the OCP proposed in the FDA policy on combination products is a potential mechanism for ensuring the effective coordination of the different components of a pharmacogenomic product. Short of a separate unit for coordinating the approval of combination products, simply establishing more formalized procedures for consultation between the relevant regulatory directorates could help to reinforce the importance of reviewing the drug and test components in relation to one another. As a starting point, Canada's rather outdated policy on combination products should be updated to more accurately reflect the modern development of more complex therapies that combine pharmaceutical products and medical devices, including pharmacogenomic products.

Coordinating the review of the drug and test components is even more challenging for LDTs since authority over laboratories is devolved to the provincial level. However, an interprovincial body for quality management in medical laboratories, such as the proposed CCQLM, could serve as the focal point for coordinating the review of pharmacogenomic testing and could interface with the Therapeutic Products Directorate to ensure that both organizations are kept up to date regarding the latest safety and efficacy data for the associated drug and test components. Further, interprovincial cooperation in HTA activities would be an additional layer of assessment that could help to ensure the quality and consistency of review for pharmacogenomic products, including the clinical validity of diagnostic tests. The recent launch by CADTH of an environmental scan to gain more insight into the impact of companion diagnostics in guiding clinical use of pharmaceutical products is a positive sign that the agency may soon be taking on a more central role in coordinating the assessment of both drugs and companion diagnostics for targeted therapies – an important step in ensuring consistency in the safety and efficacy of pharmacogenomic treatments across the country.

### ***C. Clear standards for evidence generation and risk management***

Pharmacogenomic therapies may present a number of evidentiary challenges, not only because they require assessment of both the drug and test component, but also because these treatments often target narrow patient populations with a particular genetic biomarker, which may result in drugs being approved on the basis of smaller, less robust clinical trials. Further, researchers often employ biomarker-based enrichment strategies – where clinical trials are only conducted in patients with a particular biomarker status – which may leave open questions about the use of the drug in broader patient populations and about how to establish diagnostic cut-off points. Further, pharmacogenomic products often treat serious or life-threatening diseases for which few or no alternative treatments are available, which may increase pressure on regulatory authorities to provide earlier access to these drugs, even in the face of uncertainty around their safety and efficacy.<sup>311</sup>

As the pharmaceutical industry turns more attention towards the development of niche market therapies, including pharmacogenomics, there

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<sup>311</sup> For a more detailed discussion of these trends, see Shannon Gibson & Trudo Lemmens, “Niche Markets and Evidence Assessment in Transition: A Critical Review of Proposed Reforms” (2014) 22:2 Med L Rev 200.

will likely be increased utilization of the NOC/c process and other expedited review mechanisms. While there may often be good reason to provide earlier access to promising new therapies that treat serious or life-threatening conditions, there is a need for caution in expanding the approval of drug products based on incomplete evidence – namely, on the basis of surrogate endpoints. Reforms should be considered to improve the transparency of the existing NOC/c process and ensure that the post-market commitments imposed thereby are monitored and enforced. Better control of preclinical data, including through making this data transparent in a way that enables the scientific community to critically engage with the evidence provided, seems crucial in this context.

As reform efforts towards the life-cycle approach continue to increase the emphasis on the post-market phase, care must be taken in weighing demands for earlier access to promising new treatments against the need for robust evidence on safety and efficacy. There is a concern that in the absence of good coordination of the approval systems for both diagnostic tests and drug products, weaknesses in the system with respect to, for example, post-market surveillance and control of off-label prescription may be exploited to get products on the market prematurely and on the basis of limited evidence. Health Canada should continue to develop stricter requirement for risk-management planning, including measures equivalent to REMS that would allow regulators to put firmer restrictions on the ability to prescribe certain drugs without first conducting pharmacogenomic testing. The new provisions in *Vanessa's Law* allowing regulators to attach terms and conditions to market authorizations should give Health Canada the authority it needs to make risk-management measures legally binding and strictly enforceable.

