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Yann Joly

Emma Ramos-Paque

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Approval of New Pharmacogenomic Tests: Is the Canadian Regulatory Process Adequate?

Yann Joly, Emma Ramos-Paque*

INTRODUCTION

Pharmacogenomics and pharmacogenetics study the genetic factors behind individual variability in drug response.¹ The idea is that certain genetic polymorphisms (i.e. differences in DNA sequence among individuals or populations) can determine the way in which a person will respond to certain drugs.² Whereas pharmacogenetics is focused on the effects of single genes on drug response, pharmacogenomics evaluates genetic variations across the entire genome.³ For the sake of readability, the term “pharmacogenomics” will be used to refer to both pharmacogenomics and pharmacogenetics.

Since its inception in the early 1950s,⁴ many hopes have been attached to pharmacogenomic research because, in the clinical setting, variations among individuals in the efficacy and toxicity of drugs are common.⁵ Ultimately, pharmacogenomic research will allow researchers to develop new drugs and modify existing ones to better respond to genetic differences among patients. It will facilitate a

* Yann Joly, Ph.D. (DCL), Lawyer and Professional Associate, Centre of Genomics and Policy, Faculty of Medicine, McGill University. Emma Ramos-Paque, LL.B., Lawyer and Research Student, Centre of Genomics and Policy, Faculty of Medicine, McGill University. Financial support for this research was primarily provided by Genome Canada and Genome British Columbia. The authors would like to thank Bruce Carleton and Michael Hayden from the CPNDS, Anne-Marie Tassé for her helpful comments and Gregory Harris for his editorial assistance.

¹ Nuffield Council on Bioethics, “Pharmacogenetics: Ethical Issues” (2003) at 94, online: HumGen <http://www.humgen.org/virtual_library/1816_1/web/images/1816.pdf>; Avinash Puri, “Pharmacogenomics: Benefits of Personalized Medicines” (2009) 1:4 Int. J. Med. Med. Sci. 91 at 91.

² Michel Eichelbaum, Magnus Ingelman-Sundberg and William E. Evans, “Pharmacogenomics and Individualized Drug Therapy” (2006) 57 Annu. Rev. Med. 119 at 120.

³ Nuffield Council on Bioethics, *supra* note 1 at 94; Ann K. Daly, “Genome-Wide Association Studies in Pharmacogenomics” (2010) 11 Nat. Rev. Genetics 241 at 241; Scott T. Weiss, Howard L. McLeod, David A. Flockhart, M. Eileen Dolan, Neal L. Benowitz, Julie A. Johnson, Mark J. Ratain and Kathleen M. Giacomini, “Creating and Evaluating Genetic Tests Predictive of Drug Response” (2008) 7 Nat. Rev. Drug Discov. 568 at 568.

⁴ M.V. Relling and J.M. Hoffman, “Should Pharmacogenomic Studies be Required for New Drug Approval?” (2007) 81:3 Clinical Pharmacology & Therapeutics 425 at 425.

⁵ Grant R. Wilkinson, “Drug Metabolism and Variability among Patients in Drug Response” (2005) 352:21 N. Engl. J. Med. 2211 at 2211.

more accurate prediction of drug responses, reduce adverse drug reactions and allow for the personalization of drug therapy by allowing for the selection of a drug or the determination of its dosage on the basis of the genotype of the patient.⁶

In Canada, the regulatory framework applicable to pharmacogenomic tests depends on whether they fall within federal or provincial jurisdiction. As will be discussed, this depends on whether the tests are marketed as commercial kits or as laboratory services. The two sets of regulations are quite different because they have distinct objectives: whereas the federal regime is focused on the tests intended to be sold or imported in Canada, the provincial process regulates laboratories.

For the manufacturer of a pharmacogenomic test, the federal process can be a lengthy one because of all the evidence that must be provided. Fast tracking mechanisms exist (such as the *Special Access Program* and the *Priority Review*), but, as will be discussed, they are difficult to invoke in the context of pharmacogenomic tests. From the perspective of patients and healthcare providers, pharmacogenomics is seen as a tool that could be beneficial to patients and to the development of safer and more efficient drugs. Thus, one question that arises in this field is whether the current regulations inhibit the progress and the development of pharmacogenomic tests and whether a fast track approval mechanism is warranted. Is the regulatory framework adapted to the reality of pharmacogenomics?

In the first part of our analysis, we will examine the impact which pharmacogenomics is expected to have on drug research and development, on the drug approval process and on post-marketing surveillance and clinical practice. This will allow us to show how pharmacogenomic testing could be beneficial to drug companies, regulatory bodies, and patients. The second part of our analysis will focus on the regulatory framework applicable to the approval of pharmacogenomic tests in Canada, although we are aware of the fact that most manufacturers decide to approve their tests outside of Canada. As mentioned, the applicable regulations will depend on the way the test is marketed; the federal and provincial requirements will both be covered in detail. It is interesting to note that very few pharmacogenomic test developers currently choose to get their tests approved by Health Canada. Most often they will commercialize their product in the United States first and go through the provincial approval route when seeking approbation in Canada.⁷

The review of the expected benefits and of the Canadian regulatory framework governing pharmacogenomic tests will then allow us to evaluate if the latter is appropriate considering the positive impact pharmacogenomics could have on pharmaceutical development and the health care system. We will discuss the question of whether it should be changed and simplified so that manufacturers could obtain faster (or simplified) approval for their tests in order to commercialize them more rapidly.

⁶ Amalia M. Issa, "Ethical Perspectives on Pharmacogenomic Profiling in the Drug Development Process" (2002) 1 Nat. Rev. Drug Discov. 300 at 300.

⁷ Leslie Tucker, "Pharmacogenomics: A Primer for Policymakers" National Health Policy Forum (28 January 2008) at 14, online: <http://www.nhpf.org/library/background-papers/BP_Pharmacogenomics_01-28-08.pdf>.

I. EXPECTED BENEFITS OF PHARMACOGENOMICS

Pharmacogenomics is expected to yield several benefits. In this section of our analysis, we will look at those benefits from different perspectives, including those of the pharmaceutical industry, the regulatory bodies, and patients. This section will be relevant to the subsequent investigation of whether these anticipated benefits are important enough to justify a change in the approval process applicable to pharmacogenomic tests.

As will be discussed in this part of our analysis, among the benefits anticipated are the possibilities of improving drug research and development, making the approval of new drugs faster and more efficient, improving drug efficacy and safety, and tailoring treatment in clinical practice by allowing prediction of individual response.

Pharmacogenomics can be used with the objective of reducing the incidence of adverse events before patients experience them in the clinical practice setting.⁸ In this scenario, pharmacogenomic data are studied as the drug is being developed to prevent adverse events in the clinical setting. Upon its release, the drug will be marketed with the pharmacogenomic test.

Pharmacogenomics can also be used to identify and correlate genotypes with drug responsiveness upon observation of adverse reactions. Thus, once a drug has been developed and marketed, pharmacogenomic studies may be carried out when adverse reactions have been noted among patients. Such studies will shed light on differences in drug responsiveness among patients and permit researchers to correlate it with some polymorphisms to develop a test *a posteriori*.

(a) Impact on drug research and development

One of the major impacts expected is that pharmacogenomics will change the way in which clinical drug trials are conducted and thereby change the drug development process.⁹ Pharmacogenomics is believed to have the potential to affect every stage of drug development, from the Preclinical Phase to Phase III.¹⁰

From an economic perspective, at the Preclinical Phase, it is expected that

⁸ Pharmacogenomic tests can be used either prospectively or retrospectively: Issa, *supra* note 6 at 302.

⁹ *Ibid.* at 300.

¹⁰ Preclinical phase includes animal, *in vitro* and *in vivo* experiments designed to verify the safety, therapeutic potential and toxicity of drug candidates: Trudo Lemmens and Ron A. Bouchard, "Regulation of pharmaceuticals in Canada" in J. Downie, T. Caulfield and C. Flood, eds., *Canadian Health Law and Policy*, 3d ed. (Toronto: Butterworths, 2007) 318 at 321.

Phase I consists of initial safety studies on humans designed to provide information about pharmacokinetics, pharmacodynamics, safety and side effects of the drug; Phase II is conducted to evaluate the efficacy and side effects of the drug on patients affected with the medical condition the drug is supposed to treat; Phase III is intended to gather additional information about the efficacy and safety of the drug: Health Canada, *Guidance for clinical trial sponsors: Clinical Trial Applications (Guidance)* (Ottawa: Minister of Public Works and Government Services Canada, 2002) at section 2 [Health Canada, CTA].

pharmacogenomics could be used in the selection of drug candidates that will enter clinical development, and which will be tested on humans in such a way that compounds responsible for variable drug response and toxicity may be eliminated.¹¹ But pharmacogenomics could also be used in a public health objective: during Phase I of the clinical trials, pharmacogenomic testing could serve to reduce risk by analyzing genetic differences in drug metabolism.¹² However, the small number of participants involved could make it difficult to prove any correlation.¹³ Nevertheless, because usually only healthy subjects are enrolled in Phase I trials,¹⁴ and because safety is a primary focus, pharmacogenomics could ensure that the participants selected are not put at an unnecessary risk.¹⁵ Individuals with particular polymorphisms could be excluded from the study on the basis that they would not benefit from it or would suffer adverse effects.¹⁶

Pharmacogenomics will likely be most useful during Phase II and Phase III trials.¹⁷ Phase II trials mainly focus on establishing drug efficacy and short-term side effects¹⁸ and, because they involve more volunteers than Phase I, the odds of demonstrating a role for genetic variation in drug efficacy are greater.¹⁹ Identifying genotypes that affect drug response in Phase II trials would enable more successful Phase III trials that would be more efficient in size, time and cost.²⁰ As a matter of fact, Phase III trials are extremely expensive because they are conducted on a large population sample²¹ to gather additional information about drug efficacy, safety, and long-term side effects.²² The results from Phase I and II pharmacogenomic

¹¹ Lawrence J. Lesko and Janet Woodcock, "Pharmacogenomic-Guided Drug Development: Regulatory Perspective" (2002) 2 *The Pharmacogenomics Journal* 20 at 20 [Lesko and Woodcock, "Pharmacogenomic-guided"]; Laurent Essioux, Benoît Destenaves, Philippe Jais and François Thomas, "Association Studies in Pharmacogenomics" in Julio Licinio and Ma-Li Wong, eds., *Pharmacogenomics: The Search for Individualized Therapies* (Weinheim: Wiley-Vch, 2002) 57 at 74.

