

FOOD AND DRUG LAW JOURNAL

*Analyzing the Laws, Regulations, and Policies
Affecting FDA-Regulated Products*

Regulatory Approval for New Pharmacogenomics Tests: A Comparative Overview

Yann Joly

Georgia Koutrikas

Anne-Marie Tassé

Amalia Issa

Bruce Carleton

Michael Hayden

Michael J. Rieder

Emma Ramos-Paque

Denise Avard



Regulatory Approval for New Pharmacogenomic Tests: A Comparative Overview

YANN JOLY
GEORGIA KOUTRIKAS
ANNE-MARIE TASSÉ
AMALIA ISSA
BRUCE CARLETON
MICHAEL HAYDEN
MICHAEL J. RIEDER
EMMA RAMOS-PAQUE
DENISE AVARD*

I. INTRODUCTION

Variability in human drug response has serious implications with respect to both drug efficacy and also drug safety, notably with respect to risk for adverse drug reactions (ADRs). The field of pharmacogenomics seeks to link genetic variants to individual variability in drug response.¹ This developing area of genomic science stems from the increasing knowledge about how certain genetic polymorphisms (i.e. differences in DNA sequence among individuals or populations) can affect the way in which a patient will respond to certain drugs.² Thus, pharmacogenomics aims to predict individual responses to drugs and to minimize ADRs by informing the choice and dose of drugs that are most appropriate for a patient based on their genetic factors.³

To date, the application of pharmacogenomics in the clinical setting has yet to reach its full potential. Drugs with pharmacogenomic information appearing on the drug label represent only a fraction of drugs with known pharmacogenomic information in their scientific literature.⁴ For example, currently only 10 percent

* Dr. Joly is a Lawyer and an Assistant Professor at the Centre for Genomics and Policy, Faculty of Medicine, McGill University. Ms. Koutrikas is a Research Student at the Centre for Genomics and Policy, Faculty of Medicine, McGill University. Ms. Tassé is a Lawyer and a Professional Associate at the Centre for Genomics and Policy, Faculty of Medicine, McGill University. Dr. Issa is Founding Director of the Program in Personalized Medicine & Targeted Therapeutics, University of Houston. Dr. Carleton is Director of the Pharmaceutical Outcomes Programme, BC Children's Hospital, University of British Columbia. Dr. Hayden is a Professor at the Department for Medical Genetics, University of British Columbia and Director and Senior Scientist at the Centre for Molecular Medicine and Therapeutics, Vancouver, Canada. Dr. Rieder is a member of the Department of Paediatrics, Children's Hospital at the London Health Sciences Centre, London, Canada. Ms. Ramos-Paque is a Lawyer and a member of the Centre for Genomics and Policy, Faculty of Medicine, McGill University. Dr. Avard is an Associate Professor at the Centre for Genomics and Policy, Faculty of Medicine, McGill University. Financial support for this research was provided by Genome Canada and Genome British Columbia through the Canadian Pharmacogenomics Network for Drug Safety research initiative.

¹ Nuffield Council on Bioethics, *Pharmacogenetics – ethical issues*, 2003, available at <http://www.nuffieldbioethics.org/sites/default/files/Pharmacogenetics%20Report.pdf>; Avinash Puri, *Pharmacogenomics: Benefits of Personalized Medicines*, 2(4) INT. J. MED. MED. SCI. 091, 091 (2009).

² Michel Eichelbaum, Magnus Ingelman-Sundberg & William E. Evans, *Pharmacogenomics and Individualized Drug Therapy* 57 ANNU. REV. MED. 119, 120 (2006).

³ Werner Kalow, *A Pharmacogeneticist's Look at Drug Effects and the Drug Development Process: An Overview*, 6(8) EXPERT OPIN. PHARMACOTHER. 1299, 1300 (2005).

⁴ Felix W. Frueh, Shashi Amur, Padmaja Mummaneni, Robert S. Epstein, Ronald E. Aubert, Teresa M. DeLuca, Robert R. Verbrugge, Gilbert J. Burckart, & Lawrence J. Lesko, *Pharmacogenomic Biomarker Information in Drug Labels Approved by the United States Food and Drug Administration: Prevalence of Related Drug Use*, 28(8) PHARMACOTHERAPY, 992, 996 (2008).

of drugs approved in the United States contain pharmacogenomic information in the drug label, and only a few of those labels required or recommended pharmacogenomic testing before use.⁵ The Pharmacogenomics Knowledge Base cited 14 drugs for which genetic testing is required, recommended or mentioned by the Food & Drug Administration (FDA) in the drug label, and two drugs for which FDA was considering including pharmacogenomic evidence in the label.⁶ However, since some of these drugs are commonly prescribed, it was estimated that, in 2006, almost one in four patients in the United States received a prescription for which pharmacogenomic information was included in the product label.⁷

Recently in the United States, pharmacy benefit managers (PBMs), who provide coverage for pharmaceuticals, are very interested in undertaking pharmacogenomic initiatives that would encourage or even require pharmacogenomic testing for individuals taking certain drugs.⁸ PBMs believe that pharmacogenomics has the potential to save costs related to drug prescribing. Whether the cost of drugs is covered directly by patients or by providers, pharmacogenomics can reduce spending on drugs that will not be useful, or that may even be harmful.

While innovation in pharmacogenomics as well as encouragement of its clinical application is desirable, regulation of the safety and effectiveness of pharmacogenomics testing is necessary. Striking a balance between these two goals is a difficult task, but is imperative in order to reap the benefits of this emerging field.

This article will first present the potential of pharmacogenomics in making drugs safer and more effective, and its impact on the drug development process. The second part will describe the current regulatory framework applicable to pharmacogenomic tests in Canada, the United States and Europe. It will also examine how new regulatory structures developing in these jurisdictions aim to advance knowledge in the field of pharmacogenomics, make drugs safer and make better products available to consumers. This review will allow for an evaluation of the issues raised by the regulatory framework in relation to ensuring public safety and promoting the advancement of the field.

II. PHARMACOGENOMICS: RATIONALIZING THE DRUG DEVELOPMENT PROCESS

Pharmacogenomics promises to deliver considerable public health benefits. These benefits include making drugs safer and more effective, improving drug research and development and helping new drugs become available more quickly.⁹ Furthermore, pharmacogenomics research offers the possibility of monitoring the safety of drugs which are already marketed by identifying genetic factors linked to ADRs.¹⁰

⁵ US FOOD AND DRUG ADMINISTRATION, TABLE OF VALID GENOMIC BIOMARKERS IN THE CONTEXT OF APPROVED DRUG LABELS, http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm (last visited November 15, 2010).

⁶ Pharmacogenomics Knowledge Base, *Clinical Pharmacogenomics*, <http://www.pharmgkb.org/clinical/index.jsp> (last visited November 15, 2010).

⁷ Frueh et al., *supra* note 4, at 995.

⁸ Eric J. Topol, *Pharmacy Benefit Managers, Pharmacies, and Pharmacogenomic Testing: Prescription for Progress?* 2(44) *SCI. TRANSL. MED.* 44cm22, 44cm22 (2010).

⁹ Amalia M. Issa, *Ethical perspectives on pharmacogenomic profiling in the drug development process*, 1 *NAT. REV. DRUG DISCOV.* 300, 300 (2002).

¹⁰ Shashi Amur, Felix W. Frueh, Lawrence J. Lesko & Shiew-Mei Huang, *Integration and use of biomarkers in drug development, regulation and clinical practice: a US regulatory perspective*, *BIOMARKERS IN MEDICINE* 305, 307 (2008).

First, patients and physicians can expect pharmacogenomics to provide safer and more effective drug prescription practices. Some drugs have been estimated to be effective only in 50 percent of people receiving them,¹¹ and ADRs are among the leading causes of hospitalization and death.¹² Indeed, a 2008 review found that 59 percent of drugs that often have ADRs are metabolized by an enzyme known to be linked to genetic polymorphisms for altered metabolism.¹³ The use of pharmacogenomic tests can help determine if a patient will benefit from a particular drug, determine the appropriate dose for each patient and predict side effects.¹⁴ Thus, pharmacogenomic information can help physicians decide the most appropriate dosing schedule for patients based on their genotype,¹⁵ or whether a patient should be prescribed a particular drug at all.¹⁶ This type of personalized drug therapy can therefore help reduce the incidence of side effects¹⁷ and increase the overall safety and effectiveness of drugs.

Second, in order for drug development to become cheaper and more efficient, pharmacogenomic studies can be undertaken throughout the drug development process. Pharmacogenomics has been cited as one of the tools that could help bring safer and more effective drugs to market by informing the drug development process in each of its stages, thereby reducing its time and cost.¹⁸ Drug development is long and expensive, estimated to cost between US \$350 million and US \$1 billion, and last up to 12 years from initial development to commercialization.¹⁹ In recent years, despite advances in biomedical research, there has been a decline in the amount of new drugs brought to market: for example, only 10 percent of drug candidates developed by industry are successfully commercialized, and even these drugs sometimes present serious adverse effects following their introduction to the market.²⁰ Moreover, the massive monetary investments made by industry in the field of drug development are not being matched by an increase in the number of available new drugs. This productivity crisis affecting the pharmaceutical industry is known as the ‘innovation gap.’²¹

Pharmacogenomic research could be particularly useful in the clinical trial phases of drug development. Drugs often fail in clinical trials because they do not show significant therapeutic benefit or meet safety standards in patient groups.²² Clinical trials, required to show the safety and efficacy of new drugs, are the most costly stage of the drug development process.²³ Pharmacogenomics could be applied in each of

¹¹ Leslie Tucker, *Pharmacogenomics: A Primer for Policymakers*, NATIONAL HEALTH POLICY FORUM, at 3 (2008).

¹² Jason Lazarou, Bruce H. Pomeranz, & Paul N. Corey., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies*, 279(15) JAMA 1200, 1204 (1998).

¹³ Kathryn A. Phillips, David L. Veenstra, Eyal Oren, Jane K. Lee & Wolfgang Sadec, *Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review*, 286 JAMA 2270 (2001).

¹⁴ Tucker, *supra* note 11, at 3.

¹⁵ Lawrence J. Lesko & Janet Woodcock, *Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective*, 3 NATURE REVIEWS DRUG DISCOVERY 763, 768 (2004).

¹⁶ John A. Robertson, Baruch Brody, Allen Buchanan, Jeffrey Kahn & Elizabeth McPherson, *Pharmacogenetic challenges for the health care system*, 21(4) HEALTH AFFAIRS 155, 157 (2002).

¹⁷ Issa, *supra* note 9.

¹⁸ Kalow, *supra* note 3.