#### ***D. More proactive post-market surveillance***

Rapid advancements in genomics and personalized medicine will require smarter and more flexible regulations that are capable of evolving alongside these developments, and additional mechanisms will be required to effectively coordinate the approval and assessment of the drug and test components of pharmacogenomic therapies both within and across jurisdictions in Canada. Particular consideration should be given to how to promote better evidence generation and regulatory oversight during the post-market phase without weakening the level of evidence required for approval and regulatory review prior to market-entry. The regulatory system should be responsive enough to ensure that important new safety and efficacy data about pharmacogenomic products is reflected in product labelling in a

timely matter. The new provisions in *Vanessa's Law* granting regulatory authorities the power to demand that manufacturers update product labelling are an important step forward in ensuring that drug labelling is up to date. Similarly, Health Canada should expand the existing guidance document on pharmacogenomic information to include more standardized direction on how pharmacogenomic information should be presented in drug labelling, as the FDA has done.

The passage of *Vanessa's Law* represents an important step forward in improving Health Canada's regulatory oversight during the post-market phase. In particular, the newly acquired authority to require sponsors to compile information or conduct additional studies about drug products after market entry and to attach terms and conditions to market authorizations serve as important new forms of oversight that can help ensure that evidence on drug safety and efficacy continues to evolve after market entry. However, the effectiveness of these new provisions will ultimately depend on Health Canada actively exercising and enforcing its new powers – an authority that industry will hopefully take seriously now that this oversight is coupled with the significant increase in available penalties for contraventions of the *Food and Drugs Act* and associated regulations.

### ***E. Improving transparency***

A detailed discussion of the importance of transparency in the context of pharmaceutical regulation exceeds the scope of this article.<sup>312</sup> Yet, it is worth emphasizing in the context of pharmacogenomic drug development that transparency is a necessary, albeit not sufficient, step in ensuring an overall reliable system of drug regulation. The dominant power of industry in the creation of pharmaceutical knowledge throughout the process of drug development, from preclinical data gathering to the reporting of the outcome of clinical studies in scientific journals, makes it essential to exercise tight control over the sharing of data and the reliability of results reporting. The scientific community at large plays an important role in the creation of reliable information on pharmaceuticals through, for example, careful meta-analysis of industry-run clinical trials and evaluation of the relevance

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<sup>312</sup> For a more detailed discussion of the importance of transparency, particularly in the context of post-marketing surveillance, see Lemmens & Gibson, *supra* note 236 at 972-85. See also more generally Trudo Lemmens, "Pharmaceutical Knowledge Governance: A Human Rights Perspective" (2013) 41:1 *JL Med & Ethics* 163 [Lemmens, "Pharmaceutical Knowledge Governance"].

of adverse events. Transparency is also essential to establishing public trust in an accountable drug regulatory structure. The federal government should commit to promoting transparency through the registration of clinical trials, the reporting of results, and the sharing of full clinical study reports. Provincial governments should also ensure the same in the context of the development of diagnostic laboratory testing and all other issues that fall under its jurisdiction.

Information submitted to drug regulatory agencies, whether clinical trials data, adverse event reports, or reports of mishaps in clinical trials or post-marketing, are of direct public health importance. The public also has the right to be informed about how drug regulatory agencies deal with relevant safety and efficacy information. Fortunately, *Vanessa's Law* has introduced a number of important new provisions into the *Food and Drugs Act* aimed at increasing the transparency of the regulatory process, including requirements around public disclosure by the government. In particular, orders requiring a licence holder to provide information to the Minister about a therapeutic product (section 21.1), to change product labelling (section 21.2), to recall a product (section 21.3(a)), to conduct an assessment of a therapeutic product (section 21.31), or to conduct tests or studies of a product (section 21.32), are required to be made publicly accessible.<sup>313</sup> Such requirements of public disclosure will help to ensure that the public and the medical and scientific community is kept up to date regarding any important new information on the safety or efficacy of therapeutic products.

*Vanessa's Law* also contains provisions with respect to the controversial topic of “confidential business information.”<sup>314</sup> These provisions aim at delineating what information submitted to drug regulatory authorities

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<sup>313</sup> *Food and Drugs Act*, *supra* note 19, ss 21.1-21.2, 21.3(a), 21.31-21.32, as amended by *Vanessa's Law*, *supra* note 149, ss 3-4. Further, under the new section 30(1.2) of the *Food and Drugs Act* (as amended by *Vanessa's Law*, s 6(1)), the government may also pass additional regulations requiring the public disclosure of orders or reports.