¹² Karine Morin, "Canadian Legal Oversight of Pharmacogenomics and Nutrigenomics" (2008) 16:3 *Health L. Rev.* 21 at 24.

¹³ Tilo Mandry, "Legal Implications of Pharmacogenomics Regarding Drug Trials, Drug Labeling, and Genetic Testing for Drug Prescription: An International Approach" (2004) 59 *Food & Drug L.J.* 519 at 526.

¹⁴ Unless it is unethical to do so: Health Canada, *CTA*, *supra* note 10 at section 2, *s.v.* "Phase I".

¹⁵ Barbara Ann Binzak, "How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process" (2003) 58 *Food & Drug L.J.* 103 at 119.

¹⁶ Mandry, *supra* note 13 at 526.

¹⁷ Yann Joly, "Biotechnologies et brevets : le cas de la pharmacogénomique" (2005) 10:2 *Lex Electronica* at 55, online: <http://www.lex-electronica.org/docs/articles_88.pdf> [Joly, "Biotechnologies et brevets"].

¹⁸ Lemmens and Bouchard, *supra* note 10 at 322.

¹⁹ Mandry, *supra* note 13 at 526.

²⁰ Joly, "Biotechnologies et brevets", *supra* note 17 at 55.

²¹ Lemmens and Bouchard, *supra* note 10 at 322.

²² *Ibid.* at 322; Mandry, *supra* note 13 at 526.

studies will help design an optimal Phase III trial,²³ limited to individuals with a high probability of responding well to the drug.²⁴

Lowering costs and reducing time in drug development is a major issue today. Drug research and development is a process involving a lot of time and resources.²⁵ It has become essential for pharmaceutical companies to improve the success of pharmaceutical research and development.²⁶ Drug safety and efficacy are major problems facing pharmaceutical companies that can lead to the rejection of their submissions to Health Canada. Pharmacogenomic testing could be used to segment the participants in two categories (responders and non-responders) on the basis of their genetic profiles, so that non-responders are removed from the trial, instead of stopping the development process of the compound.²⁷ Pharmacogenomics would also rescue compounds that fail in development because of adverse reactions.²⁸ By decreasing the incidence of non-responders and adverse drug responses, and requiring fewer subjects and less time, pharmacogenomic testing could allow pharmaceutical companies to obtain faster approval to market the drug and increase their chances of success.²⁹ Thus, pharmacogenomics is seen as a tool that could move the development process from trial-and-error drug discovery towards rational drug design³⁰ by providing the ability to predict if a drug will succeed or fail in meeting the safety and efficacy requirements early in the development process.³¹

²³ Issa, *supra* note 6 at 304.

²⁴ Lawrence J. Lesko, Ronald A. Salerno, Brian B. Spear, Donald C. Anderson, Timothy Anderson, Celia Brazell, Jerry Collins, Andrew Dorner, David Essayan, Baltazar Gomez-Mancilla, Joseph Hackett, Shiew-Mei Huang, Susan Ide, Joanne Killinger, John Leighton, Elizabeth Mansfield, Robert Meyer, Stephen G. Ryan, Virginia Schmith, Peter Shaw, Frank Sistare, Mark Watson and Alexandra Worobec, "Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making: Report of the First FDA-PWG-PhRMA-DruSafe Workshop" (2003) 43 *J. Clin. Pharmacol.* 342 at 352.

²⁵ Joly, "Biotechnologies et brevets", *supra* note 17 at 7; Jai Shah, "Concept and Putative Application of Pharmacogenetics and Pharmacogenomics" (2004) 12:2 *Health L. Rev.* 3 at paras. 21-22 [Shah, "Concept and Putative"].

²⁶ Lawrence J. Lesko and Janet Woodcock, "Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective" (2004) 3 *Nat. Rev. Drug Discov.* 763 at 763 [Lesko and Woodcock, "Translation"].

²⁷ Allen D. Roses, "Pharmacogenetics and Drug Development: The Path to Safer and More Effective Drugs" (2004) 5 *Nat. Rev. Genetics* 645 at 648.

²⁸ Yann Joly, "La pharmacogénomique : perspective et enjeux éthico-juridiques" (2004) 9:3 *Lex Electronica* at 5, online: http://www.lex-electronica.org/docs/articles_99.pdf [Joly, "La pharmacogénomique"]; Patricia A. Deverka, John Vernon and Howard L. McLeod, "Economic Opportunities and Challenges for Pharmacogenomics" (2010) 50 *Annu. Rev. Pharmacol. Toxicol.* 423 at 428.

²⁹ Lesko and Woodcock, "Translation", *supra* note 26 at 763-764.

³⁰ Shah, "Concept and Putative", *supra* note 25 at paras. 21-22.

³¹ Lesko and Woodcock, "Translation", *supra* note 26 at 764.

(b) Impact on the Approval Process of Drugs

As stated above, pharmacogenomics could increase the chances of obtaining market approval for a drug, because it minimizes the incidence of non-responders and adverse drug reactions during clinical trials. It could also help obtain faster approval by aiding in the assessment of the efficacy and safety of the compound and by reducing the time allotted to the research and development of new drugs. The importance of pharmacogenomics in the drug approval process is now even more recognized by the fact that submission of pharmacogenomic data is encouraged when filing a new drug submission by guidelines adopted by Health Canada (similar guidelines were adopted by the FDA in the United States).³² In our opinion, the study of those guidelines is relevant to our analysis because they demonstrate that obtaining pharmacogenomic data on new pharmaceutical drugs is becoming increasingly important.

In Canada, Health Canada adopted in 2007 a *Guidance Document on Submission of Pharmacogenomic Information*.³³ With this guidance document, Health Canada recognized that the application of pharmacogenomics is becoming an integral part of the drug development process.³⁴ Pharmacogenomic data will gradually be submitted at different moments of the drug approval process to Health Canada: first, during the application to start clinical trials and then when filing a New Drug Submission.

In the *Food and Drug Regulations*,³⁵ Parliament requires that the clinical trial application for a new drug contain information on the pharmacological and pharmacokinetic aspects of the drug, its toxicological effects, its safety and efficacy and its dose responses.³⁶ In accordance with this requirement, sponsors will be required to submit pharmacogenomic data if relevant to those questions.³⁷ According to Health Canada, pharmacogenomic data shall also be submitted as part of the clinical trial application if they are used by the sponsor to support the design of the proposed clinical trial, to justify human testing or to support the proposed labelling of the drug.³⁸

As for the new drug submission, sponsors shall comply with sections C.08.002, C.08.002.1, and C.08.003 of the *Food and Drug Regulations*.³⁹ Thus, sponsors will have to submit pharmacogenomic data providing evidence of the safety and clinical effectiveness of the new drug, or supporting the proposed dosage

³² Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (Ottawa: Public Works and Government Services Canada, 2008) at section 1.3 [Health Canada, *Submission of Pharmacogenomic*]; U.S. Department of Health and Human Services, Food and Drug Administration (FDA), *Guidance for Industry: Pharmacogenomic Data Submissions* (March 2005) at 5 [FDA, *Pharmacogenomic Data Submissions*].

³³ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32.

³⁴ *Ibid.* at section 1.1.

³⁵ C.R.C., c. 870.

³⁶ *Ibid.*, s. C.05.005(e).

³⁷ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32 at section 2.1.

³⁸ *Ibid.*

³⁹ *Food and Drug Regulations*, *supra* note 35, ss. C.08.002, C.08.002.1, C.08.003.

and contra-indications of the drug, as well as the claims to be made for the drug.⁴⁰

Finally, if no pharmacogenomic test is available for use in Canada and if sponsors intend to use a pharmacogenomic test to support a therapeutic decision, like the choice or dosing of a drug, Health Canada encourages them to apply for a licence during the drug development process.⁴¹

In the United States, the Food and Drug Administration (FDA) also released, in 2005, a guidance document on pharmacogenomic data submission to facilitate the use of pharmacogenomic data in drug development.⁴² The FDA recognizes that, for the moment, most pharmacogenomic data are of an exploratory or research nature and thus does not require that they be submitted. It nevertheless encourages voluntary submission, considering the benefits it brings to both the industry and the FDA.⁴³

Some authors are of the opinion that some degree of pharmacogenetic testing should be required for new drug applications, because it should not be acceptable to approve drugs without knowing if they are subject to variability due to common germline variation.⁴⁴ This review of the guidance on pharmacogenomic data submission demonstrates that pharmacogenomics is becoming more and more important in the drug development and approval process. Thus, the appropriateness of the regulatory framework applicable to pharmacogenomic testing could be questioned if drug companies have to comply with stringent requirements to be able to use pharmacogenomic tests during the drug development process (in part 2 of our analysis we will study those requirements and in part 3 we will discuss whether they are too stringent).

Until now, we have examined the expected benefits of pharmacogenomic tests at different phases before the commercialization of drugs. However, the impacts of pharmacogenomics do not stop at the pre-marketing phase of the process. Pharmacogenomics could also be very useful once the drug is marketed, whether it is in post-marketing surveillance pharmacovigilance of adverse reactions or in the daily practice of medicine.

(c) Impact in Post-Marketing Surveillance and in Clinical Practice

Although a drug can be sold in Canada once it has received marketing approval, studies on its efficacy and safety continue as post-marketing surveillance pharmacovigilance. Indeed, post-marketing studies are often called Phase IV of the drug development process. Those studies aim at identifying morbidity, mortality, and adverse events.⁴⁵ The role pharmacogenomics is likely to have at this post-marketing phase is to provide a better understanding of the exact relationship between drug activity/toxicity and polymorphisms.⁴⁶ Pharmacogenomic testing could

⁴⁰ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32 at section 2.2.