¹⁹ OECD, *Pharmacogenomics: Opportunities and Challenges for Health Innovation* (2009) at 44.

²⁰ *Id.*

²¹ Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg & Aaron L. Schacht, *How to improve R&D productivity: the pharmaceutical industry’s grand challenge*, 9 NATURE REVIEWS DRUG DISCOVERY 203, 203 (2010).

²² Tucker, *supra* note 11, at 6.

²³ OECD, *supra* note 19, at 50.

the two key outcomes of clinical trials and help to identify early on medicines that are likely to fail.²⁴ As early as Phase I trials, which study the safety of the chemical compound in small samples of trial participants, pharmacogenomic investigations can help identify genetic factors that explain pharmacokinetic concepts (i.e. absorption, distribution, metabolism and excretion) and pharmacodynamics (physiological effects of the drug).²⁵ If genetic factors are determined to be highly relevant in the pharmacokinetic and/or pharmacodynamic action of the drug, the decision might be made early to not pursue further studies of the drug as it would likely fail in later clinical development. Therefore, the cost of investment in larger-scale studies could be saved, and attrition rates of drug candidates could be reduced.²⁶

In Phase II studies, which evaluate the chemical compound's therapeutic efficacy and safety in a sample of about 200-300 individuals,²⁷ patients can be grouped according to biomarkers in order to identify those individuals who are more likely to respond to the drug.²⁸ The results of Phase II can then be used to guide Phase III of clinical trials, which determines whether a drug succeeds in meeting the standards for regulatory approval and can be marketed.²⁹ For instance, smaller sample sizes could be used in Phase III: the identification of genetic markers affecting drug response could lead to clinical trials being designed to specifically include individuals or subpopulations that are more likely to respond to the drug, therefore increasing the observed efficacy (and even therapeutic effectiveness compared to placebo or standard therapies).³⁰ Although this might reduce the size of the target population for the drug downstream, individuals who are more likely to experience adverse effects could also be excluded from the trial.³¹ However, careful consideration should be given to the ethics of excluding patients from access to experimental drugs. Regulatory agencies will probably still require drugs to be tested in the overall population in order to meet safety standards and to evaluate safety in the population that might receive the drug in the absence of pharmacogenomic testing.³² Still, clinical trials designed with pharmacogenomic information in mind could lead to better data on the safety and efficacy of drugs. Pharmacogenomic testing can improve the safety and efficacy of a drug in this phase, by identifying parameters for drug prescribing based on genotype before the drug enters the market.³³ The label of an approved drug could contain information regarding the association of a patient genotype with the effectiveness of a drug, and might include a recommendation for pharmacogenomic testing.³⁴

Perhaps the most interesting role of pharmacogenomics, however, is in improving the safety of drugs after they are released into the market, sometimes referred to as Phase IV of drug development or postmarket pharmacovigilance. Serious and rare ADRs are often not detected until drugs are used in the "real world" by larger and more varied populations than those included in clinical trials.³⁵ When ADRs are observed, pharmacogenomic research could help identify biomarkers

²⁴ *Id.* at 51.

²⁵ Kalow, *supra* note 3, at 1301.

²⁶ *Id.*

²⁷ OECD, *supra* note 19, at 50.

²⁸ Lesko & Woodcock, *supra* note 15, at 764.

²⁹ OECD, *supra* note 19, at 50.

³⁰ Kalow, *supra* note 3, at 1301.

³¹ Louis P. Garrison *et al.*, *A review of public policy issues in promoting the development and commercialization of pharmacogenomic applications: challenges and implications*, 40 DRUG METABOLISM REVIEWS 377, 381 (2008).

³² *Id.*

³³ Scott T. Weiss *et al.*, *Creating and evaluating genetic tests predictive of drug response*, 7 NATURE REVIEWS DRUG DISCOVERY 568, 570 (2008).

³⁴ Lesko & Woodcock, *supra* note 15, at 766.

³⁵ Amur *et al.*, *supra* note 10.

predictive of adverse effects, leading to pharmacogenomic tests that could inform drug therapy,³⁶ as well as changing drug labels to include this type of information related to safety.³⁷ Regulatory agencies are particularly interested in the role of pharmacogenomics in improving the risk/benefit ratio of drugs already on the market, especially those with a narrow therapeutic range and frequent ADRs, through personalized dosing based on genetic variation.³⁸ As of 2009, FDA had approved the inclusion of pharmacogenomic information to 58 drug labels,³⁹ although it requires (e.g., trastuzumab, dasatinib) or recommends (e.g. codeine, carbamazepine) testing only for few of them. Studies of genetic factors associated with ADRs could help determine which patients can safely use a drug and those who should avoid it.⁴⁰

A. *The case of CPNDS/cisplatin*

In order to illustrate the benefits of pharmacogenomics in post-marketing pharmacovigilance, the research of the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) on the drug cisplatin will serve as an example. Cisplatin is a chemotherapy drug widely used to treat malignancies, including neuroblastomas and germ cell tumours.⁴¹ Despite its common use, it can cause serious adverse effects. One of its most important adverse effects is ototoxicity, causing permanent hearing loss in up to 25 percent of adults and 60 percent of children receiving treatment.⁴² The potential adverse reaction leads to a treatment dilemma; namely, the dose is sometimes reduced or treatment is prematurely discontinued, leading to potential decreased survival rates or, if treatment is pursued, impaired cognitive development in children (a secondary effect of hearing loss) may result.⁴³

The CPNDS, a large-scale international consortium funded by the Canadian Institutes of Health Research, the Canada Foundation for Innovation, Genome British Columbia and other funding partners, launched in 2009 a system to monitor ADRs in children and increase drug safety.⁴⁴ Through the establishment of a national database of clinical and genetic information, the CPNDS works to identify biomarkers predictive of adverse drug reactions with the goal of developing diagnostic tools to guide personalized drug therapy for commonly used drugs.⁴⁵ In this vein, the CPNDS

³⁶ OECD, *supra* note 19, at 105.

³⁷ Lesko & Woodcock, *supra* note 15, at 767.

³⁸ *Id.*

³⁹ Sara Katsanis & Gail Javitt, *Pharmacogenomics: Hope and Hype*, September 2008, <http://www.dnapolicy.org/images/issuebriefpdfs/PGx%20IB.pdf> (last visited October 22, 2010).

⁴⁰ Amur et al., *supra* note 10.

⁴¹ L. Riedemann, et al., *Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin*, 8 THE PHARMACOGENOMICS JOURNAL, 23, 23 (2007).

⁴² 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 & the CPNDS Consortium, *Genetic variants in TPMT and COMP are associated with hearing loss in children receiving Cisplatin chemotherapy*, 41(2) NAT. GENETICS 1345, 1345 (2009).

⁴³ *Id.*

⁴⁴ *New research project aims to unlock genetic keys to childhood ADRs and help reduce their incidence*, 142(2) CPJ/RPC 57 (2009); Bruce C. Carleton et al., *Adverse drug reaction active surveillance : developing a national network in Canada's children's hospitals*, 18 PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 713, 715 (2009).

⁴⁵ Colin J.D. Ross, Bruce Carleton, Dana G. Warn, Sunita B. Stenton, Shahrhad Rod Rassekh & 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*, 1110 ANN. N.Y. ACAD. SCI. 177, 180 (2007); Turna Ray, *Genome BC project aims to launch PGx test to predict adverse drug reactions in children*, PHARMACOGENOMICS REPORTER (11 February 2009), <http://www.genomeweb.com/dxpgx/genome-bc-project-aims-launch-pgx-test-predict-adverse-drug-reactions-children> (last visited October 22, 2010).

in 2006 conducted a study of 54 children treated with cisplatin in British Columbia, Canada, of which 60 percent suffered from serious hearing impairment following the use of cisplatin.⁴⁶ The study identified two genetic polymorphisms associated with this adverse reaction.⁴⁷ The gene encoding thiopurine S-methyltransferase (TPMT) and the gene encoding catechol O-methyltransferase (COMT) were found to be highly predictive of cisplatin-induced hearing loss.⁴⁸ The results were replicated in a second cohort of 112 children (66 percent of whom suffered from serious hearing loss following cisplatin use) across Canada who received the drug.⁴⁹

These results indicate that it is possible to identify patients at high risk of developing ototoxicity as an adverse effect of cisplatin, to allow physicians to decide whether to recommend a lower dose of the drug, monitor hearing function more often or target these patients for inclusion in experimental otoprotectant studies.⁵⁰ Thus, the availability of a pharmacogenomic test to detect these polymorphisms could be very useful in helping to avoid this serious adverse effect of cisplatin and to guide treatment decisions. As these results can have a significant impact on the future use of cisplatin, the study's authors met with FDA's Drug Safety Oversight Board in February 2010 to discuss the published findings.⁵¹

Having seen the potential of pharmacogenomics to deliver public health benefits, we can observe the importance of advancements in this field. An important consideration in the transfer of technology is whether the regulatory framework is conducive to the development of this field. Our focus will now turn to a comparative analysis of the regulation of pharmacogenomic tests in Canada, the United States and Europe.

III. LEGAL LANDSCAPE

Before embarking on a discussion of the regulatory frameworks surrounding pharmacogenomic tests, two preliminary points should be highlighted. First, the vast majority of pharmacogenomic tests that exist are available in the United States and Europe, but are reaching the market more slowly in Canada. Second, although pharmacogenomic tests could be considered medical devices in Canada, the United States and Europe, in all three of these regions the vast majority of pharmacogenomic tests generally become available as laboratory-developed tests (LDTs) or "home-brews." This distinction is likely due to the fact that the regulation of LDTs, which are considered laboratory services rather than medical devices in Canada and the United States (less so in Europe), is less stringent for test developers (although laboratories are still thoroughly regulated). This point will be examined in greater detail in the description of the regulation of pharmacogenomic tests in each of the jurisdictions studied.

A. Canada

In Canada, the route chosen by the manufacturer to market the pharmacogenomic test will determine which level of government will have competence.⁵² The

⁴⁶ Ross et al., *supra* note 41.

⁴⁷ S. Rod Rassekh, *Adverse events in pediatric oncology – The GATC Cancer Study*, 8 PEDIATRIC ONCOLOGY HEMATOLOGY NETWORK NEWSLETTER (BC Children's Hospital, Vancouver, Canada), Spring 2007 at 3, 4.

⁴⁸ Ross et al., *supra* note 41, at 1346.

⁴⁹ *Id.* at 1345.

⁵⁰ *Id.* at 1348.

⁵¹ E-mail from CPNDS to Yann Joly (June 28, 2010) (on file with author).