<sup>314</sup> “Confidential business information” is now defined in section 2 of the *Food and Drugs Act*, *supra* note 19, as amended by *Vanessa's Law*, *supra* note 149, s 2(3), as:

... business information

(a) that is not publicly available,

(b) in respect of which the person has taken measures that are reasonable in the circumstances to ensure that it remains not

may be disclosed by the Minister, even when pharmaceutical companies invoke a claim that the specified information is confidential business information.<sup>315</sup> While the explicit prioritization of public health interests over business interests is positive, it is unfortunate that *Vanessa's Law* does not explicitly limit the use of the concept of confidential business information itself. The pharmaceutical industry is increasingly using concepts such as confidential business information or trade secrets to try to create an additional legal buffer against the obligatory sharing of clinical trials data.<sup>316</sup> *Vanessa's Law* nevertheless includes an interesting provision that may allow the government to correct this significant limit on the proposed transparency rules: it has created a new section 30(1.2)(d.1) of the *Food and Drugs Act*,<sup>317</sup> which grants the government the power to pass regulations setting out what does not constitute confidential business information under the *Act* or the

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publicly available, and

(c) that has actual or potential economic value to the person or their competitors because it is not publicly available and its disclosure would result in a material financial loss to the person or a material financial gain to their competitors.

<sup>315</sup> Under the new section 21.1 of the *Food and Drugs Act*, *supra* note 19, as amended by *Vanessa's Law*, *supra* note 149, s 3, where “the Minister believes that a therapeutic product may present a serious risk of injury to human health, the Minister may order a person to provide the Minister with information that is in the person’s control” or “may disclose confidential business information about a therapeutic product without notifying the person to whose business or affairs the information relates or obtaining their consent.”

<sup>316</sup> Trudo Lemmens, “EMA’s Proposed Data Release Policy: Promoting Transparency or Expanding Pharma Control over Data?”, *PLoS Medical Journals’ Community Blog* (30 May 2014), online: PLOS <<http://blogs.plos.org/speakingofmedicine/2014/05/30/emas-new-data-release-policy-promoting-transparency-expanding-pharma-control-data/>>. Most recently, in the context of ongoing efforts to promote far-reaching transparency of clinical trials data in Europe, industry even appears to have pushed the EMA to propose contractual recognition of clinical trials data as “confidential business information” in documents that would have to be signed by researchers who request access to data for public health associated research purposes. For a discussion of the controversy surrounding these initiatives, see Tania Rabesandratana, “Researchers slam transparency ‘U-turn’ at E.U. Medicines Agency”, *Science Insider* (19 May 2014), online: SI <[news.sciencemag.org/europe/2014/05/researchers-slam-transparency-u-turn-e.u.-medicines-agency/](http://news.sciencemag.org/europe/2014/05/researchers-slam-transparency-u-turn-e.u.-medicines-agency/)>.

<sup>317</sup> *Vanessa's Law*, *supra* note 149, s 6(1), amending *Food and Drugs Act*, *supra* note 19, s 30(1.2)(d.1).

circumstances under which business information ceases to be considered confidential. Although we would have preferred to see this established in the new statute, the regulatory power resulting from this provision could be used to firmly establish a principle that clinical trials data and clinical study reports submitted in the context of drug regulatory approval should not be considered confidential business information. We recommend that such regulations be developed as quickly as possible. As has been argued,<sup>318</sup> in our view convincingly, there are strong reasons to characterize clinical trials data as “public goods.” Sharing of data should be the rule, and governmental agencies should not have to provide strong evidence that sharing of data is necessary to prevent “serious risk of injury to human health.”<sup>319</sup> Even seemingly trivial data or small adverse-event reports can, when combined with other information or put together in the context of critical independent analysis, turn out to be important information that indicates an issue to be addressed.<sup>320</sup> As the history of data sharing in Canada and Europe shows, requiring governments to specify why sharing is necessary risks undermining transparency. Enabling data sharing with the wider scientific community and other regulatory agencies is essential to promoting drug safety and effectiveness.

In relation to this concept of data sharing, it is also important to mention that *Vanessa's Law* includes a provision that allows the Minister to disclose confidential business information to other governments (including provincial and foreign governments and international organizations of states)<sup>321</sup> or

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<sup>318</sup> See Jerome H Reichman, “Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case for a Public Goods Approach” (2009) 13:1 *Marquette Intell Prop L Rev* 1. This argument has also more recently been made by Mark A Rodwin & John D Abramson, “Clinical Trials Data as Public Goods” (2012) 308:9 *JAMA* 871. In earlier publications, we have also supported this notion. See most recently Lemmens & Gibson, *supra* note 236 at 970. See also Lemmens, “Pharmaceutical Knowledge Governance”, *supra* note 312 at 169-70; Trudo Lemmens & Candice Telfer, “Access to Information and the Right to Health: The Human Rights Case for Clinical Trials Transparency” (2012) 38:1 *Am JL & Med* 63 at 89-91.