⁴¹ *Ibid.* at section 2.2.1.

⁴² FDA, *Pharmacogenomic Data Submissions*, *supra* note 32 at 1.

⁴³ *Ibid.* at 7.

⁴⁴ Relling and Hoffman, *supra* note 4 at 427.

⁴⁵ Issa, *supra* note 6 at 303.

⁴⁶ Essioux, Destenaves, Jais and Thomas, *supra* note 11 at 75.

thus allow a superior surveillance of drugs on the market by enabling the assessment of the population for whom the drug is best suited.⁴⁷

In the daily practice of medicine, once a drug is brought to market, the hope for pharmacogenomics is to allow true individualization of therapy by providing a more precise diagnosis.⁴⁸ Pharmacogenomic studies and testing could change the way drugs are prescribed in the clinical setting, because the use of the drug could be restricted according to genotypes.⁴⁹ Pharmacogenomic tests could be given before the prescription of drugs to determine whether a patient would have access to a particular drug⁵⁰ or to determine the appropriate dosage.⁵¹ Better choices for drug therapies could help maximize the likelihood of efficacious treatment, minimize the risk for adverse reactions⁵² and prevent drug withdrawal.

Thus, pharmacogenomics promises considerable benefits. From a better understanding of drug response mechanisms to a more streamlined drug development and approval process, as well as the salvage of drugs that have been removed from the market for safety reasons, pharmacogenomics offers the possibility for patients to have access to safer, and more effective drugs and for pharmaceutical companies to maximize their investments.⁵³

Now that we have introduced the possible impacts of pharmacogenomics, we will illustrate the situation by providing the example of Canadian Pharmacogenomics Network for Drug Safety (CPNDS)/Cisplatin.

(d) The Case of CPNDS/Cisplatin

The example of Cisplatin offers a good illustration of the benefits pharmacogenomics could provide. Cisplatin is a drug used for the treatment of childhood malignancies, such as neuroblastomas and germ cell tumours.⁵⁴ Cisplatin is one of the most ototoxic drugs used in oncology: it can cause permanent

⁴⁷ Joly, "La pharmacogénomique", *supra* note 28 at 6.

⁴⁸ Lesko and Woodcock, "Pharmacogenomic-guided", *supra* note 11 at 20.

⁴⁹ Allen Buchanan, Andrea Califano, Jeffrey Kahn, Elizabeth McPherson, John Robertson and Baruch Brody, "Pharmacogenetics: Ethical Issues and Policy Options" (2002) 12:1 Kennedy Institute of Ethics Journal 1 at 2-3 [Buchanan, Califano, Kahn, McPherson, Robertson and Brody, "Ethical Issues"].

⁵⁰ John A. Robertson, Baruch Brody, Allen Buchanan, Jeffrey Kahn and Elizabeth McPherson, "Pharmacogenetic Challenges for the Health Care System" (2002) 21:4 Health Affairs 155 at 157 [Robertson, Brody, Buchanan, Kahn and McPherson, "Pharmacogenetic Challenges"].

⁵¹ Joly, "La pharmacogénomique", *supra* note 28 at 5.

⁵² *Ibid.* at 6; Brian B. Spear, Margo Heath-Chiozzi and Jeffrey Huff, "Clinical Application of Pharmacogenetics" (2001) 7:5 Trends in Molecular Medicine 201 at 201.

⁵³ Buchanan, Califano, Kahn, McPherson, Robertson and Brody, "Ethical issues", *supra* note 49 at 2.

⁵⁴ L. Riedemann, C. Lanvers, D. Deuster, U. Peters, J. Boos, H. Jürgens and A. am Zehnhoff-Dinnesen, "Megalyn Genetic Polymorphisms and Individual Sensitivity to the Ototoxic Effect of Cisplatin" (2008) 8 The Pharmacogenomics Journal 23 at 23.

bilateral hearing loss in up to 25% of adults and 60% of children receiving it.⁵⁵ This side effect often leads to dose reduction or premature termination of the treatment which may affect overall survival rates or lead to learning difficulties for children.⁵⁶

The CPNDS project aims at establishing an active surveillance system for adverse drug reactions in children and at promoting safe prescription medications by identifying predictive biomarkers of drug risks.⁵⁷ It is a \$3.9 million project funded by Genome BC and other funding partners.⁵⁸ The CPNDS has been developing a national database of clinical and genetic information relevant to the occurrence of serious adverse drug reactions to identify genes associated with adverse drug reactions in order to use those results to develop diagnostic tests that would allow personalized recommendations for commonly used drugs.⁵⁹ In 2006, three adverse drug reactions in children were targeted by the CPNDS for surveillance, one of which was Cisplatin-induced hearing loss.⁶⁰ The findings of CPNDS have, so far, been very encouraging: researchers have identified genetic polymorphisms that are associated with hearing loss following Cisplatin use.⁶¹ According to studies, two single nucleotide polymorphisms are highly associated with Cisplatin-induced

⁵⁵ Colin J.D. Ross, Hagit Katzov-Eckert, Marie-Pierre Dubé, Beth Brooks, S. Rod Rassekh, Amina Barhdadi, Yassamin Feroz-Zada, Henk Visscher, Andrew M.K. Brown, Michael J. Rieder, Paul C. Rogers, Michael S. Phillips, Bruce C. Carleton, Michael R. Hayden and the CPNDS Consortium, “Genetic Variants in TPMT and COMP are Associated With Hearing Loss in Children Receiving Cisplatin Chemotherapy” (2009) 4:12 *Nat. Genetics* 1345 at 1345.

⁵⁶ *Ibid.*

⁵⁷ “New Research Project Aims to Unlock Genetic Keys to Childhood ADRs and Help Reduce Their Incidence”, Notes (2009) 142:2 CPJ/RPC 57; B.C. Carleton, R.L. Poole, M.A. Smith, J.S. Leeder, R. Ghannadan, C.J.D. Ross, M.S. Phillips and M.R. Hayden, “Adverse Drug Reaction Active Surveillance: Developing a National Network in Canada’s Children’s Hospitals” (2009) 18 *Pharmacoepidemiology and Drug Safety* 713 at 715.

⁵⁸ Genome BC, “News releases: New research will help predict potentially fatal adverse reactions to specific children’s drugs” (23 January 2009), online: <<http://www.genomebc.com/index.php?cID=341>>.

⁵⁹ Colin J.D. Ross, Bruce Carleton, Dana G. Warn, Sunita B. Stenton, Shahrad Rod Rassekh and Michael R. Hayden, “Genotypic Approaches to Therapy in Children: A National Active Surveillance Network (GATC) to Study the Pharmacogenomics of Severe Adverse Drug Reactions in Children” (2007) 1110 *Ann. N.Y. Acad. Sci.* 177 at 180; Turna Ray, “Genome BC project aims to launch PGx test to predict adverse drug reactions in children” *Pharmacogenomics Reporter* (11 February 2009), online: <<http://www.genomeweb.com/dxpgx/genome-bc-project-aims-launch-pgx-test-predict-adverse-drug-reactions-children>>.

⁶⁰ Genome British Columbia, “Genotype-Specific Approaches to Therapy in Childhood: The Canadian Pharmacogenomics Network for Drug Safety”, online: <<http://www.genomebc.ca/portfolio/projects/health-projects/current/genotype-specific-approaches-to-therapy-in-childhood-the-canadia/>>; Carleton, Poole, Smith, Leeder, Ghannadan, Ross, Phillips and Hayden, *supra* note 57 at 716.

⁶¹ S. Rod Rassekh, “Adverse events in pediatric oncology: The GATC Cancer Study” (2007) 8 *Pediatric Oncology Hematology Network Newsletter* 3 at 4.

deafness: one was found in the gene encoding thiopurine S-methyltransferase (TPMT) and the other one in the gene encoding catechol O-methyltransferase (COMT).⁶² Thus, it could become possible to identify individuals presenting a high risk of developing hearing loss after receiving Cisplatin by genotyping patients before giving the treatment.⁶³ At risk patients would have the possibility of reducing their dose of Cisplatin or the possibility to be selected for experimental otoprotectant studies.⁶⁴ The marketing of a pharmacogenomic test could then help patients avoid ototoxicity and consider alternative treatment options.

Now that we have introduced the possible impacts of pharmacogenomics on the development of drugs, the drug approval process, the post-marketing surveillance of drugs, and clinical practice, it is time to examine the requirements imposed in Canada on manufacturers of pharmacogenomic tests.

II. REGULATORY FRAMEWORK APPLICABLE TO THE APPROVAL OF PHARMACOGENOMIC TESTS IN CANADA

The *Constitution Act, 1867*⁶⁵ divides the power to legislate between the federal and provincial governments. According to this separation of powers, pharmacogenomic tests control, or broadly speaking genetic tests control, falls within both federal and provincial jurisdiction. Whether the federal or provincial regulations apply to a pharmacogenomic test will depend on the marketing strategy chosen by its provider.⁶⁶ Whereas the control of laboratory services is devolved to provinces as a consequence of their power in the management of health services, the federal government will regulate the marketing and publicity of therapeutic products within its competence over criminal matters.⁶⁷

Only genetic tests sold as a test kit are subject to the federal provisions.⁶⁸ A test kit is defined in the federal legislation as an *in vitro* diagnostic device that

⁶² Ross, Katzov-Eckert, Dubé, Brooks, Rassekh, Barhdadi, Feroz-Zada, Visscher, Brown, Rieder, Rogers, Phillips, Carleton, Hayden and the CPNDS Consortium, *supra* note 55 at 1346; Jacquelyn K. Beals, “Children’s hearing loss from Cisplatin chemotherapy associated with gene variants” *Medscape Medical News* (20 November 2009), online: <<http://www.medscape.com/viewarticle/712849>>.