⁵² MYLÈNE DESCHÈNES, RÉFLEXION SUR L'ENCADREMENT NORMATIF DE LA MISE EN MARCHÉ DES TESTS GÉNÉTIQUES 52-53 (2005).

division of powers set out in the *Constitution Act, 1867*⁵³ gives both the federal and provincial governments power over the regulation of genetic tests, which include pharmacogenomic tests. The federal government's regulatory agency, Health Canada, has authority over the marketing and publicity of therapeutic products by virtue of its jurisdiction over criminal matters (s. 91(27)), while the provincial governments regulate genetic tests offered as laboratory services within their competence over the management of health services.⁵⁴

Therefore, genetic test kits which are commercially available in Canada are defined as an *in vitro* diagnostic device (IVD) "consisting of reagents or articles intended to be used to conduct a specific test"⁵⁵ under the *Medical Devices Regulations*, and are subject to approval by Health Canada.⁵⁶ However, laboratories can also develop their own pharmacogenomic tests and offer them as laboratory services. These LDTs do not meet the definition of a medical device since they are not sold as a kit but rather offered as services,⁵⁷ and are therefore subject to control by the Canadian provinces by virtue of their regulation of the laboratories themselves.⁵⁸ This distinction between test kits and LDTs will also be important in the other jurisdictions we will discuss.

1. Federal Regulation

Health Canada is the federal regulatory authority in charge of the evaluation of the safety and effectiveness of health products marketed for human use in Canada.⁵⁹ The Therapeutic Products Directorate within Health Canada is responsible for granting market authorization for medical devices in conformity with the provisions of the *Food and Drugs Act*⁶⁰, the *Food and Drug Regulations*⁶¹ and the *Medical Devices Regulations*.⁶² With respect to pharmacogenomic tests, the *Medical Devices Regulations*⁶³ require that such medical devices distributed in Canada are safe and effective and meet quality standards in order for the manufacturer to obtain a license to sell the product on the Canadian market.⁶⁴ Sections 10 to 20 of the *Medical Devices Regulations* set out the safety and effectiveness requirements.⁶⁵

Medical devices in Canada are categorized according to their level of risk into Classes I to IV, with Class IV representing the highest risk⁶⁶ (risk classification systems are also found in the United States and Europe), and with each class being subject to different standards of evaluation for safety and effectiveness. In general, IVDs used for genetic testing are specifically classified as Class III medical devices,

⁵³ Constitution Act, 1867, 30 & 31 Vict., Ch. 3 (U.K.), as reprinted in R.S.C., No. 5 (Appendix 1985).

⁵⁴ Constitution Act, 1867, 30 & 31 Vict., Ch. 3 (U.K.), as reprinted in R.S.C., No. 5 (Appendix 1985) § 91 (27), 92 (7), 92 (13) and 92 (16); Anne-Marie Tassé & Béatrice Godard, L'encadrement législatif de la vente directe des tests génétiques et le système de santé québécois, 15 HEALTH L.J. 441, ¶ 9 (2007).

⁵⁵ Medical Devices Regulations, S.O.R./98-282 at s. 1.

⁵⁶ *Id.*

⁵⁷ *Id.*; Health Canada, Guidance for the risk based classification system of in vitro diagnostic devices (Draft Guidance) (1998) § 2.2.

⁵⁸ DESCHÈNES, *supra* note 51, at 52-53.

⁵⁹ Health Canada, Submission of Pharmacogenomic Information (Guidance Document), § 2.0, http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/pharmaco/pharmaco_guid_id-eng.php (last visited October 22, 2010); Food and Drugs Act, R.S.C., ch. F-27 (1985) § 30; Medical Devices Regulations, S.O.R./98-282.

⁶⁰ Food and Drugs Act, R.S.C., ch. F-27 (1985).

⁶¹ Food and Drug Regulations, C.R.C., c. 870.

⁶² Medical Devices Regulations, S.O.R./98-282.

⁶³ *Id.*

⁶⁴ Health Canada, Preparation of a Premarket Review Document for Class III and Class IV Device/Licence Applications (Guidance) (1998) § 1.2.

⁶⁵ Medical Devices Regulations, S.O.R./98-282 § 10-20.

⁶⁶ *Id.* § 6.

although similar devices intended to be used for purposes other than genetic testing are considered Class II.⁶⁷ Class III devices are “considered to present either a moderate public health risk or a high individual risk”.⁶⁸ Section 32(3) of the *Medical Devices Regulations* sets out the requirements for obtaining a licence for a new Class III medical device,⁶⁹ which include a summary of all studies providing evidence of the safety and effectiveness of the device.⁷⁰ In the case of a near patient *in vitro* diagnostic device, defined as an IVD “that is intended for use outside a laboratory, for testing at home or at the point of care,”⁷¹ the manufacturer must also conduct investigational testing before applying for a license to sell the product in Canada.⁷²

Health Canada’s review of Class III devices therefore requires manufacturers to provide evidence of analytical validity (accuracy with which the test identifies the genotype of interest), clinical validity (accuracy with which a test predicts a clinical outcome)⁷³ and clinical utility (likelihood that the use of the test will lead to an improved health outcome).⁷⁴ In order to establish clinical validity, manufacturers can use scientific literature as evidence for known biomarkers, but formal clinical trials⁷⁵ may be required for “new biomarkers or biomarkers for which there is conflicting data in the literature.”⁷⁶ The review of a Class III medical device licence application takes approximately 60 days.⁷⁷

Drug manufacturers may wish to conduct pharmacogenomic studies during the drug development process, instead of investigating genetic markers associated with ADRs a posteriori. In this way, the drug may be marketed with the diagnostic test or may include pharmacogenomic information on the label. Developers of pharmacogenomic tests can be exempt from some of the safety and effectiveness requirements set out in ss. 10-20 of the *Medical Devices Regulations* if the tests are distributed for use in an investigational context to a qualified investigator,⁷⁸ but must still satisfy certain, less stringent, safety requirements to obtain an authorization from Health Canada.⁷⁹ An application for authorization for investigational testing must contain all available data supporting the analytical validity of the genetic test,⁸⁰ including a risk assessment of the use of the IVD in the proposed investigational study.⁸¹ 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

⁶⁷ See *id.* Sch. I, part 2, rule 4(b).

⁶⁸ Health Canada, Guidance for the risk based classification system of in vitro diagnostic devices (Draft Guidance) (1998) § 3.

⁶⁹ Medical Devices Regulations, S.O.R./98-282 § 32(3).

⁷⁰ *Id.* § 32(3)(f).

⁷¹ See *id.* § 1, s.v. “near patient *in vitro* diagnostic device”.

⁷² *Id.* §. 32(3)(h).

⁷³ Refers to the accuracy with which a test predicts a clinical outcome.

⁷⁴ Refers to the likelihood that the use of the test result will lead to an improved health outcome.

⁷⁵ Definition of a clinical trial, according to Health Canada: An investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug. Food and Drug Regulations, C.R.C., c. 870, C.05.001.

⁷⁶ E-mail from Patrice Sarrazin, Senior Scientific Evaluator, In Vitro Diagnostic Devices, Medical Devices Bureau, Health Canada, to Georgia Koutrikas (July 27, 2010) (on file with author).

⁷⁷ Health Canada, Access to Therapeutic Products – The Regulatory Process in Canada (2006) at 11; Health Canada, Management of Applications for Medical Device Licences and Investigational Testing Authorizations (2001) § 7.

⁷⁸ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008) § 2.1.1., Medical Devices Regulations, S.O.R./98-282 § 80(2)

⁷⁹ *Id.* § 83.

⁸⁰ *Id.* § 79 and 88., Karine Morin, *Canadian Legal Oversight of Pharmacogenomics and Nutrigenomics*, 16(3) HEALTH L. REV. 21, 21 (2008).

⁸¹ Medical Devices Regulations, S.O.R./98-282 § 81.

patients can be expected, that the testing is in the best interests of patients and that the objective of the testing will be achieved.⁸²

Recent developments in Health Canada's regulatory framework could impact the field of pharmacogenomics. Indicating that it considers pharmacogenomics to have the potential to play an integral role in drug development, Health Canada issued in 2007 a *Guidance Document on Submission of Pharmacogenomic Information*.⁸³ These guidelines encourage the submission of pharmacogenomic data when filing a new drug submission.⁸⁴ The *Food and Drug Regulations* require that the Clinical Trial Application for a new drug include data on the pharmacokinetics, pharmacodynamics, safety, efficacy and dose responses of a drug.⁸⁵ In accordance with this requirement, pharmacogenomic data relevant to these aspects must be submitted if they support the safety and/or efficacy of the drug.⁸⁶ As well, pharmacogenomic information shall also be submitted as part of the clinical trial application if it intends to support the design of the proposed clinical trial, to justify human testing or to support the proposed labeling of the drug.⁸⁷ In accordance with sections C.08.002, C.08.002.1 and C.08.003 of the *Food and Drug Regulations*,⁸⁸ pharmacogenomic data shall be submitted as part of a New Drug Submission (NDS) if it provides evidence of the safety and clinical effectiveness of the drug and supports the proposed dosage, contra-indications and adverse reactions.⁸⁹ Furthermore, Health Canada can request additional pharmacogenomic information related to the safety and effectiveness of the drug.⁹⁰ Health Canada also encourages the application for a medical device license for a pharmacogenomic test that is intended to be used to guide drug therapy⁹¹ if one is not already licensed in Canada. The agency also encourages drug sponsors to consider including the relevant pharmacogenomic information in the drug label.⁹² As for postmarket information, Health Canada encourages drug sponsors to communicate with Health Canada pharmacogenomic information relating to the safety and efficacy of drugs that are already on the market in order to discuss strategies to address these issues, such as considering changes to the drug label.⁹³ The agency recommends that drug sponsors integrate pharmacogenomic testing as part of the International Conference on Harmonization (ICH) E2E guidance document on Pharmacovigilance Planning,⁹⁴ which provides direction on planning pharmacovigilance activities, and which Health Canada is in the process of implementing.⁹⁵

Other initiatives could have an impact on the application of pharmacogenomics in Canada. One of the major changes which could affect the area of pharmacogenomics is Health Canada's proposed Progressive Licensing Model.⁹⁶ This new model of drug regulation might encourage, or eventually require or impose, the submission

⁸² *Id.* § 83.

⁸³ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008).

⁸⁴ *Id.* § 1.3.

⁸⁵ Food and Drug Regulations, C.R.C., c. 870 § C.05.005 (e).

⁸⁶ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008) § 2.1.

⁸⁷ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008) § 2.1.

⁸⁸ Food and Drug Regulations, C.R.C., c. 870 § C.08.002. C.08.002.1 and C.08.003.

⁸⁹ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008) § 2.2.