<sup>319</sup> *Food and Drugs Act*, *supra* note 19, s 21.1, as amended by *Vanessa's Law*, *supra* note 149, s 3.

<sup>320</sup> For further discussion of this issue, with examples showing why extensive data sharing is so important, see Lemmens & Telfer, *supra* note 318 at 91-93.

<sup>321</sup> *Vanessa's Law*, *supra* note 149, s 3, amending *Food and Drugs Act*, *supra* note 19, ss 21.1(3)(a), 21.1(4)(f). An “international organization of states” would

to persons functioning in an advisory role or in the area of health protection or promotion or public safety, “if the purpose of the disclosure is related to the protection or promotion of human health or the safety of the public.”<sup>322</sup> In addition, the new law grants the government the authority to pass regulations requiring authorization holders to provide the Minister with information they hold or receive about risk or label changes that has arisen outside of Canada, and information about “recalls, reassessments and suspensions or revocations of authorizations . . . outside Canada.”<sup>323</sup> The ability to share confidential business information submitted by industry and to compel the reporting of safety information from outside of Canada will allow for greater national and international cooperation in flagging potential safety concerns with drug products and medical devices. This type of cooperation may be particularly important with niche market products, including many pharmacogenomic products, because the number of patients being treated with a particular therapeutic product in one jurisdiction may be limited and identifying potential safety concerns may depend on compiling information from multiple jurisdictions. It is also worth noting in this context that a key focus of the draft Canadian orphan drug framework “will be on international information-sharing and collaboration for the development and regulation of orphan drugs,” which will allow “Canadian scientists and regulators to participate with trusted global counterparts will make better use of scarce resources and benefit Canadian patients.”<sup>324</sup> Overall, Health Canada should work with regulatory authorities in other jurisdictions to ensure that all parties have access to the most recent safety and efficacy data on health products from across jurisdictions and are kept up to date in international best practices.<sup>325</sup>

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presumably include organizations such as the United Nations and World Health Organization.

<sup>322</sup> *Ibid.*

<sup>323</sup> *Vanessa’s Law*, *supra* note 149, s 6(1), amending *Food and Drugs Act*, *supra* note 19, s 30(1.2).

<sup>324</sup> Health Canada, “An Orphan Drug Framework for Health Canada” (3 October 2012), online: HC <[www.hc-sc.gc.ca/ahc-asc/media/nr-cp/\\_2012/2012-147a-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2012/2012-147a-eng.php)>.

<sup>325</sup> The *Food and Drugs Act*, *supra* note 19, s 30.5(1), as amended by *Vanessa’s Law*, *supra* note 149, s 7, now provides that regulations made under the *Act* “may incorporate by reference any document, regardless of its source, either as it exists on a particular date or as it is amended from time to time.” Such a provision will presumably make it easier for Health Canada to incorporate

## CONCLUSION

Overall, the current regulatory framework in Canada is not yet well adapted to the pharmacogenomic context. Striking the right balance between requiring robust evidence on safety and efficacy on a more systematic and ongoing basis and ensuring timely access to promising new therapies is no simple task – it will require not only infrastructure for monitoring and data collection, but also the resources and political will to insist upon compliance with increased post-market commitments. The passage of *Vanessa's Law* marks an important step forward on this front, particularly with regard to increasing Health Canada's authority to mandate post-market studies and in increasing the sanctions available for contravention of the *Food and Drugs Act* and regulations. But these are only first steps, and broader reforms are needed to improve the transparency, reliability, and responsiveness of the regulatory system, not only for pharmacogenomic therapies, but for all health products.

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international standards, such as the International Conference on Harmonisation Good Clinical Practice guidelines (see International Conference on Harmonisation, "Vision", online: ICH <[www.ich.org/about/vision.html](http://www.ich.org/about/vision.html)>) or ISO standards, into Canadian legislation – and, in the process, keep Canada up to date with international best practices in drug and medical device regulation.