⁶³ Ross, Katzov-Eckert, Dubé, Brooks, Rassekh, Barhdadi, Feroz-Zada, Visscher, Brown, Rieder, Rogers, Phillips, Carleton, Hayden and the CPNDS Consortium, *supra* note 55 at 1348.

⁶⁴ *Ibid.*

⁶⁵ *Constitution Act, 1867* (U.K.), 30 & 31 Vict., c. 3, reprinted in R.S.C. 1985, App. II, No. 5.

⁶⁶ Mylène Deschênes, *Réflexion sur l’encadrement normatif de la mise en marché des tests génétiques* (Montreal : Thémis, 2005) at 52-53.

⁶⁷ *Constitution Act, 1867*, *supra* note 65, ss. 91(27), 92(7), 92(13), 92(16); See also Anne-Marie Tassé and Béatrice Godard, “L’encadrement législatif de la vente directe des tests génétiques et le système de santé québécois” (2007) 15 Health L.J. 441 at para. 9 [Tassé and Godard, “L’encadrement législatif”].

⁶⁸ *Medical Devices Regulations*, S.O.R./98-282, s. 1; See also Tassé and Godard, “L’encadrement législatif”, *supra* note 67 at para. 11.

consists of reagents or articles intended to be used to conduct a specific test.⁶⁹ Excluded from the definitions of “*in vitro* diagnostic device”, “near patient *in vitro* diagnostic device” and “test kit”, are genetic tests offered as laboratory services.⁷⁰ In order to illustrate the difference between a test kit and a laboratory service, consider the following: if the patient has to take a sample of his DNA and send it to a laboratory to analyze it, the test will be considered a laboratory service; however, if the test is sold as a kit, where the sample is not sent to a laboratory because the analysis is done by the patient (as it is the case for pregnancy tests) or by his or her physician, then it will be considered a test kit. Therefore, if the test is marketed as an *in vitro* diagnostic device, it will mostly be subject to federal control, whereas if it is offered as a laboratory service, it will fall outside the scope of the federal regulations and fall under provincial jurisdiction. The Canadian regulatory framework applicable to genetic testing is not harmonized across the provinces and between the federal and provincial jurisdictions.⁷¹ As will be seen, only test kits falling under federal competence are required to be approved by Health Canada.

In the United States, contrary to “home-brew” tests, only test kits are regulated by the FDA and are subject to pre-market approval.⁷² A home-brewed test is a test developed and used by a laboratory “in-house” only, in contrast to a test developed for sale and use outside the laboratory (test kit).⁷³ Thus, the distinction in the United States between “home-brewed test” and “test kit” is very similar to the distinction in Canada between “test kits” and tests offered as laboratory services. For the moment, most pharmacogenomic tests are developed and approved in the United States or in Europe, and are brought to the market as home-brews to avoid having to go through a large portion of the regulatory process.⁷⁴ It will be interesting to keep this information in mind as we analyze the Canadian regulatory framework, including the federal regulation applicable to tests marketed as test kits.

The fact that a pharmacogenomic test is manufactured as a test kit or as a laboratory service does not directly impact its coverage by provincial health insurance plans.⁷⁵ The review of the applicable regulatory frameworks in Canada will

⁶⁹ *Medical Devices Regulations*, *supra* note 68, s. 1, s.v. “test kit”.

⁷⁰ *Ibid.*, s. 1; Health Canada, *Guidance for the Risk Based Classification System of In Vitro Diagnostic Devices* (Draft Guidance) (Ottawa: Therapeutic Products Programme, 1998) at section 2.2 [Health Canada, *Guidance for the Risk*].

⁷¹ Élodie Petit, Anne Marie Tassé and Béatrice Godard, “The Empirical Analysis of the Legal Frameworks Governing Genetic Services Labs in Canadian Provinces” (2008) 16:3 *Health L. Rev.* 65 at 65 [Petit, Tassé and Godard, “Empirical Analysis”].

⁷² Louis P. Garrison Jr., Rick J. Carlson, Josh J. Carlson, Patricia C. Kuszler, Lisa M. Meckley and David L. Veenstra, “A Review of Public Policy Issues in Promoting the Development and Commercialization of Pharmacogenomic Applications: Challenges and Implications” (2008) 40 *Drug Metabolism Reviews* 377 at 386; Tucker, *supra* note 7 at 14.

⁷³ Gregorio M. Garcia, “The FDA and Regulation of Genetic Tests: Building Confidence and Promoting Safety” (2008) 48 *Jurimetrics* 217 at 218.

⁷⁴ Garrison Jr., Carlson, Carlson, Kuszler, Meckley and Veenstra, *supra* note 72 at 386.

⁷⁵ For example, in Quebec, see the applicable legislation: *Health Insurance Act*, R.S.Q. c. A-29; *Regulation respecting the application of the Health Insurance Act*, R.R.Q. 1981,

allow us to evaluate if they are appropriate, or if they should be changed or simplified considering the benefits pharmacogenomic tests are likely to bring to drug companies and patients.

(a) The Federal Regulations

At the federal level, Health Canada is the regulatory authority responsible for evaluating the safety, efficacy, and quality of health products available in Canada, including medical devices.⁷⁶ Within Health Canada, it is the Therapeutic Products Directorate that is responsible for granting market authorization for pharmaceutical drugs and medical devices intended for human use in conformity with the provisions of the *Food and Drugs Act*,⁷⁷ the *Food and Drugs Regulations*⁷⁸ and the *Medical Devices Regulations*.^{79,80}

According to the definitions set out in section 1 of the *Medical Devices Regulations* and in section 2 of the *Food and Drugs Act*, a medical device is any article, instrument or apparatus manufactured for use in the diagnosis, treatment, mitigation or prevention of a disease or its symptoms, in human beings.⁸¹ Pharmacogenomic tests are considered medical devices because they are used with the intent of choosing an effective treatment plan or the best suited drug for a patient, and thus are themselves part of the treatment.⁸² More precisely, pharmacogenomic tests are *in vitro* diagnostic devices.⁸³ Thus, pharmacogenomic tests are regulated by the Therapeutic Products Directorate's Medical Devices Bureau in accordance with the *Food and Drugs Act* and the *Medical Devices Regulations*.⁸⁴

At the federal level, the *Medical Devices Regulations* set out the requirements governing the sale of pharmacogenomic tests. Its goal is to ensure that medical

c. A-29, r. 1; *Hospital Insurance Act*, R.S.Q. c. A-28; *Regulation respecting the application of the Hospital Insurance Act*, R.R.Q. 1981, c. A-28, r. 1; Régie de l'assurance maladie, *Medical Services — Services covered*, online: <http://www.ramq.gouv.qc.ca/en/citoyens/assurancemaladie/serv_couv_queb/serv_med_sc.shtml>; Régie de l'assurance maladie, *Medical Services — Services not covered*, online: <http://www.ramq.gouv.qc.ca/en/citoyens/assurancemaladie/serv_couv_queb/serv_med_snc.shtml>.

⁷⁶ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32 at section 2.0.

⁷⁷ R.S.C. 1985, c. F-27.

⁷⁸ *Supra* note 35.

⁷⁹ *Supra* note 68.

⁸⁰ Ron A. Bouchard and Monika Sawicka, "The Mud and the Blood and the Beer: Canada's Progressive Licensing Framework For Drugs Approval" (2009) 3 McGill J.L. & Health 49 at 54.

⁸¹ *Medical Devices Regulations*, *supra* note 68, s. 1; *Food and Drugs Act*, *supra* note 77, s. 2.

⁸² Deschênes, *supra* note 66 at 54.

⁸³ *Medical Devices Regulations*, *supra* note 68, s. 1, s.v. "in vitro diagnostic device".

⁸⁴ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32 at section 2.0.

devices distributed in Canada are safe and effective and meet quality standards.⁸⁵ Sections 10 to 20 enumerate the general safety and effectiveness requirements applicable to all medical devices, except devices sold for custom or special access purposes and for investigational testing purposes.⁸⁶ Among others, section 12 requires that the medical device perform as intended, and be effective for the purposes and uses for which it is manufactured, sold or represented.⁸⁷ Requirements in sections 10 to 20 focus on the physical safety of the test and its reliability (i.e., its analytical validity, or the accuracy with which the genetic polymorphism can be identified in the test).⁸⁸ Beside those general requirements, medical devices presenting a higher level of risk are subject to additional standards that will vary according to the importance of the risk associated with the device. Under section 6 of the *Medical Devices Regulations*, medical devices are classified into one of Classes I to IV, where Class I represents the lowest risk and Class IV represents the highest risk.⁸⁹ With the exception of Class I medical devices, prior to marketing a medical device in Canada, the manufacturer has to obtain a licence from the Medical Devices Bureau of Health Canada, which will determine whether the device meets the safety and effectiveness requirements.⁹⁰

To determine the class to which a medical device belongs, the Medical Devices Bureau will examine its intended use, application, instructions for use, the technical, scientific or medical expertise needed for its use, the importance of the information to the diagnosis, and the impact of the result on the individual.⁹¹ The classification rules are set out in Schedule 1 of the *Medical Devices Regulations*. Genetic tests in general are classified as Class III medical devices.⁹² Health Canada stated that, in Canada, all devices intended to be used for pharmacogenomic testing were also Class III medical devices.⁹³ Class III medical devices are considered to present either a moderate public health risk or a high individual risk.⁹⁴

Section 32 of the *Medical Devices Regulations* indicates the information that an application for a new Class III medical device shall contain in order to obtain a licence from Health Canada.⁹⁵ The application must contain the name, class, and identifier of the device, as well as information about its manufacturer and the estab-

⁸⁵ Health Canada, *Preparation of a Premarket Review Document for Class III and Class IV Device/Licence Applications* (Guidance) (Ottawa: Therapeutic Products Programme, 1998) at section 1.2 [Health Canada, *Premarket Review Document*].

⁸⁶ *Medical Devices Regulations*, *supra* note 68, ss. 10–20; Health Canada, *Preparation of an Application for Investigational Testing: In Vitro Diagnostic Devices (IVDD)* (Guidance) (Ottawa: Therapeutic Products Programme, 1999) at section 1.1 [Health Canada, *Investigational Testing*].