⁹⁰ Food and Drug Regulations, C.R.C., c. 870 at Part C, Division 8.

⁹¹ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008) § 2.2.1.

⁹² *Id.* § 2.2.2.

⁹³ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008) § 4.0.

⁹⁴ ICH E2E Pharmacovigilance Planning, http://www.ich.org/cache/compo/MediaServer.jsr?@_ID=1195&@_TYPE=MULTIMEDIA&@_TEMPLATE=616&@_MODE=GLB (last visited November 15, 2010).

⁹⁵ Health Canada, *Submission of Pharmacogenomic Information* (Guidance) (2008) § 4.0.

⁹⁶ Health Canada, Progressive Licensing Model, <http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/index-eng.php> (last visited October 22, 2010).

of pharmacogenomic information affecting drug safety when submitting licenses for new drugs. Health Canada proposes to require risk management plans⁹⁷ for therapeutic products presenting a safety concern, such that pharmacogenomic information on which patients are more likely to experience an ADR should be used to develop strategies to avoid these risks: for example, this information could be imparted to healthcare professionals and patients to aid them in making appropriate decisions about drug therapy.⁹⁸

The Progressive Licensing Model also intends to monitor drugs and evaluate associated risks throughout a drug's life-cycle, gathering and assessing information about a product's safety before and after it has been brought to market.⁹⁹ Under the new regulatory model, testing for genetic factors affecting drug response may be required in every step of the development and marketing process of drugs, and pharmacovigilance (strategic planning to detect ADRs) could be incorporated at the pre-marketing stage in order to predict adverse effects and manage risks before the need arises to withdraw drugs from the market due to safety concerns.¹⁰⁰

However, the way in which the new Progressive Licensing Model will most likely relate to pharmacogenomics is in its role in providing postmarket evidence of safety. Because adverse reactions to drugs often only become apparent after their commercialization, Health Canada is concerned that the *Food and Drug Regulations* do not currently provide Health Canada the authority to request new data on the safety or efficacy of drugs once they have received marketing authorization.¹⁰¹ Bill C-51—*An Act to Amend the Food and Drugs Act*, introduced in the House of Commons in April 2008, proposed to grant authorization to Health Canada to require post-marketing studies and the submission of data related to the safety and efficacy of drugs, as well as to require labels to be revised.¹⁰² Pharmacogenomic information could therefore be required in postmarket examination of the safety of drugs, and thus the disclosure of this type of data could be required. Bill C-51 died when Parliament was dissolved later in 2008, but Health Canada intended to reintroduce the proposed legislation.¹⁰³ This regulatory amendment would mirror the authority that the European Medicines Agency (EMA) and FDA have to require postmarket studies as a condition of market approval, although these agencies can require such studies only under exceptional or special circumstances.¹⁰⁴

⁹⁷ Health Canada, Progressive Licensing Model, Risk Management and Planning, <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/commun-ris/commun-ris06-eng.php> (last visited October 22, 2010).

⁹⁸ Health Canada, Progressive Licensing Model, Risk Management and Planning, <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/commun-ris/commun-ris06-eng.php> (last visited November 17, 2010).

⁹⁹ Health Canada, Progressive Licensing Model, Life-cycle Management, <http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/life-cycle-vie-eng.php> (last visited November 17, 2010).

¹⁰⁰ Health Canada, Pharmacovigilance Planning, <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/condition/condition03-eng.php> (last visited November 17, 2010).

¹⁰¹ Health Canada, Progressive Licensing, Discussion Paper: Authority to Require Post-market Studies, <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/pma-aac/pma-aac04-eng.php> (last visited October 22, 2010).

¹⁰² An Act to amend the Food and Drugs Act and to make consequential amendments to other Acts, Bill C-51, House of Commons, 39th Parliament - 2nd Session (2008).

¹⁰³ Maurica Maher, The Emerging Role of Post-Market Evidence Generation in Decision-Making: Linkages to the Product Lifecycle Approach (2009) http://www.cadth.ca/media/symp-2009/presentations/CS-4/Maurica%20Maher%20-%20The%20Emerging%20Role%20of%20Post-Market%20Evidence%20Generation%20in%20Decision-Making_%20Linkages%20to%20the%20Product%20Lifecycle%20Approach.pdf (last visited October 22, 2010).

¹⁰⁴ Health Canada, Progressive Licensing, Discussion Paper: Authority to Require Post-market Studies, <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/pma-aac/pma-aac04-eng.php> (last visited October 22, 2010). EMA or European Union (EU) member states can require postmarket studies under exceptional circumstances, such as safety and efficacy data cannot be provided at the pre-market stage under "normal conditions of use". FDA can only under special circumstances require drug sponsors to commit to conducting postmarketing studies as a condition of market approval, such as in the case of new drugs for serious or life-threatening illnesses, where long clinical trials may not be ethical or feasible.

2. Provincial Regulations

The regulation of pharmacogenomic tests by the Canadian provincial governments is carried out through the oversight of services delivered by genetic laboratories, by virtue of the provinces' jurisdiction over health services management.¹⁰⁵ The provinces evaluate laboratory proficiency, but do not evaluate pharmacogenomic tests in the sense that Health Canada approves drugs and medical devices through the lens of a safety and effectiveness review. Provincial regulatory requirements for laboratories vary by province, but generally include that of holding a licence issued by the government officially authorizing them to carry out certain analyses¹⁰⁶ and establishing that the personnel is qualified. Laboratories must also obtain a peer-delivered accreditation and establish internal and external quality controls of the laboratory.¹⁰⁷

For example, in Quebec, private laboratories offering genetic tests must obtain an operating license from the provincial Minister of Health¹⁰⁸ specifically permitting medical biology examinations and analyses¹⁰⁹ in the field of biochemistry.¹¹⁰ While public laboratories, usually in hospitals, do not themselves need to hold a license, the institutions where the laboratories are operated must hold one.¹¹¹ Similarly, in British Columbia laboratories must obtain a license from the Medical Services Commission,¹¹² which grants one if it is satisfied that the quality of the diagnostic services is high.¹¹³ Additional quality controls are provided in the *Medical and Health Care Services Regulation*, ensuring that the laboratory complies with diagnostic protocols and guidelines adopted by the Commission,¹¹⁴ and that personnel are qualified and supervised by medical personnel.¹¹⁵

In addition, laboratories in Quebec and British Columbia are required to be accredited from an independent body certifying their competence to carry out the analyses offered on site.¹¹⁶ This evaluation by independent professionals aims to ensure the safety and quality of the tests offered, good operations and practices of the laboratory and that the personnel are competent.¹¹⁷ In Canada, provincial accreditation standards vary, but all are inspired by the ISO 15189—*Medical lab-*

¹⁰⁵ Constitution Act, 1867, 30 & 31 Vict., Ch. 3 (U.K.), as reprinted in R.S.C., No. 5 (Appendix 1985) § 92 (7), 92 (13) and 92 (16); See also ANNE-MARIE TASSÉ & BÉATRICE GODARD, L'INTERNATIONALISATION DES SERVICES GÉNÉTIQUES – ANALYSE COMPARATIVE DES NORMES DE GOUVERNANCE CANADIENNES, AMÉRICAINES, BRITANNIQUES ET AUSTRALIENNES 41 (2009).

¹⁰⁶ ANNE-MARIE TASSÉ & BÉATRICE GODARD, L'INTERNATIONALISATION DES SERVICES GÉNÉTIQUES – ANALYSE COMPARATIVE DES NORMES DE GOUVERNANCE CANADIENNES, AMÉRICAINES, BRITANNIQUES ET AUSTRALIENNES 41 (2009).

¹⁰⁷ *Id.*

¹⁰⁸ An Act Respecting Medical Laboratories, Organ Tissue, Gamete and Embryo Conservation, and the Disposal of Human Bodies, R.S.Q. ch. L-0.2 § 31.

¹⁰⁹ *Id.* § 91.

¹¹⁰ Ministry of Health and Social Services, Laboratoire de biologie médicale – Mesure de la production (2003), at 5-6; DESCHÊNES, *supra* note 51, at 69.

¹¹¹ An Act respecting health services and social services, R.S.Q. c. S-4.2 § 437.

¹¹² *Medicare Protection Act*, R.S.B.C. 1996, c. 286 § 33(1).

¹¹³ Medical and Health Care Services Regulation, B.C. Reg. 426/97.

¹¹⁴ *Id.*

¹¹⁵ *Id.*

¹¹⁶ Hui Li, *Laboratory quality regulations and accreditation standards in Canada*, 42 CLINICAL BIOCHEMISTRY 249, 249 (2009).

¹¹⁷ Élodie Petit, Anne Marie Tassé & Béatrice Godard, *The Empirical Analysis of the Legal Frameworks Governing Genetic Services Labs in Canadian Provinces*, 16(3) HEALTH L. REV. 65, ¶ 11 and 16 (2008).

oratories—*Particular requirements for quality and competence*¹¹⁸ standard and its Canadian version CAN/CSA Z15189-03—*Medical laboratories Particular requirements for quality and competence*.¹¹⁹ However, in Quebec no such accreditation is required for private laboratories offering genetic tests,¹²⁰ whereas the institutions which operate public laboratories must be accredited by a body recognized by the Ministry of Health and Social Services.¹²¹ It is notable that recent laboratory diagnostic errors in Quebec, particularly those involving testing for the HER2/neu gene, have generated much concern and debate.¹²² Finally, the provinces also require medical laboratories to establish internal¹²³ and external¹²⁴ quality controls guaranteeing the quality and reliability of the data produced.

In comparison to federal regulation, the oversight of pharmacogenomic tests at the provincial level is less demanding, as it focuses on the quality and functioning of the laboratories delivering these tests, but it does not examine individual tests for evidence of clinical validity and clinical utility.¹²⁵ Of course, laboratories are restricted to offering only those services authorized by their license, but the rigour with which they are scrutinized makes the regulation of LDTs less burdensome. Thus, LDTs can be made more readily available to consumers. However, LDTs can only be used in-house, and cannot be commercially marketed to consumers or sold to other laboratories. Thus, the availability of LDTs is limited by the capacity of each laboratory to offer its services.

B. *United States*

To date, in the United States, the distinction between test kits and LDTs also has an impact on the level of regulation required over pharmacogenomic tests. FDA plays a role similar to that of Health Canada in regulating pharmacogenomic tests developed for distribution in the United States. Genetic test kits developed for sale to laboratories or directly to consumers¹²⁶ are regulated by FDA as medical devices.¹²⁷ In contrast, LDTs developed and used by a single laboratory “in-house” are considered medical services and do not need to be approved by FDA, but are instead regulated by the Centers for Medicare and Medicaid Services (CMS) and the Center for Disease Control (CDC).¹²⁸ However, FDA announced in July 2010 that it would exercise its authority over LDTs as well,¹²⁹ a move that could change the landscape for pharmacogenomics in the United States. A discussion of the current state of affairs will help clarify the reasons behind this recent development in the United States.