⁸⁷ *Medical Devices Regulations*, *supra* note 68, s. 12.

⁸⁸ *Ibid.*, ss. 10–20.

⁸⁹ *Ibid.*, s. 6.

⁹⁰ *Ibid.*, s. 26.

⁹¹ Health Canada, *Guidance for the Risk*, *supra* note 70 at section 3.

⁹² *Medical Devices Regulations*, *supra* note 68, Sch. I, part 2, rule 4(b).

⁹³ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32 at section 2.2.1.

⁹⁴ Health Canada, *Guidance for the Risk*, *supra* note 70 at section 3.

⁹⁵ *Medical Devices Regulations*, *supra* note 68, s. 32.

ishment where the device is being manufactured. Also, it shall include: a description of the device and the features of the device that permit it to be used for the purposes and uses for which it is sold; a list of the countries where the device has been sold and a summary of any reported problems; a list of the standards complied with in the design and manufacturing of the device to satisfy the safety and effectiveness requirements; and a summary of all studies on which the manufacturer relies to ensure the safety and efficacy of the device (all preclinical physical testing, preclinical studies, and previous clinical investigations).⁹⁶ The manufacturer must present a bibliography of all published reports dealing with the use, safety and effectiveness of the device as well as a copy of the quality management system certificate attesting that the system under which the device is designed and manufactured satisfies the requirements of *National Standard of Canada CAN/CSA-ISO 13485:03*. Another relevant requirement is that the manufacturer has to submit a summary of investigational testing conducted on the device using human subjects representative of the intended users and under conditions similar to the conditions of use. This requirement is only applicable in the case of a near patient *in vitro* diagnostic device, which consists of an *in vitro* diagnostic device intended for use outside a laboratory for testing at home or at a point of care.⁹⁷ Pharmacogenomic tests sold as test kits correspond to the definition of a near patient *in vitro* diagnostic device, which means that the manufacturer will have to conduct investigational testing and that, prior to making a licence application, it will have to apply for an investigational testing authorization (this process will be studied later on).

The submitted evidence on safety and effectiveness will then undergo a scientific and medical review before the licence application can be authorized.⁹⁸ The federal regulatory process applicable to the approval of pharmacogenomic test is focused on the safety and efficacy of tests. There has to be scientific and medical evidence that the test will perform as intended and as represented to the public. The test must present strong analytical and clinical validity⁹⁹ as well as clinical utility¹⁰⁰ before Health Canada can issue a licence to the manufacturer allowing its sale or importation in Canada. Hence the need imposed by section 32(3)(h) to conduct investigational testing on subjects representative of the intended users and under conditions similar to the conditions of use.¹⁰¹ These requirements ensure that Health Canada will meet its mandate to evaluate the health-related risks and benefits of health products and food and to minimize health risk factors of Canadians while maximizing the safety and promoting conditions that enable them to make healthy choices.¹⁰² According to Health Canada, the review of a Class III medical

⁹⁶ Health Canada, *Investigational Testing*, *supra* note 86 at section 5.2.3.

⁹⁷ *Medical Devices Regulations*, *supra* note 68, s. 1, s.v. “near patient *in vitro* diagnostic device”.

⁹⁸ Health Canada, *Investigational Testing*, *supra* note 86 at section 1.1.

⁹⁹ Refers to the accuracy with which a test predicts a clinical outcome.

¹⁰⁰ Refers to the likelihood that the use of the test result will lead to an improved health outcome.

¹⁰¹ Deschênes, *supra* note 66 at 141.

¹⁰² Health Canada, “About Health Canada — Health Products and Food Branch”, online: <<http://www.hc-sc.gc.ca/ahec-asc/branch-dirgen/hpfb-dgpsa/index-eng.php>>.

device licence application takes approximately 60 days.¹⁰³

The above mentioned process is applicable to the approval of a pharmacogenomic test intended to be sold or imported in Canada. However, Health Canada recognizes that pharmacogenomic testing is often conducted for exploratory research purposes. In that case, authorization is not required when the test is labelled “For Research Use Only” and is not labelled or represented for a specific diagnostic application.¹⁰⁴

Another possibility is that the pharmacogenomic test is to be developed for use in an investigational context, where the objective is to obtain information to determine its safety and effectiveness prior to marketing.¹⁰⁵ To be able to conduct investigational testing, the manufacturer of the test will have to obtain an authorization from Health Canada. As mentioned before, according to section 32(3)(h) of the *Medical Devices Regulations*, conducting investigational testing is a pre-requisite to obtain a Class III medical device licence for near patient *in vitro* diagnostic device.¹⁰⁶ This means that every time a manufacturer wants to sell a pharmacogenomic test kit in Canada, it has to conduct investigational testing prior to applying for a licence. According to Health Canada, authorization for investigational testing is also required when a pharmaceutical company wishes to conduct pharmacogenomic studies during the different phases of drug development.¹⁰⁷ The company could then evaluate and assess the toxicity and efficacy of the new drug compound prior to marketing it or it could select patients for clinical trials on the basis of their genotype to ensure that the selected participants react well to the drug. A pharmaceutical company could have a great interest in conducting pharmacogenomic studies during the drug development process so that the drug is marketed with the test or labelled according to the results of the pharmacogenomic studies, instead of developing the test once adverse reactions to the drug have been observed in clinical practice.

The provisions applicable to investigational testing can be found in sections 79 to 88 of the *Medical Devices Regulations*.¹⁰⁸ To obtain authorization for investigational testing, the manufacturer will have to submit to Health Canada all available data supporting the analytical validity of the pharmacogenomic test.¹⁰⁹ Section 81 of the *Medical Devices Regulations* indicates that the records of the manufacturer must contain, among others things: a risk assessment, including the results of any previous studies and a description of the methods currently used to diagnose the medical condition for which the investigational testing is being proposed; and a

¹⁰³ Health Canada, *Access to Therapeutic Products: The Regulatory Process in Canada* (Ottawa: Health Products and Food Branch, 2006) at 11 [Health Canada, *Regulatory Process*]; Health Canada, *Management of Applications for Medical Device Licences and Investigational Testing Authorizations* (Ottawa: Therapeutic Products Directorate, 2001) at section 7 [Health Canada, *Management of Applications*].

¹⁰⁴ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32 at section 2.1.2.

¹⁰⁵ Health Canada, *Investigational Testing*, *supra* note 86 at section 4.1.

¹⁰⁶ *Medical Devices Regulations*, *supra* note 68, s. 32(3)(h).

¹⁰⁷ Health Canada, *Submission of Pharmacogenomic*, *supra* note 32 at section 2.1.1.

¹⁰⁸ *Medical Devices Regulations*, *supra* note 68, ss. 79, 88.

¹⁰⁹ Morin, *supra* note 12 at 21.

protocol of the proposed investigational testing, including the objective of the testing, the period of time during which the testing will be carried out and a copy of the patient consent form.¹¹⁰ According to section 83, the authorization will be granted only if it is determined that no serious danger to the life, health or safety of the patients can be expected, that the testing is in the best interests of patients and that the objective of the testing will be achieved.¹¹¹

The fact that the manufacturer obtained an investigational testing authorization in order to use the test in the drug development process does not spare the manufacturer from having to apply for a Class III medical device licence if it later wishes to sell or import the test in Canada. The investigational testing authorization only allows the manufacturer to conduct studies on humans to collect evidence on the safety and efficacy of the pharmacogenomic test. However, the data gathered during investigational testing will be considered by the Medical Devices Bureau when issuing the licence as evidence of the safety and efficacy of the device,¹¹² which could speed up the licensing process.

Before analyzing the provincial requirements applicable to pharmacogenomic testing, we would like to highlight an interesting American initiative which could simplify the process applicable to tests developed during the drug development process, so that both products could be licensed at the same time, instead of having to follow two parallel approval processes. The FDA released, in April 2005, a concept paper summarizing its preliminary thoughts on how to efficiently co-develop a drug and a device, such as a pharmacogenomic test.¹¹³ This concept paper is still a draft and the guidance document still has not been released.

The paper provides an optimum process for the development of a drug and test together. The test is part of drug development from its inception and the clinical phase of drug development demonstrates the clinical validity and utility of the test.¹¹⁴ This process would enable the pharmacogenomic test kit to be ready for approval at the same time as the drug. The FDA recommends co-development when the pharmacogenomic test and its results are intended to be included in the drug labelling to determine the dose and to identify patients at risk or patient responders for clinical and efficacy trials.¹¹⁵ The co-development process would not be limited to combination products as defined in section 21 CFR 3.2(e) and thus would apply to drugs and diagnostic tests separately marketed.¹¹⁶ This co-development concept paper represents an interesting initiative that could simplify the ap-

¹¹⁰ *Medical Devices Regulations*, *supra* note 68, s. 81.

¹¹¹ *Ibid.*, s. 83.

¹¹² Health Canada, *Investigational Testing*, *supra* note 86 at section 4.1.

¹¹³ U.S. Department of Health and Human Services, Food and Drug Administration (FDA), *Drug-Diagnostic Co-Development Concept Paper (Draft)* (April 2005) at 1 [FDA, *Co-Development*].

¹¹⁴ Stuart Hogarth, Kathy Liddell, Tom Ling, David Melzer, Simon Sanderson and Ron Zimmern, *Regulating Pharmacogenomics: An Overview of Developments in Various Countries and Industry Response to Regulatory Incentives: A Report for Health Canada* (Cambridge: 2006) at 31.

¹¹⁵ FDA, *Pharmacogenomic Data Submissions*, *supra* note 32 at 6.

¹¹⁶ FDA, *Co-Development*, *supra* note 113 at 4.

proval process for drugs and pharmacogenomic tests, in the way that manufacturers could have both products approved at the same time, without having to go through different processes. However, as mentioned, the guidance document still has not been released and it would be interesting to see how the FDA will manage this new process and what will be expected from the industry.