¹¹⁸ ISO 15189 - *Medical laboratories -- Particular requirements for quality and competence*.

¹¹⁹ CAN/CSA Z15189-03 - *Medical laboratories Particular requirements for quality and competence*

¹²⁰ An Act Respecting Medical Laboratories, Organ Tissue, Gamete and Embryo Conservation, and the Disposal of Human Bodies, R.S.Q. ch. L-0.2 § 30.4 and 40.3.2(2)(1).

¹²¹ An Act respecting health services and social services, R.S.Q. c. S-4.2 § 107.1.

¹²² R. Seguin, *Quebec doctors call for retesting*, THE GLOBE AND MAIL, June 1, 2009; *Labs to re-examine samples from 2,100 Quebec breast cancer patients*, CBC NEWS, JUNE 5, 2009.

¹²³ Regulation Respecting the Application of the Public Health Protection Act, R.R.Q., c. L-0.2, r. 1 § 139-140.

¹²⁴ *Id.* § 140.1.

¹²⁵ DESCHÉNES, *supra* note 51, at 74-75; Petit, Tassé and Godard, *supra* note 118, ¶ 23.

¹²⁶ Gregorio M. Garcia, *The FDA and Regulation of Genetic Tests: Building Confidence and Promoting Safety*, 48 JURIMETRICS 217, 218 (2007-2008).

¹²⁷ Food, Drug, and Cosmetic Act, 21 U.S.C. § 201(h).

¹²⁸ Tucker, *supra* note 11, at 14.

¹²⁹ 75 Fed. Reg. 34,463-34,464 (June 17, 2010).

Presently, FDA, like Health Canada, regulates genetic test kits as IVDs through FDA's Center for Device and Radiological Health (CDRH).¹³⁰ Similar to Canada, medical devices are classified according to their level of risk (Class I to Class III), and FDA's control over safety and effectiveness varies accordingly.¹³¹ FDA classifies pharmacogenomic tests as Class II subject to special controls.¹³² This categorization applies to devices "which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance [...]"¹³³ This moderate risk classification level, lower than that adopted by Health Canada, was determined appropriate because, on the one hand, pharmacogenomic tests are not themselves physically risky. On the other hand, the possibility of inaccurate results may lead to mistakes about the appropriate course of drug treatment or incorrect dosage,¹³⁴ in addition to the degree of psycho-social concern about genetic discrimination associated with genetic tests generally.¹³⁵ However, some pharmacogenomic tests may be categorized as Class III and therefore require submission of a Premarket Approval (PMA).¹³⁶ Those devices which "cannot be classified as a class II device because insufficient information exists to determine that the special controls [...] would provide reasonable assurance of its safety and effectiveness"¹³⁷ require additional oversight to reasonably ensure safety and effectiveness. There is also an investigational device exemption (IDE) available for devices intended for use in clinical studies "in order to collect safety and effectiveness data required to support a PMA application or a Premarket Notification 510(k) submission to the FDA."¹³⁸

For most pharmacogenomic tests, in addition to registering their facility with FDA, manufacturers of Class II IVDs must submit a Premarket Notification (also known as a 510(k)) which requires evidence that the device is as safe and effective, or substantially equivalent, to a device that has already been legally marketed in the United States.¹³⁹ A 510(k) application must include, among other information, a description of the intended use of the device (e.g., state which biomarkers it measures) and data supporting the claimed use; information on the design of the device (e.g. methodology for extracting DNA) and analytical performance data.¹⁴⁰ FDA

¹³⁰ 21 C.F.R. Part 814; FDA, OVERVIEW OF MEDICAL DEVICE REGULATION (2009), <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm> (last visited October 22, 2010); See also Tucker, *supra* note 11, at 14.

¹³¹ 21 C.F.R. Part 860.

¹³² 21 C.F.R. §862.3360.

¹³³ Food, Drug, and Cosmetic Act, 21 U.S.C. § 360c, sec. 513(a)(1)(b).

¹³⁴ Michele Schoonmaker, *The U.S. Approval Process for Medical Devices: Legislative Issues and Comparison with the Drug Model*, CRS Report (2005) at 20.

¹³⁵ Mark A. Rothstein & Yann Joly, *Genetic Information and Insurance Underwriting: Contemporary Issues and Approaches in the Global Economy*, in HANDBOOK OF GENETICS AND SOCIETY: MAPPING THE NEW GENOMIC ERA 127 Paul Atkinson, Peter Glasner and Margaret Lock, eds., (2009).

¹³⁶ FDA, GUIDANCE ON PHARMACOGENETIC TESTS AND GENETIC TESTS FOR HERITABLE MARKERS (2007).

¹³⁷ Food, Drug, and Cosmetic Act, 21 U.S.C. §360c, sec. 513(a)(1)(c).

¹³⁸ 21 C.F.R. §812.

¹³⁹ FDA, MEDICAL DEVICES PREMARKET NOTIFICATION (510(k)), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm> (last visited October 22, 2010).

¹⁴⁰ FDA, Guidance on Pharmacogenetic Tests and Genetic Tests for Heritable Markers (2007), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm> (last visited October 22, 2010).

requires IVD developers to demonstrate the analytical validity and clinical validity of their tests.¹⁴¹ Clinical studies are not required to show the safety and effectiveness for established biomarkers if sufficient evidence exists in the literature, but are needed for devices that use new markers.¹⁴² As for the special controls, they include special labeling requirements, description of the device and performance characteristics, and method-comparison studies demonstrating that the test detects the genotype claimed.¹⁴³ FDA review of a 510(k) application takes approximately 90 days.¹⁴⁴ However, FDA has expressed concern that the “substantial equivalence” criterion in the 510(k) process allows IVD developers to avoid a rigorous evaluation of the safety and effectiveness of their test.¹⁴⁵

Moreover, in practice, as is the case in Canada, the vast majority of pharmacogenomic tests are offered as LDTs in order to circumvent the cost and time delay of FDA review.¹⁴⁶ However, it is difficult to mass produce and market tests in this way, such that the availability of LDTs is limited by the ability of laboratories to offer their services. Nonetheless, the fact that pharmacogenomic tests could be offered in laboratories without the intervention of FDA provided an attractive alternative route to providing pharmacogenomic testing services.¹⁴⁷ An estimate from 2008 confirmed that of the more than 1,200 genetic tests available, only about a dozen had been cleared by FDA (of which only a subset are pharmacogenomic tests).¹⁴⁸ Since laboratories do not commercially distribute LDTs but instead provide laboratory services, it is the CMS and CDC which regulate them in accordance with the *Clinical Laboratory Improvement Amendments of 1988 (CLIA)*.¹⁴⁹ CLIA sets the federal minimum standards for laboratory proficiency, ensuring that quality control standards are in place, inspecting quality assurance, recordkeeping and personnel qualification.¹⁵⁰ It also requires that the tests offered in the laboratory perform well analytically, i.e. test results must be accurate, reliable and not pose a risk of harm to patients.¹⁵¹ Evidence of the clinical validity of the actual tests, however, is not required by CLIA.¹⁵² Regulatory agencies at the state level may apply CLIA requirements, but some states (e.g. New York and Washington) have set stricter regulations for genetic testing laboratories. For example, New York requires pre-approval of genetic tests before they are offered as services.¹⁵³

¹⁴¹ Schoonmaker, *supra* note 135, at 21.

¹⁴² FDA, GUIDANCE ON PHARMACOGENETIC TESTS AND GENETIC TESTS FOR HERITABLE MARKERS (2007), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm> (last visited October 22, 2010).

¹⁴³ FDA, CLASS II SPECIAL CONTROLS GUIDANCE DOCUMENT: DRUG METABOLIZING ENZYME GENOTYPING SYSTEM - GUIDANCE FOR INDUSTRY AND FDA STAFF, available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077933.htm> (last visited October 22, 2010).

¹⁴⁴ FDA, MEDICAL DEVICES PREMARKET NOTIFICATION (510(k)), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm> (last visited October 22, 2010).

¹⁴⁵ *Under New Leadership, FDA Diagnostics Office To Tighten Its Control*, THE GRAY SHEET, July 27, 2009.

¹⁴⁶ John A. Robertson, Baruch Brody, Allen Buchanan, Jeffrey Kahn & Elizabeth McPherson, *Pharmacogenetic challenges for the health care system*, 21(4) HEALTH AFFAIRS 155, 159 (2002).

¹⁴⁷ Gail Javitt & Kathy Hudson, *Federal Neglect: Regulation of Genetic Testing*, ISSUES SCI. & TECH. 59, 61 (Spring 2006).

¹⁴⁸ Tucker, *supra* note 11, at 14.

¹⁴⁹ P.L. 100-578, 102 Stat. 2903 (amending U.S. Code 263a).

¹⁵⁰ U.S. Department of Health and Human Services (HHS), U.S. SYSTEM OF OVERSIGHT OF GENETIC TESTING: A RESPONSE TO THE CHARGE OF THE SECRETARY OF HEALTH AND HUMAN SERVICES (2008) at 3.

¹⁵¹ *Id.*

¹⁵² *Id.* at 4.

¹⁵³ *Id.* at 3.