Health Canada has adopted a similar policy. The *Drug and Medical Device Combination Products Policy* has been effective since May 13, 1999, but has since been modified, and the new version has been effective since March 1, 2006. This policy aims at ensuring timely access to drug/medical device combination products and establishes a more efficient submission process for those products.¹¹⁷ Health Canada recognized the burden created by the fact that drugs and medical devices had to follow distinct regulatory processes under different regulations and the disincentive this burden created to marketing combination products.¹¹⁸ From now on, the combination products will be subject to either the *Medical Devices Regulations* or the *Food and Drug Regulations* according to the principal mechanism of action by which the claimed effect of the product is achieved. However, both components have to meet acceptable standards of safety, efficacy and quality.¹¹⁹ To this day, the Canadian legislation and regulations still have not been amended to reflect this policy on combination products.

The problem is that the Canadian policy does not apply to combination products where the drug component and the device component can be used separately, such as products sold together in procedure packages.¹²⁰ Health Canada defines a combination product as a therapeutic product combining a drug and a device component where the distinctive nature of the two components is integrated in a singular product.¹²¹ Thus, it seems that this policy does not apply to the case of a drug sold with a pharmacogenomic test because such tests are kits and each component is used separately.

(b) Provincial Regulations

According to the *Constitution Act, 1867*,¹²² provinces independently regulate the services delivered by genetic laboratories within their borders through their power over health services management.¹²³ There is no law in any Canadian provinces specifically regulating laboratories offering genetic testing services, thus they

¹¹⁷ Health Canada, *Drug/Medical Device Combination Products (Policy)* (Health Canada, 2005) at section 1 [Health Canada, *Combination Products*].

¹¹⁸ *Ibid.* at section 2.

¹¹⁹ *Ibid.* at section 5.

¹²⁰ *Ibid.* at section 3.

¹²¹ *Ibid.* at section 4.

¹²² *Constitution Act, 1867*, *supra* note 65.

¹²³ *Ibid.*, ss. 92(7), 92(13), 92(16); See also Anne-Marie Tassé and Béatrice Godard, *L'internationalisation des services génétiques — Analyse comparative des normes de gouvernance canadiennes, américaines, britanniques et australiennes* (Montreal : Thémis, 2009) at 41 [Tassé and Godard, *L'internationalisation*].

fall under laws governing medical laboratories.¹²⁴ Generally speaking, provincial requirements include the need to hold a licence issued by the government, to obtain a peer-delivered accreditation, and the need to establish internal and external quality controls.¹²⁵ Canadian provinces choose different terms to refer to the notions of licence and accreditation; for example a licence is called a “permit” in Quebec and a “certificate of approval” in British Columbia.¹²⁶ In order to avoid confusion, in the present text, we will use the vocabulary employed by the Organisation for Economic Co-operation and Development (OECD). Thus, the term “licence” will refer to “a legal permit or a formal permission from a constituted authority or governmental agency to operate a laboratory”¹²⁷ and the term “accreditation” to “a procedure by which an authoritative body gives formal recognition that a body is competent to carry out specific tasks,”¹²⁸ this authoritative body being constituted by peers.

Because the regulatory framework varies in each province, the present section of the text will illustrate the requirements of provincial regulations using, as examples, the rules applicable in Quebec and British Columbia.

Both provinces require laboratories to obtain a licence. As mentioned earlier, a licence is an official authorization to carry out certain analyses given to laboratories by a competent administrative provincial authority.¹²⁹ Although neither province grants a licence specific to genetic testing services, both grant general licences which indicate which type of tests the laboratory is authorized to run.¹³⁰

In Quebec, private laboratories must obtain an operating licence from the provincial minister of health according to section 31 of the *Act Respecting Medical Laboratories, Organ Tissue, Gamete and Embryo Conservation, and the Disposal of Human Bodies*.¹³¹ The minister can refuse to issue a licence if the needs of the region where the laboratory is to be located do not justify it¹³² and, if granted, the licence is issued for one year with the possibility of renewing it every year.¹³³ The *Regulation Respecting the Application of the Public Health Protection Act*¹³⁴ provides more information on the licence. It states at section 91 that the licence may be

¹²⁴ Petit, Tassé and Godard, “Empirical Analysis”, *supra* note 71 at 66.

¹²⁵ *Ibid.*

¹²⁶ The same problem is encountered at the international level, read to this effect: Anne Marie Tassé, Élodie Petit et Béatrice Godard, “Differences in Regulatory Frameworks Governing Genetic Laboratories in Four Countries” (2009) 37:2 *The Journal of Law, Medicine & Ethics* 351 at 356 [Tassé, Petit and Godard, “Differences in Regulatory Frameworks”].

¹²⁷ Organisation for Economic Co-operation and Development (OECD), *OECD Guidelines for Quality Assurance in Molecular Genetic Testing* (OECD, 2007) at 25, online: <www.oecd.org/dataoecd/43/6/38839788.pdf>.

¹²⁸ *Ibid.* at 24.

¹²⁹ Tassé and Godard, *L'internationalisation*, *supra* note 123 at 41.

¹³⁰ Petit, Tassé and Godard, “Empirical Analysis”, *supra* note 71 at 67.

¹³¹ R.S.Q. c. L-0.2, s. 31 [hereinafter: *Act Respecting Medical Laboratories*].

¹³² *Ibid.*, s. 36(3).

¹³³ *Ibid.*, s. 37.

¹³⁴ R.R.Q. 1981, c. P-35, r. 1.

issued for three fields of activities: for prosthetic devices or orthoses, medical biology examinations and analyses or for radioisotope or radiology examinations.¹³⁵ When the laboratory conducts medical biology examinations and analyses, the licence is issued for one of four fields of operation: pathological anatomy, biochemistry, microbiology, or haematology.¹³⁶ A laboratory offering pharmacogenomic testing would fall into the biochemistry category.¹³⁷ The *Regulation Respecting the Application of the Public Health Protection Act* also enacts professional qualification requirements for the director and the staff of the laboratory at sections 132 and 133.¹³⁸ Finally, section 136 stipulates that all work carried out by a medical biology laboratory must be in response to a prescription signed by a professional empowered to do so under the regulations of his or her professional corporation, unless it is in response to a request made by a health services and social services institution.¹³⁹

Public laboratories in Quebec are not subject to the *Act Respecting Medical Laboratories* because the definition of “laboratory” in section 1 b) excludes laboratories operated inside a facility maintained by a public institution.¹⁴⁰ Nevertheless, this does not mean no licence is necessary. The *Act Respecting Health Services and Social Services*¹⁴¹ requires that hospital centres hold a licence issued by the minister.¹⁴² This licence draws up a list of the facilities at the disposal of the institution¹⁴³ and the activities of the licence holder must be carried out within the scope of the licence.¹⁴⁴ Thus, public laboratories themselves do not have to hold a licence, but the institutions where the laboratories are operated must obtain one. According to section 442, the licence issued to an institution is valid until modified, cancelled, or withdrawn.¹⁴⁵ The *Permits for Institutions (Issue and Renewal) Regulation*¹⁴⁶ provides additional information to obtain a licence; in particular, its schedule provides the application form.¹⁴⁷

In British Columbia, a licence to open a laboratory is granted by the Medical Services Commission under section 33(1) of the *Medicare Protection Act*.¹⁴⁸

135 *Ibid.*, s. 91.

136 *Ibid.*, s. 93.

137 Ministry of Health and Social Services, *Laboratoire de biologie médicale — Mesure de la production* (Quebec : Direction des communications du ministère de la Santé et des Services sociaux, 2003) at 5-6; Deschênes, *supra* note 66 at 69.

138 *Regulation Respecting the Application of the Public Health Protection Act*, *supra* note 134, ss. 132, 133.

139 *Ibid.*, s. 136.

140 *Act Respecting Medical Laboratories*, *supra* note 131, s. 1(b).

141 R.S.Q., c. S-4.2.

142 *Ibid.*, s. 437.

143 *Ibid.*, s. 440.

144 *Ibid.*, s. 444.

145 *Ibid.*, s. 442.

146 O.C. 1372-84, 1984, G.O. 2, 2370.

147 *Ibid.*, Sch. I.

148 *Medicare Protection Act*, R.S.B.C. 1996, c. 286, s. 33(1).

Under section 40 of the *Medical and Health Care Services Regulation*,¹⁴⁹ the Medical Services Commission can not issue a licence unless it is satisfied that there is sufficient medical need for the proposed services and that the quality of diagnostic services will be maintained at a high level.¹⁵⁰ Additional conditions for the issuance of a license are provided at section 43.¹⁵¹ For example, the laboratory has to comply with diagnostic protocols and guidelines adopted and communicated by the Medical Services Commission.¹⁵² The laboratory also has to maintain its standards of testing and analysis, its number of qualified personnel, its level of supervision by medical personnel and the range of services it provides at the level the Medical Services Commission considers satisfactory.¹⁵³

Besides the obligation to hold a licence, laboratories in Quebec and British Columbia can be required to obtain an accreditation from an independent body that certifies that they are competent to carry out the analyses they offer.¹⁵⁴ This mechanism aims at ensuring the safety and quality of the tests offered and consists of an evaluation by independent professionals of the operations and practices of the laboratory, of its equipment, technical operating conditions, and of the competence of its personnel.¹⁵⁵ Many accreditation bodies are presently working on the implementation of documents from the International Organization for Standardization (ISO).¹⁵⁶ In Canada, each accreditation body develops its own standards for accreditation.¹⁵⁷ However provincial accreditation standards are all inspired by the ISO 15189, *Medical laboratories — Particular requirements for quality and competence* standard and its Canadian version CAN/CSA Z15189-03, *Medical laboratories Particular requirements for quality and competence*, which imposes two types of requirements: those related to the management of the laboratory, and the technical requirements concerning the personnel, the environment, the material and the quality of the procedures.¹⁵⁸ In Canada, only five provinces have specific accreditation bodies for medical laboratories: Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan.¹⁵⁹

In Quebec, the *Act Respecting Medical Laboratories* contains no mention that an accreditation is required for private laboratories, except for medical imaging laboratories.¹⁶⁰ As for public laboratories, section 107.1 of the *Act Respecting Health Services and Social Services* provides that the institutions in which they are oper-

149 B.C. Reg. 426/97.

150 *Ibid.*, s. 40.