Most genetic testing laboratories voluntarily take part in proficiency testing done by private organizations, although this is not required by CLIA.¹⁵⁴

Due to concerns with the lack of oversight over LDTs (particularly the lack of evidence of clinical validity) and their potential harms, along with the desire to advance the field of personalized medicine, U.S. government committees have been advising increased regulation of LDTs as early as 1998.¹⁵⁵ Again in 2008, the Department of Health and Human Services (HHS) Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) recommended more stringent oversight over home brews.¹⁵⁶ The report emphasized that, in order for the field of personalized medicine to advance, pharmacogenomic tests must be accurate (analytically valid), be able to predict outcome (clinically valid), and provide therapeutic benefit while weighing the risks of using the test (clinically useful).¹⁵⁷ Because, in the case of LDTs, CLIA only reviews analytical validity and does not authorize CMS to assess clinical validity, and due to concerns over the extent of oversight over laboratories,¹⁵⁸ the report suggested that increased oversight would help to clarify information on how pharmacogenomics could improve health care delivery.¹⁵⁹ FDA asserted that it had jurisdiction over LDTs (it considers laboratories to be manufacturing medical devices),¹⁶⁰ but had chosen not to enforce it, while leaving the door open to reevaluate its position in the future.¹⁶¹

Smaller steps towards increased regulation were taken in the meantime. In 1997, FDA decided to regulate certain chemical components (e.g. nucleic acid sequences, chemical reagents), called analyte-specific reagents (ASRs) used in LDTs to identify or measure substances in biological samples.¹⁶² ASRs were classified as restricted devices and could only be sold to manufacturers of IVDs, clinical laboratories able to perform high complexity tests under CLIA regulations, and research or non-clinical laboratories.¹⁶³ In addition, tests that use ASRs could not be sold directly to consumers, as they must be ordered by physicians (although physicians working in clinical laboratories may also order them).¹⁶⁴ However, most laboratories do not use commercially available ASRs, such that most LDTs are still not subject to FDA regulation.¹⁶⁵

Then in 2007, FDA proposed to regulate a subset of LDTs called In Vitro Diagnostic Multivariate Index Assays (IVDMIAs).¹⁶⁶ These devices use a patient's multiple variables to generate a single score that is meant to be used in diagnosing disease or in informing treatment, and the test's result cannot be analyzed

¹⁵⁴ Tucker, *supra* note 11, at 3. As genetic tests are considered to be highly complex, standards for proficiency testing of genetic tests have been recommended, but have not been adopted, "A draft report by the Secretary's Committee on Genetics, Health and Society (SACGHS) [...] recommended that the [HHS] take specific steps to increase the use of proficiency testing for genetic tests": SACGHS, *supra* note 150.

¹⁵⁵ See Louis P. Garrison et al., *A review of public policy issues in promoting the development and commercialization of pharmacogenomic applications: challenges and implications*, 40 *DRUG METABOLISM REVIEWS* 377, 386-387 (2008).

¹⁵⁶ SACGHS *supra* note 151.

¹⁵⁷ *Id.* at 1.

¹⁵⁸ *Id.* at 4.

¹⁵⁹ *Id.* at 5.

¹⁶⁰ 62 Fed. Reg. 62249.

¹⁶¹ 61 Fed. Reg. 10,484-10,485.

¹⁶² 21 C.F.R. §809.30 (1997).

¹⁶³ 21 C.F.R. §809.30 (1997).

¹⁶⁴ 21 C.F.R. § 809.30 (1997).

¹⁶⁵ Gail Javitt, *In Search of a Coherent Framework: Option for FDA Oversight of Genetic Tests*, 62 *FOOD & DRUG L.J.* 617, 633 (2007).

¹⁶⁶ FDA, *DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF - IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS* (2007), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm> (last visited October 22, 2010).

or verified by a clinician.¹⁶⁷ FDA felt that the safety and effectiveness of these devices was worrisome because patients might rely on them to make important healthcare decisions (for example, an IVDMA might be used to predict breast cancer prognosis)¹⁶⁸ and they were thus perceived as having a “high risk intended use.” In addition, since the clinical validity of the results cannot be verified by clinicians, it was particularly important that the clinical validity of IVDMIAs be evaluated by FDA.¹⁶⁹ Thus, most IVDMIAs were classified as Class II (moderate risk) or Class III (high risk), requiring a Premarket Notification submission (510(k)) or an application for PMA, respectively.¹⁷⁰

Finally in June 2010, FDA announced that it intended to “exercise its authority over LDTs.”¹⁷¹ This move followed the clamp-down on direct-to-consumer genetic tests (DTC-GTs), with FDA sending letters to companies notifying them that FDA approval was needed in order to continue marketing these devices.¹⁷² It seems that concerns over the safety and effectiveness of both DTC-GTs and LDTs, with some DTC-GTs considered to be LDTs, have combined to suggest the need for increased regulation.

FDA’s proposal is also in line with the view that the regulation of pharmacogenomic tests, particularly with respect to clinical validity, is important for the promise of pharmacogenomics to be realized. Many authors have commented that the lack of clinical validation of pharmacogenomic tests is an obstacle to the clinical implementation of pharmacogenomics, since it makes it difficult for health care providers to base decisions on these tests.¹⁷³ They argue that prescribing a drug based on genotyping should be done with reasonable assurance that the results of genetic tests are accurate and validly predict drug response.¹⁷⁴ However, it could also be argued that FDA regulation is only one way of making validity data available to health care professionals. For example, the National Institutes of Health have begun the Genetic Testing Registry, a resource that allows test developers to submit test information that would become available to concerned stakeholders.¹⁷⁵

The commitment to advance the field of pharmacogenomics is also evident in several initiatives undertaken by FDA. In 2005, FDA released a guidance document on the submission of pharmacogenomic data in the drug development process.¹⁷⁶ Unlike its Canadian counterpart, FDA does not require pharmacogenomic information to be submitted as part of the drug approval process, since it recognizes that, currently, most pharmacogenomic data are of an exploratory or research

¹⁶⁷ *Id.*

¹⁶⁸ 21 C.F.R. §866.6040.

¹⁶⁹ FDA, DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF - IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS (2007), available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm> (last visited October 22, 2010).

¹⁷⁰ *Id.*

¹⁷¹ 75 Fed. Reg. 34,463-34,464 (June 17, 2010).

¹⁷² Food and Drug Administration. Letters to Manufacturers Concerning Genetic Tests, available at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm219582.htm (last visited October 22, 2010).

¹⁷³ Sara Katsanis & Gail Javitt, *Pharmacogenomics: Hope and Hype*, September 2008, available at <http://www.dnapolicy.org/images/issuebriefpdfs/Pgx%20IB.pdf> (last visited October 22, 2010).

¹⁷⁴ Jai Shah, *Criteria influencing the clinical uptake of pharmacogenomic strategies*, 328 *BMJ* 1482, 1483 (2004).

¹⁷⁵ National Institutes of Health, Office of Biotechnology Activities, Genetic Testing Registry, available at http://oba.od.nih.gov/gtr/gtr_intro.html (last visited October 22, 2010).

¹⁷⁶ FDA, GUIDANCE FOR INDUSTRY – PHARMACOGENOMIC DATA SUBMISSIONS (March 2005), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf> (last visited October 22, 2010).

nature.¹⁷⁷ FDA also noted that industry hesitated to submit pharmacogenomic data due to concerns that FDA would use such exploratory data in their regulatory decision-making.¹⁷⁸ Instead, it encourages voluntary genomic data submissions, considering the benefits it brings to both the industry and FDA.¹⁷⁹ The concept of a “safe harbour” was found to be more appropriate, where industry could discuss pharmacogenomic data with FDA without regulatory impact.¹⁸⁰ In the same vein, FDA initiated the voluntary exploratory data submissions (VXDS) programme in 2004, in which industry can meet with the regulator to discuss scientific, clinical and technical aspects of genomic data in drug development, but this discussion does not result in regulatory decisions about a pharmaceutical product.¹⁸¹ As of 2009, FDA had received over 40 submissions and held 35 meetings with industry.¹⁸² FDA and EMA also hold joint briefing meetings with industry, outside the formal regulatory process, to discuss the regulators’ perspectives.¹⁸³

Also in 2005, FDA released the Drug-Diagnostic Co-Development Concept Paper, a draft outlining a single approval process for a drug and a diagnostic device, such as a pharmacogenomic test, developed together.¹⁸⁴ The document addresses “the development of *in vitro* diagnostics [...] for mandatory use in decision making about drug selection for patients in clinical practice.”¹⁸⁵ The concept paper discusses considerations involved in the parallel development of a drug/test combination, and issues related to analytical test validation, clinical utility and validity of diagnostics, noting that experimental pharmacogenomic data often have not been scientifically established to a sufficient degree upon which to base regulatory decisions.¹⁸⁶ Thus, this document intends to “assist in advancing the field of pharmacogenomics” by outlining policies to address some of the same concerns raised about LDTs.¹⁸⁷

It should be noted that, in 2006, Health Canada also released its *Drug and Medical Device Combination Products Policy*,¹⁸⁸ which would allow combination products to be subject to regulatory approval under either the *Medical Devices Regulations* or the *Food and Drug Regulations* instead of both.¹⁸⁹ However, unlike its American counterpart, the *Policy* currently applies only to products in which a drug and device are integrated into a singular product, and not to products where the drug component and the device component (such as a drug and pharmacogenomic test) can be used separately.¹⁹⁰ However, the Canadian legislative framework has yet to be amended to reflect policy.

¹⁷⁷ *Id.*

¹⁷⁸ Federico M. Goodsaid, *et al.*, *Voluntary Exploratory Data Submission to the US FDA and the EMA: Experience and Impact*, 9 NATURE REVIEWS DRUG DISCOVERY 435, 435 (2010).

¹⁷⁹ FDA, GUIDANCE FOR INDUSTRY – PHARMACOGENOMIC DATA SUBMISSIONS (March 2005) at 7, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf> (last visited October 22, 2010).

¹⁸⁰ Goodsaid, *supra* note 179, at 435.

¹⁸¹ *Id.* at 435.

¹⁸² *Id.* at 435.

¹⁸³ FDA & EMA, GUIDING PRINCIPLES – PROCESSING JOINT FDA EMEA VOLUNTARY GENOMIC DATA SUBMISSIONS (VGDSs) WITHIN THE FRAMEWORK OF THE CONFIDENTIALITY ARRANGEMENT, available at <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf> (last visited October 22, 2010).

¹⁸⁴ FDA, DRUG-DIAGNOSTIC CO-DEVELOPMENT CONCEPT PAPER (DRAFT), April 2005, at 1.

¹⁸⁵ *Id.* at 2.

¹⁸⁶ *Id.*

¹⁸⁷ *Id.*

¹⁸⁸ HEALTH CANADA, *DRUG/MEDICAL DEVICE COMBINATION PRODUCTS* (2005), available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/combo_mixte_pol_2006-eng.php (last visited November 17, 2010).

¹⁸⁹ *Id.* §5.

¹⁹⁰ *Id.* §3.

C. Europe

In Europe, the regulatory framework related to pharmacogenomic tests varies somewhat from that found in North America. While EMA has the authority to regulate drugs throughout the European Union (EU), the approval of biomedical tests is undertaken by national regulatory agencies in each member state.¹⁹¹ The *In Vitro Diagnostic Medical Devices Directive* (Council Directive 98/79/EC) (*IVD Directive*) provides for common regulatory requirements for the evaluation of IVDs, setting minimum standards for safety, quality and performance of IVDs that should be evidenced before national regulators certify them with the CE marking of conformity (Council Directive 98/79/EC). The *IVD Directive* aims to achieve regulatory harmonization on technical standards to be used in evaluating IVDs, but the review process remains decentralized. However, once a national agency certifies a product, it can move freely across national borders within the EU internal market.¹⁹²

The procedure to follow in order to get a pharmacogenomic test certified is set out in Annex III of the *IVD Directive*.¹⁹³ Technical documentation must include data on the reliability of the IVD, performance evaluation supporting the manufacturer's claimed intended use, information on product design and a risk analysis showing that the device is safe, as well as other technical data.¹⁹⁴ The *IVD Directive* classifies pharmacogenomic tests as low-risk devices, which allows manufacturers to self-declare conformity with the requirements of the *IVD Directive*, and there is therefore no requirement for premarket evaluation by a notified body (regulatory bodies in the EU who perform reviews of drugs and other medical products).¹⁹⁵ The absence of this requirement is indicative of the view that devices such as pharmacogenomic tests do not involve a direct physical risk, especially since the results are interpreted by medical professionals.¹⁹⁶ In the case of devices for self-testing, additional measures are in place, such as the requirement for manufacturers to apply for examination with a notified body, which includes data showing that laypersons are able to use the device according to its labeled intended use.¹⁹⁷ For pharmacogenomic tests, while evidence of analytical validity is necessary, evidence of clinical validity is not required before such a device can enter the European market.¹⁹⁸ Some national regulatory agencies, however, may require evidence of clinical validity before granting the CE mark.¹⁹⁹ In addition, EMA has suggested that the absence of the requirement to show clinical utility (i.e. therapeutic benefit) before certifying a product is a concern, but national regulators do not seem to agree.²⁰⁰

Because it is often less expensive for laboratories to develop their own tests rather than purchasing commercial test kits, the majority of pharmacogenomic tests in Europe are LDTs.²⁰¹ According to article 9(13) of the *IVD Directive*, LDTs which

¹⁹¹ UK Pharmacogenetics Study Group, Policy Issues in Pharmacogenetics (2006) at 9, available at <http://www.york.ac.uk/media/satsu/res-pgx/PGxpolicyissues2006.pdf> (last visited October 22, 2010).

¹⁹² Council Directive 98/79/EC, art. 4, 1998 O.J. (L331).

¹⁹³ *Id.* art. 9.

¹⁹⁴ *Id.* Annex III, art. 3.

¹⁹⁵ UK Pharmacogenetics Study Group, Policy Issues in Pharmacogenetics (2006) at 10, available at <http://www.york.ac.uk/media/satsu/res-pgx/PGxpolicyissues2006.pdf>.

¹⁹⁶ Eleni Zika, Pharmacogenetics and Pharmacogenomics: State-of-the-art and potential socio-economic impact in the EU, at 82, (2006).

¹⁹⁷ Council Directive 98/79/EC, Annex III, art. 6, 1998 O.J. (L331).

¹⁹⁸ UK Pharmacogenetics Study Group, Policy Issues in Pharmacogenetics (2006) at 10, available at <http://www.york.ac.uk/media/satsu/res-pgx/PGxpolicyissues2006.pdf>.

¹⁹⁹ Zika, *supra* note 197, at 82.

²⁰⁰ *Id.* at 120.

²⁰¹ *Id.* at 96.

are offered as laboratory services are considered medical devices and are also subject to the same technical standards and certification procedure as test kits destined for the market.²⁰² For example, the UK Medicines and Healthcare products Regulatory Agency (MHRA), which regulates medical devices, requires technical data on the methods used and operating procedures of the pharmacogenomic test, a risk analysis showing the measures in place to minimize errors, evidence that measures are in place to detect errors, in addition to other information on the assay.²⁰³

However, an important distinction exists for public laboratories. Those laboratories operating in health institutions are exempt from the *IVD Directive*, so that “devices manufactured and used only within the same health institution and on the premises of their manufacture or used on the premises in the immediate vicinity without having been transferred to another legal entity” are not subject to evaluation by regulatory authorities.²⁰⁴ Therefore, private laboratories and manufacturers of test kits are scrutinized more heavily than public laboratories,²⁰⁵ creating an imbalance between the private and public sectors. Some public laboratories may engage, and indeed have done so in the past (for example, the NHS laboratories in the UK), in the review process provided for in the *IVD Directive* in order to benefit from the added value obtained from affixing the CE mark to their assays.²⁰⁶ This certification allows them to provide their services to third parties (e.g. drug manufacturers) in the same way as manufacturers of test kits.²⁰⁷

With respect to home-brews, apart from the common standards for LDT safety set out in the *IVD Directive*, the oversight over the quality of clinical laboratory services varies between member states.²⁰⁸ Each country sets its own procedures for accrediting laboratories, issuing licenses and assessing the quality of services.²⁰⁹ There are concerns, though, with the quality of some LDTs and laboratory practices generally, especially in hospital laboratories.²¹⁰ One example is that these laboratories can purchase commercial test kits, but deviate from the test’s “labeled use” and use their own preferred preparation methods instead of the one indicated.²¹¹ Another example is that public laboratories sometimes purchase and use test kits marked for “research use only,”²¹² which are not evaluated according to the standards of the *IVD Directive*.²¹³

The regulation of pharmacogenomic tests in Europe may seem less stringent than that found in North American jurisdictions, but the standards for LDTs offered by public laboratories in Europe, along with the multiplicity of regulators, can have a stifling effect on the clinical transfer of this technology. A 2006 report by the Institute for Prospective Technological Studies (IPTS) (sponsored by the European Commission) commented that among the key barriers to the advancement of pharmacogenomics was the decentralized nature of the regulation of IVDs across Europe.²¹⁴ The centralized approval process for drugs under EMA, while

²⁰² Council Directive 98/79/EC, art. 9(13), 1998 O.J. (L331).

²⁰³ Zika, *supra* note 197, at 96.

²⁰⁴ Council Directive 98/79/EC, art. 1(5), 1998 O.J. (L331).

²⁰⁵ Zika, *supra* note 197, at 123.

²⁰⁶ *Id.* at 96.

²⁰⁷ *Id.*

²⁰⁸ *Id.* at 95.

²⁰⁹ *Id.*

²¹⁰ *Id.*

²¹¹ *Id.* at 96.

²¹² *Id.*

²¹³ See Council Directive 98/79/EC, Preamble at para. 8, 1998 O.J. (L331).

²¹⁴ Zika, *supra* note 197, at 124.

related pharmacogenomic tests are under the authority of national regulatory agencies, might create additional hurdles for the commercialization of personalized medicine. There is already an example where EMA approved the drug trastuzumab for the treatment of breast cancer, but did not have the authority to approve the Her2 pharmacogenomic test used to assess whether patients are eligible for treatment.²¹⁵ It should be noted that, although it is still possible for drug manufacturers to choose to have their drug approved through national regulatory agencies instead of through the centralized EMA procedure,²¹⁶ the fact that many member states have a separate authority regulating medical devices does not make this route less burdensome. Moreover, the powers of EMA extend only to including a recommendation to use a pharmacogenomic test in a drug label, but it cannot require such testing.²¹⁷ EMA has stated that it does not intend to assume responsibility for regulating pharmacogenomic tests, nor for the co-approval of drugs/diagnostics, but it may collaborate with national regulators in evaluating the clinical utility of a pharmacogenomic test in informing the better use of a drug.²¹⁸

The IPTS concluded that some of the other key barriers to the advancement of pharmacogenomics in Europe were the lack of guidance on drug/test co-development, the lack of information on the cost-effectiveness of applying this technology, as well as the fact that physicians were lagging behind in knowledge about pharmacogenomics.²¹⁹

On this note, EMA released a draft *Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development* in June 2010.²²⁰ This document is similar to FDA's co-development concept paper. It should be noted, though, that even though EMA encourages co-development, it still has no regulatory oversight over the commercialization of pharmacogenomic tests.²²¹ Consequently, it is not clear how co-development will be coordinated in the current context of multiple regulators.

In addition, in 2005 EMA published a guideline on pharmacogenomics briefing meetings, outlining the process in which industry can meet with EMA's Pharmacogenetics Working party to informally discuss the "technical, scientific and regulatory issues that arise by the inclusion of pharmacogenetics and pharmacogenomics in the development strategy and to assess their potential implications in the regulatory processes."²²² EMA strongly recommends that the outcome of the meeting be included in any subsequent applications to the agency.²²³ As already discussed, EMA also holds joint briefing meetings with FDA,²²⁴ allowing industry to simultaneously explore the response of both regulatory agencies towards pharmacogenomic data.

²¹⁵ UK Pharmacogenetics Study Group, Policy Issues in Pharmacogenetics (2006) at 10, available at <http://www.york.ac.uk/media/satsu/res-pgx/PGxpolicyissues2006.pdf> (last visited October 22, 2010).

²¹⁶ Zika, *supra* note 197, at 79.

²¹⁷ *Id.* at 120.

²¹⁸ *Id.* at 86.

²¹⁹ *Id.* at 124.

²²⁰ EMA, Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development, (2008), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094445.pdf (last visited October 22, 2010).