151 *Ibid.*, s. 43.

152 *Ibid.*

153 *Ibid.*

154 Hui Li and Khosrow Adeli, "Laboratory Quality Regulations and Accreditation Standards in Canada" (2009) 42 *Clinical Biochemistry* 249 at 249.

155 Petit, Tassé and Godard, "Empirical Analysis", *supra* note 71 at 67-68.

156 Li and Adeli, *supra* note 154 at 250.

157 *Ibid.* at 251-252.

158 Tassé and Godard, *L'internationalisation*, *supra* note 123 at 45-46.

159 Li and Adeli, *supra* note 154 at 251.

160 *An Act Respecting Medical Laboratories*, *supra* note 131, ss. 30.4, 40.3.2(1).

ated must be accredited, every three years, for the services they offer.¹⁶¹ The law does not specify the accreditation body; institutions have the choice between two accreditation bodies recognized by the ministry of Health and Social Services: the Canadian Council on Health Services Accreditation and the Conseil québécois d'agrément.¹⁶² Since 2005, the Circulaire 2005-007, *Conformité des laboratoires de biologie médicale à la norme CAN/CSA-15189 "Laboratoire d'analyses de biologie médicale — Exigences particulières concernant la qualité et la compétence"* requires that public laboratories conform with the national accreditation standard CAN/CAS-Z15189-03.

In British Columbia, laboratories must be accredited under section 121 of the *Medical Practitioners Act*.¹⁶³ Laboratories are accredited by the College of Physicians and Surgeons, and more specifically by the Diagnostic Accreditation Program.¹⁶⁴ The granting of an accreditation is subject to section 125 of the *Rules Made Under the Medical Practitioners Act* and the accreditation is delivered for a maximum of five years.¹⁶⁵

Finally, the last provincial requirement concerning medical laboratories is the establishment of internal and external quality controls to guarantee the quality and reliability of the data produced. Generally, internal quality control is the responsibility of laboratory directors, whereas external quality control is exercised by an independent and external assessment of the accuracy of the analyses usually managed by the same body responsible for accreditation.¹⁶⁶

In Quebec, internal quality control of private laboratories is regulated by sections 139 and 140 of the *Regulation Respecting the Application of the Public Health Protection Act*, which stipulate that the director of the laboratory must establish quality control programs complying with standards generally recognized in hospital centre laboratories and a program for quality control of examinations or analyses made.¹⁶⁷ Concerning external quality control, the provincial Ministry of Health entrusted the Laboratoire de santé publique du Québec with the responsibility to put in place a quality control program for medical biology analyses.¹⁶⁸ Section 140.1 of the *Regulation Respecting the Application of the Public Health Protection Act* requires that the director of a private laboratory participate in the quality control programs established by the Laboratoire de santé publique du Québec.¹⁶⁹

¹⁶¹ *Act Respecting Health Services and Social Services*, *supra* note 141, s. 107.1.

¹⁶² Petit, Tassé and Godard, "Empirical Analysis", *supra* note 71 at 68.

¹⁶³ R.S.B.C. 1996, c. 285 at s. 121.

¹⁶⁴ Lillian Bayne, *BC Laboratory Services Review* (British Columbia: Ministry of Health Services, 2003) at 24.

¹⁶⁵ *Rules Made Under the Medical Practitioners Act*, *supra* note 163, s. 125(f).

¹⁶⁶ Petit, Tassé and Godard, "Empirical Analysis", *supra* note 71 at 69.

¹⁶⁷ *Regulation Respecting the Application of the Public Health Protection Act*, *supra* note 134, ss. 139, 140.

¹⁶⁸ Laboratoire de santé publique du Québec, *Programmes de contrôle externe de la qualité*, online: Institut national de santé publique <http://www.inspq.qc.ca/lspq/contrôle_qualité/default.asp?Page=2>.

¹⁶⁹ *Regulation Respecting the Application of the Public Health Protection Act*, *supra* note 134, s. 140.1.

Those programs pertain to the equipment, technical operation, and sanitary conditions of the laboratory and the qualifications of the staff. Incidentally, sections 116 to 120 provide rules concerning the quality of the equipment used and sanitary measures.¹⁷⁰

In British Columbia, sections 126 and 128 of the *Rules Made Under the Medical Practitioners Act* provide that to maintain accreditation, the laboratory shall comply with satisfactory quality controls and must meet the standards regarding its personnel, equipment, space, and safety procedures.¹⁷¹ Moreover, section 39(1)(i) of the *Medical and Health Care Services Regulation* states that for a licence application, a list and description of quality control procedures and programs planned have to be submitted.¹⁷²

At the provincial level, pharmacogenomic testing is not subject to specific regulations. The control carried out is very different from the one exercised by Health Canada on medical devices, because the provincial requirements are more focused on the quality and the proper functioning of the laboratory rather than on the clinical validity and utility of the tests.¹⁷³ Provincial requirements are less stringent than federal ones, but it has to be remembered that a laboratory can only conduct the tests authorized in its licence. Thus, it is expected that there is some control over the ability of the laboratory to run the tests authorized, but less on the clinical validity and utility of the tests.

(c) Difficulties Faced By the Industry in Relation with the Approval Process

Companies that develop pharmacogenomic tests are faced with many difficulties at the regulatory level that affect the availability of pharmacogenomic services on the market. The main problem facing manufacturers is gathering sufficient scientific data to demonstrate the efficacy, clinical validity, and utility of the tests.

Even if pharmacogenomics shows great promise, it is still considered to be in its infancy. Clinical validation of pharmacogenomic tests is still difficult to demonstrate due to the fact that the genotype/phenotype relationship is complex: individual variations in drug response are often linked to more than one gene and to non-genetic factors such as the age of the patient, the other medications he or she might be taking, and his or her state of health, environment, and diet.¹⁷⁴ Thus, pharmacogenomics is a probabilistic science and, because factors other than genotype can affect the way a patient will respond to a certain drug, it could be difficult to affirm that we could rely only on the results of a given pharmacogenomic test to make clinical decisions affecting their health. As a result, the benefits of

¹⁷⁰ *Ibid.*, ss. 116–120.

¹⁷¹ *Rules Made Under the Medical Practitioners Act*, *supra* note 163, ss. 126, 128.

¹⁷² *Medical and Health Care Services Regulation*, *supra* note 149, s. 39(1)(i).

¹⁷³ Deschênes, *supra* note 66 at 74-75; Petit, Tassé and Godard, “Empirical Analysis”, *supra* note 71 at 69.

¹⁷⁴ Hogarth, Liddell, Ling, Melzer, Sanderson and Zimmermann, *supra* note 114 at 35; Buchanan, Califano, Kahn, McPherson, Robertson and Brody, “Ethical issues”, *supra* note 49 at 3-4.

pharmacogenomics should not be overstated.¹⁷⁵ In the United States, the FDA observes that most of the current pharmacogenomic tests are insufficiently well-developed to be used in regulatory decision-making.¹⁷⁶ To establish that a test has clinical validity, the manufacturer has to carry out clinical studies that can be costly and time-consuming due to the sometimes low number of individuals with a particular characteristic drug response.¹⁷⁷

Clinical utility is also an obstacle to the development of pharmacogenomic tests: it is not sufficient that a test detect a given polymorphism; the presence of that polymorphism must also have medical importance.¹⁷⁸ Another important fact to consider relates to the existence of other preventive options: even if a pharmacogenomic test predicting an adverse reaction is produced, the drug to which it is related could be the only one available for the treatment of a serious disease. If no other treatment is available, what will be the impact of the results? Medical practitioners and patients will then be faced with the decision whether to take the treatment and accept its side effects or inefficiency, or to refuse the treatment with no other options from which to choose.

Pharmacogenomics also creates a problem of reduced revenues that result from market segmentation which may make the costs of pharmacogenomic research and development unjustifiable.¹⁷⁹ Even if nowadays the “blockbuster era” is at its end,¹⁸⁰ pharmacogenomics will likely lead to a further fragmentation of the market. This could discourage private research and development in the field, since drug companies could be resistant to producing expensive drugs that will be sold to a smaller portion of the population. One of the dangers is thus that groups characterized by less-profitable genotypes become therapeutic orphans.¹⁸¹ In other words, drug companies could neglect the development of drugs addressed to less common genotypes because they would be less lucrative in terms of sales revenue (the market being even smaller than for other drugs).¹⁸² The term “orphan drug” is usually assigned to pharmaceuticals for rare diseases, but the results would be the same in the case of pharmacogenomics.¹⁸³ One solution to this problem could be the adoption, by government, of incentives meant to stimulate research and development in less profitable fields of research. Such measures could be similar to those taken in

¹⁷⁵ Buchanan, Califano, Kahn, McPherson, Robertson and Brody, “Ethical issues”, *supra* note 49 at 3-4.

¹⁷⁶ FDA, *Pharmacogenomic Data Submissions*, *supra* note 32 at 3-4.

¹⁷⁷ Spear, Heath-Chiozzi and Huff, *supra* note 52 at 204.

¹⁷⁸ *Ibid.* at 202.

¹⁷⁹ Jai Shah, “Economic and Regulatory Considerations in Pharmacogenomics for Drug Licensing and Healthcare” (2003) 21:7 *Nature Biotechnology* 747 at 747; Issa, *supra* note 6 at 305.

¹⁸⁰ David M. Cutler, “The Demise of the Blockbuster?” (2007) 356:13 *N. Engl. J. Med.* 1292; Sarah Houlton, “The End of Blockbusters?” (2009) 6 *Chemistry & Industry* 14.

¹⁸¹ Mark A. Rothstein and Phyllis Griffin Epps, “Ethical and Legal Implications of Pharmacogenomics” (2001) 2 *Nat. Rev. Genetics* 228 at 229.