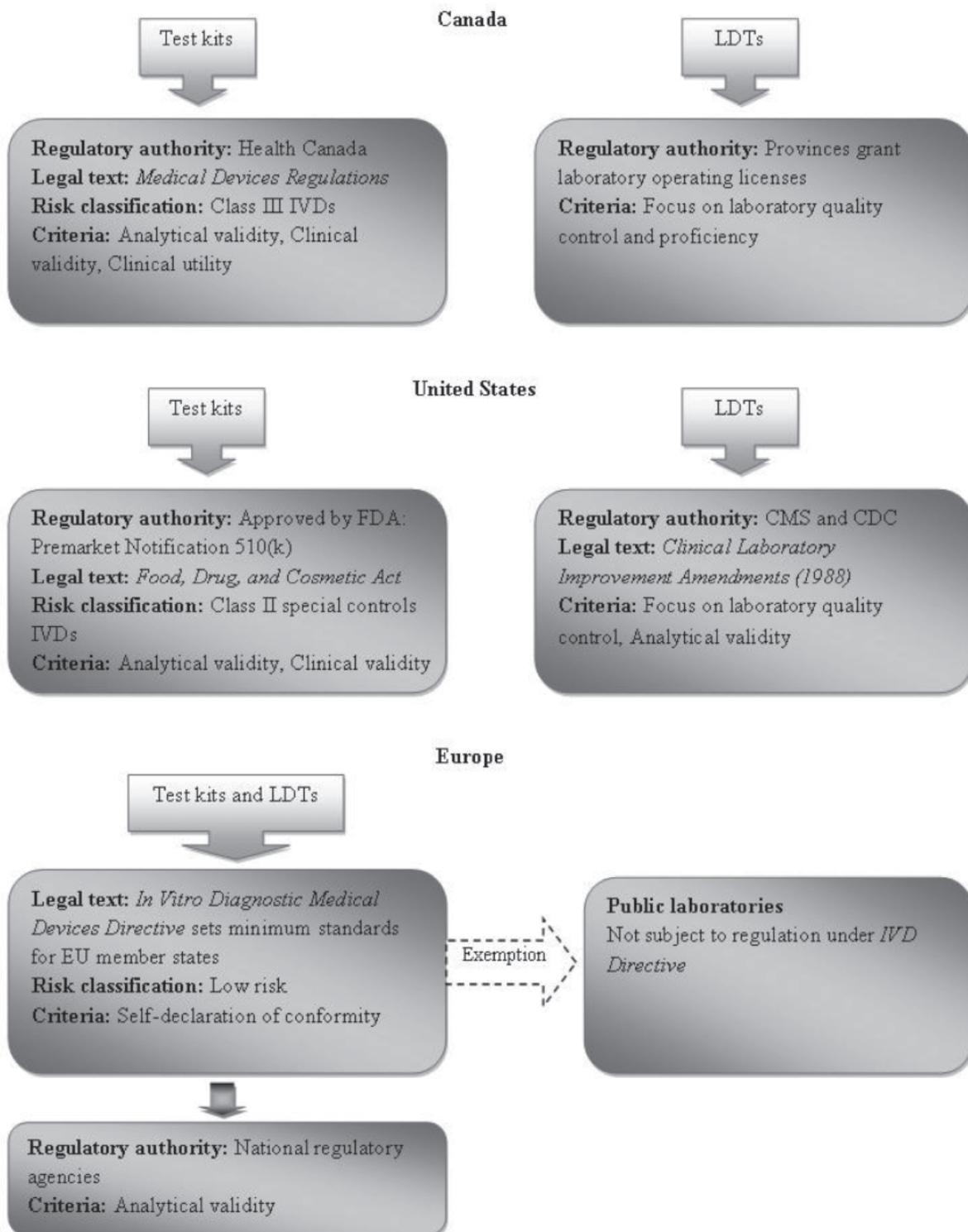
²²¹ UK Pharmacogenetics Study Group, Policy Issues in Pharmacogenetics (2006) at 10, available at <http://www.york.ac.uk/media/satsu/res-pgx/PGxpolicyissues2006.pdf> (last visited October 22, 2010).

²²² EMA, Guideline on Pharmacogenetics Briefing Meetings, at 5, (2005), http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003886 (last visited October 22, 2010).

²²³ *Id.*

²²⁴ FDA, European Commission & European Medicines Agency, General Principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement, (2006), http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003887 (last visited October 22, 2010).

Regulatory Pathways for Pharmacogenomic Tests



IV. DISCUSSION

Pharmacogenomics holds promise to improve drug safety and effectiveness, benefiting patients, drug safety regulators, clinicians and drug manufacturers. Considering the high cost of, and public interest in, drug development, an important issue is whether the current regulatory framework appropriately balances protecting the public by regulating the quality of tests with protecting the public through promoting the introduction of important new tests in the market. Recent and upcoming changes to the regulation of pharmacogenomic tests are said, by regulators, to be aimed at promoting the field.²²⁵ However, their true impact could also hinder advances if regulation is overly cumbersome.

All regulators agree that pharmacogenomic tests should be regulated to ensure safety, but the level of scrutiny that is thought to be sufficient varies across jurisdictions. The current regulation of pharmacogenomic tests is not overly burdensome in most jurisdictions. For example, FDA's classification of genetic test kits as Class II special controls indicates that the regulatory agency does not consider such tests to pose a particular physical risk. Any risk associated with the diagnostic is mostly related to the potential for inaccurate or misinterpreted (by clinicians) results.²²⁶ These diagnostic tools also receive a low-risk classification in Europe, but Health Canada places them in a higher risk category because they are genetic tests. The Canadian regulatory agency considers genetic tests to present a "high individual risk because of the stress and anxiety resulting from the information."²²⁷ However, associating pharmacogenomic tests with high individual psychosocial risk is not always appropriate. For example, learning that one poorly metabolizes a certain drug leading to an inadequate therapeutic response would not lead to the same level of anxiety as results indicating a predisposition for Alzheimer's disease. Although some pharmacogenomic tests (e.g. those identifying responsiveness to chemotherapy drugs) could raise some ethical issues,²²⁸ assigning a "high individual risk" classification to all such tests may not be appropriate. Moreover, neither the United States nor Europe focuses on the "genetic" nature of pharmacogenomic tests to justify a higher classification than otherwise similar devices.²²⁹

Furthermore, increasing oversight of pharmacogenomic tests could pose additional obstacles in advancing the field. Pharmacogenomic tests can become available more quickly as LDTs as they do not require a formal approval process (in Canada and the United States), which requires time and cost.²³⁰ However, concern over the clinical validity of LDTs, which is important in order to inform appropriate clinical treatment decisions, as well as concern over DTC-GTs, has led FDA to propose that

²²⁵ See 75 Fed. Reg. 34,463-34,464 (June 17, 2010).

²²⁶ Michele Schoonmaker, *The U.S. Approval Process for Medical Devices: Legislative Issues and Comparison with the Drug Model*, at 20, (2005), <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3282603232005.pdf>

²²⁷ Health Canada, *Draft Guidance for the Risk Based Classification System of In Vitro Diagnostic Devices*, at 6, (1998) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/ivd-rsk_idiv-rsq-eng.pdf (last visited October 22, 2010).

²²⁸ Yann Joly & Bartha M. Knoppers, *Pharmacogenomic data sample collection and storage: ethical issues and policy approaches*, 7 PHARMACOGENOMICS 219, 219 (2006).

²²⁹ FDA, *Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System - Guidance for Industry and FDA Staff*, <http://www.fda.gov/MedicalDevices/DeviceRegulation-andGuidance/GuidanceDocuments/ucm077933.htm> (last visited October 22, 2010); Council Directive 98/79/EC, art. 9, 1998 O.J. (L331).

²³⁰ FDA noted that novel tests could become available more quickly as LDTs; see 61 Fed. Reg. 10,484-10,485 (March 14, 1996).

it assume regulation of all LDTs.²³¹ In addition, test accuracy is also a concern: no diagnostic test is perfectly accurate, but a clinical (and ethical) concern relates to cases of both false positive and false negative results, particularly if these results are used to guide therapy.²³² On the one hand, this proposed regulation by FDA could be a barrier to the rapid development of pharmacogenomics, and could also involve additional costs associated with regulatory approval, that might likely be transferred to the end users of such tests. On the other hand, it might be necessary to ensure an appropriate level of safety and effectiveness, as well as to “level the playing field”²³³ between test kit developers and laboratories. Indeed, FDA commented that leveling the playing field between test kits and LDTs would encourage innovation by incentivizing manufacturers to develop commercially distributed test kits.²³⁴ In the current regulatory framework, LDTs cannot be sold on the market and are thus confined to the specific laboratories which develop them, only being offered to the extent of the laboratory’s capacity. Test kits, though, are not so restricted. In the end, the most appropriate regulation of pharmacogenomic tests would have to take into account issues of public safety, barriers to development and barriers to access (in terms of cost, through health professionals, and geographic access).

It is important to note that, although FDA proposes to assume oversight over LDTs and has long asserted that it does have jurisdiction over them, it is not yet clear whether it will or it can. FDA’s jurisdiction over LDTs depends on two assumptions: that LDTs are devices and that they are sold in interstate commerce.²³⁵ Although an in-depth legal analysis of this particular point is beyond the scope of this article, some authors have suggested that both of these elements might be satisfied according to United States law and jurisprudence.²³⁶ It would be interesting to monitor whether other countries will, or could, follow FDA’s footsteps in proposing to assume control and impose stricter regulation over LDTs. In Canada, the regulation of LDTs also depends on their characterization as devices or laboratory services. The constitutional division of powers between the federal and provincial governments²³⁷ seems to confirm the provinces’ jurisdiction over LDTs. Moreover, the *Medical Devices Regulations* specifically apply to “the sale and advertising for sale of a medical device.”²³⁸ As long as LDTs are considered to be laboratory services, LDTs are not subject to the *Regulations*. The inclusion of LDTs as medical devices could be the subject of a constitutional challenge.

The drug-diagnostic co-development initiatives proposed in the United States and Europe may provide an answer to the otherwise discouraging increasing regulation of LDTs and associated costs. The concept would encourage development of a pharmacogenomic test in parallel with a new drug, with the two products informing the design and development of one another. In addition to drug/test combinations providing a clinical benefit to patients by helping to inform the best

²³¹ 75 Fed. Reg. 34,463-34,464 (June 17, 2010).

²³² See Lena H. Sun & Carol D. Leonnig, *Georgetown U. Hospital closes lab after problems with breast cancer tests*, WASHINGTON POST, Aug. 6, 2010.

²³³ 75 Fed. Reg. 34,463-34,464 (June 17, 2010).

²³⁴ *Id.*

²³⁵ Juliana Han, *The Optimal Scope of FDA Regulation of Genetic Tests: Meeting Challenges and Keeping Promises*, 20 HARVARD JOURNAL OF LAW & TECHNOLOGY 423, 430 (2007).

²³⁶ For example, Han suggests that the distinction between device and laboratory service is increasingly semantic. For an interesting analysis on this issue, see *id.* at 430-441.

²³⁷ Constitution Act, 1867, 30 & 31 Vict., Ch. 3 (U.K.), as reprinted in R.S.C., No. 5 (Appendix 1985) § 91-92.

²³⁸ Medical Devices Regulations, S.O.R./98-282 § 2(a).

course of therapy, industry could take advantage of the benefits provided by pharmacogenomics in drug development and then market the products together. This initiative could both promote innovation in the field of pharmacogenomics and increase availability of such tests. In order to implement this concept successfully, it would be necessary to ensure coordination between regulatory agencies' different centers, specifically those evaluating drugs and medical devices.

Beyond the concerns raised by the regulatory approval process, stakeholders (insurers, government agencies, economists) will also need to elaborate policy frameworks that will help them assess which pharmacogenomic tests should and should not be provided as part of a robust healthcare plan.

In order to reap the benefits of pharmacogenomics, there must be an appropriate balance between regulating quality and promoting innovation beneficial to public health. Regulatory agencies profess an interest in the field and a desire to promote innovation. Careful attention, then, should be paid to the way in which measures impact the development, availability and cost of pharmacogenomic tests. Taking into account the benefits of pharmacogenomics, we believe it is important to involve all stakeholders (policymakers, health professionals, private sector) in determining the level of regulation that would ensure the necessary quality of pharmacogenomic tests, as well as facilitate the translation of this important science into concrete public health benefits.