¹⁸² Marlene E. Haffner, Janet Whitley and Marie Moses, “Two Decades of Orphan Product Development” (2002) 1 *Nat. Rev. Drug Discov.* 821 at 824.

¹⁸³ Rothstein and Epps, *supra* note 181 at 229.

the United States and the European Union concerning drugs treating rare diseases.¹⁸⁴

III. DISCUSSION

Pharmacogenomics is expected to benefit drug companies, patients and regulatory bodies by improving and speeding up drug research and development, the approval process and post-marketing drug surveillance. Pharmacogenomics is also likely to change clinical practice by allowing the customization of treatments to individual genetic characteristics and by producing safer and more efficient drugs to minimize the occurrence of adverse drug reactions. A pressing question is whether, considering the benefits pharmacogenomics could provide to the practice of medicine and pharmacy, the current regulatory framework is sufficiently adapted to promote the development of pharmacogenomics or instead inhibits the development of pharmacogenomic tests. Should a simpler process be instituted in order to make the tests more readily accessible to patients and to encourage the use of pharmacogenomic testing in the development of drugs?

In our opinion, the question of whether the regulatory framework applicable to pharmacogenomic tests is appropriate pertains to considerations which are more related to the federal process than the provincial one. As seen earlier, the provincial regulations are more aimed at ensuring that the laboratories can carry out the tests they offer to the public with the best quality possible than at ensuring the clinical validity and utility of the pharmacogenomic tests.

At the federal level, some fast tracking mechanisms exist, but they are not adapted to the case of pharmacogenomic testing. Sections 69 to 78 of the *Medical Devices Regulations* provide the requirements concerning special access to medical devices.¹⁸⁵ They allow for faster access to a medical device for emergency use or if conventional therapies have failed, are unavailable or are unsuitable.¹⁸⁶ The application has to be made by a health care professional.¹⁸⁷ The minister will grant the authorization if the benefits outweigh the risks associated with the use of the device, if the health or safety of patients will not be unduly affected and if no licensed device is available in Canada for the needs of the patient.¹⁸⁸ The authorization will specify the number of units of the device authorized and the name of the health care professional to whom the manufacturer may sell the device. Another fast tracking mechanism provided by the law is the priority review process. An interim policy concerning priority review of medical devices licence applications was released by Health Canada in 2000.¹⁸⁹ Priority review will be granted if the medical device is intended for the diagnosis or treatment of a serious, life-threatening disease, or

¹⁸⁴ *Ibid.* at 229-230; Issa, *supra* note 6 at 305-306.

¹⁸⁵ *Medical Devices Regulations*, *supra* note 68, ss. 69-78.

¹⁸⁶ *Ibid.*, s. 69(2).

¹⁸⁷ *Ibid.*, s. 71.

¹⁸⁸ *Ibid.*, s. 72(1).

¹⁸⁹ Health Canada, *Interim Policy on Priority Review of Medical Device Licence Applications Policy* (Interim policy) (Ottawa: Therapeutic Products Programme, 2000) [Health Canada, *Priority Review*].

when there is clinical evidence that the device provides an effective treatment of a disease for which no medical device is available in Canada or a significant risk-benefit improvement for a disease not adequately managed by existing products.¹⁹⁰ Neither program is suited to pharmacogenomic testing because pharmacogenomic tests are not used as treatments, but rather as tools that allow choosing a more appropriate treatment. Thus, it can be difficult to demonstrate that pharmacogenomic tests are needed for emergency use or to treat a disease in cases where no other treatment options are available. Also, there has to be proof that the test will be useful, which boils down to showing evidence of the clinical validity and utility of the test. Thus, those programs do not spare the manufacturer from the difficulties mentioned earlier.

The federal process applicable to the approval of pharmacogenomic tests intended to be sold or imported as kits in Canada requires the manufacturer to assess scientific and medical evidence of the safety, efficacy, and validity of the tests they propose to offer. The time taken by Health Canada to review the licence application seems adequate (around 60 days),¹⁹¹ but the process of gathering all the evidence needed to submit an application can be a lengthy one because of the difficulties faced by the industry we mentioned earlier (e.g. demonstrating clinical validity and utility). But even if the manufacturers are faced with the difficulty of providing this type of evidence given the potential benefits of pharmacogenomics, it is essential that the sensitivity, specificity, and positive predictive value of the tests be established.¹⁹² Pharmacogenomic tests have to be reliable to avoid mistakes and poor outcomes for patients.¹⁹³ In other words, pharmacogenomic tests will only achieve the great benefits their proponents expect them to have if they are valid and useful.¹⁹⁴ Otherwise, it would be difficult to claim that pharmacogenomics will benefit patients and drug research and development.

Thus, the current regulatory requirements seem adequate because, according to the regulations, where evidence of the validity and the usefulness of a new test has been gathered, the licence should be granted. If all the evidence has been submitted, then it is possible to obtain a licence from Health Canada in a reasonable timeline. Pharmacogenomic impacts do not require the current federal process for the approval of pharmacogenomic tests to be simplified. Rather they require that the validity of the tests be scientifically established so that clinical decisions can be made from the results they provide. Because it is expected that many pharmacogenomic tests will be developed in the near future, there is a need for an efficient and

¹⁹⁰ *Ibid.*

¹⁹¹ Health Canada, *Regulatory Process*, *supra* note 103 at 11; Health Canada, *Management of Applications*, *supra* note 103 at section 7.

¹⁹² Robertson, Brody, Buchanan, Kahn and McPherson, "Pharmacogenetic Challenges," *supra* note 50 at 159.

¹⁹³ *Ibid.* Timothy A. Caufield, Michael M. Burgess and Bryn Williams-Jones, "Providing Genetic Testing through the Private Sector: A View from Canada" (2001) 2:3 Canadian Journal of Policy Research 72 at 75.

¹⁹⁴ Stuart Hogarth, Gail Javitt, and David Melzer, "The Current Landscape for Direct-to-Consumer Genetic Testing: Legal, Ethical, and Policy Issues" (2008) 9 *Annu. Rev. Genomics Hum. Genet.* 161 at 168-169.

ethical regulatory oversight of the validity and utility of the tests.¹⁹⁵

Moreover, if manufacturers do not want to go through the federal process, they can always offer their pharmacogenomic tests as laboratory services, instead of selling them as test kits. They will then have to conform with provincial requirements that are far less stringent on the question of clinical validity and utility of the tests. However, in this situation, the reviewed American literature raises concerns that the regulatory oversight of pharmacogenomic tests might not be sufficient to protect the public against pharmacogenomic tests of poor quality.¹⁹⁶

In our opinion, the federal requirements seem appropriate for pharmacogenomics. The provincial ones do not, however, because they do not focus enough on the clinical validity and utility of the tests carried out by medical laboratories. Although the current federal process should not be substantially modified, some improvements could be brought to the system. One of them could be to simplify the process applicable to pharmacogenomic tests developed during the drug development process, so that both products could be licensed at the same time by Health Canada, instead of having two parallel approval processes to follow. We examined the American *Drug-Diagnostic Co-Development Concept Paper* earlier in our analysis.¹⁹⁷ As we indicated, the final guidance document still has not been released by the FDA. It will be interesting to see what form this initiative will take and if Health Canada will follow in the footsteps of the FDA. Currently, the Canadian *Drug and Medical Device Combination Products Policy* does not apply to combination products where the drug component and the device component can be used separately, such as the case of a drug sold with a pharmacogenomic test.¹⁹⁸

CONCLUSION

The fact that manufacturers are facing difficulties in demonstrating the clinical validity and utility of the pharmacogenomic tests they are developing does not necessarily mean the federal requirements of Health Canada should be relaxed. When the studies in the research context show the potential of a pharmacogenomic test to be valid and useful, investigational testing has to be conducted to demonstrate that the research findings can translate into clinical practice. When there is sufficient evidence of the analytical validity, the clinical validity and the clinical utility of the test, Health Canada will issue a licence to the manufacturer within an acceptable timeline. Considering the promises of pharmacogenomics and the fact that it can affect health outcomes of patients, it is of the utmost importance that this type of evidence be provided by the manufacturer to protect the patients from ineffective tests that could adversely impact human health. In order to benefit from a pharmacogenomic test, it has to be effective and useful. Thus, a mechanism fast tracking the approval of pharmacogenomic tests would not necessarily provide a solution to the problems faced by the industry because proof of the validity and

¹⁹⁵ Robertson, Brody, Buchanan, Kahn and McPherson, "Pharmacogenetic Challenges," *supra* note 50 at 159.

¹⁹⁶ Buchanan, Califano, Kahn, McPherson, Robertson and Brody, "Ethical Issues", *supra* note 49 at 6.

¹⁹⁷ FDA, *Co-Development*, *supra* note 113 at 1.

¹⁹⁸ Health Canada, *Combination Products*, *supra* note 117 at section 3.

utility of the tests would still be needed. One acceptable mechanism that could speed up the process would be a policy on the co-development of drugs and medical devices. This would allow the drug and the pharmacogenomic test to be approved at the same time by Health Canada in instances where a test is used during the drug development process. It could also expedite and streamline the process by requiring one licence application, rather than two. Such a policy would not relax the need for the manufacturers to demonstrate the analytical validity, clinical validity, safety, and clinical utility of both products. Aside from this co-development mechanism, financial incentives given by the government could also promote the faster development of pharmacogenomic tests. Indeed, the economic costs of developing pharmacogenomic tests are high and, considering the fact that those tests would fragment the market and reduce the revenues from drug sales, manufacturers and drug companies are not sufficiently encouraged to develop such tests. As a society, we might need to find a way to stimulate research and development in this important research field in order to one day profit from more “personalized”, safer and more efficient medicine. Indeed, the fact that manufacturers have the tendency to develop and approve their pharmacogenomic tests outside of Canada and that most of these tests are marketed as laboratory services or “home-brewed” tests could be of concern to Canadians and raise important issues relating to timely access to safe medicines.