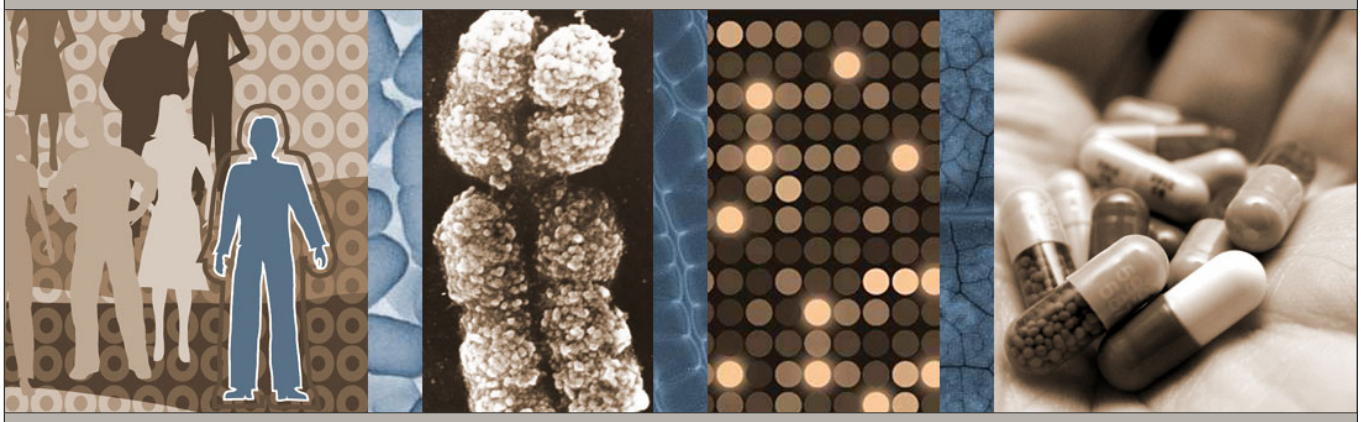
Science-Metrix & MNBC

Pharmacogenomics in Canada

April 2004



Potential for Pharmacogenomics Science and Technology in Canada: Pharmaceutical Mirage or Oasis?

Prepared for

Canadian Biotechnology Secretariat

Science-Metrix

& Michel Noiseux, Bio-conseil (MNBC)

Pharmacogenomics in Canada

Potential for Pharmacogenomics Science and Technology in Canada: Pharmaceutical Mirage or Oasis?

Alexandre Parent, Michel Noiseux

and Grégoire Côté

April 2004

Prepared for

Canadian Biotechnology Secretariat

514.495.6505 · 4572 avenue de Lorimier · Montréal · Québec · Canada · H2H 2B5
info@science-metrix.com · www.science-metrix.com

Executive Summary

This study aimed to evaluate the potential of pharmacogenomic science and technology (S&T) in Canada. In order to do so, the multiple scientific and ethical issues related to pharmacogenomic research were reviewed. Scientometric and technometric analyses were performed to provide a quantitative evaluation of Canada's performance in this field relative to that of the world and also within Canada. The position of pharmacogenomic S&T within the context of the healthcare industry was also discussed. Finally, Canada's main strengths and weaknesses together with future opportunities and threats were summarized in order to establish the potential of pharmacogenomic S&T in Canada and to provide recommendations so that Canada can benefit from this potential.

The scientometric analysis is based on papers retrieved from the Medline database using a set of keywords defining the field. It was conducted using time series (1991-2002) to outline the evolution of Canada's scientific output in pharmacogenomics both at the international level (G7 countries) and national levels. The performances of the different entities at the international and national levels are presented according to three scientometric indicators.

The technometric analysis is based on patents retrieved from the United States Patents and Trademark Office (USPTO) database and was conducted using time series (1999-2003) to outline the evolution of Canada's technological output in pharmacogenomics both at the international level (G7 countries) and national levels. The performances of the different entities at the international level are presented according to two technometric indicators. At the national level, only one technometric indicator was used due to the small number of Canadian pharmacogenomic patents.

Canada occupies a small position in pharmacogenomic S&T, both in terms of scientific and technological output. This is not an irreversible situation since the field is still in its initial phase. Most of the countries studied have just started to get involved in the field, and Canada could still be an important player. However, to stay in the pharmacogenomic race, Canada has to take serious and concrete action. This is especially important since the partially public Canadian healthcare system could be strongly affected by the advent of pharmacogenomics, and it would be wise for the country to have some say in the direction this race will take if it wants to manage its healthcare spending efficiently. This report highlights different strategies that should be prioritized by Canada to develop the field of pharmacogenomic S&T:

- Canada should invest primarily in fundamental pharmacogenomic research since most of the private enterprises concerned are situated outside the country.
- Canada should specialize in a few targeted fields of pharmacogenomic research like mental health and neurological disease.
- Canada should use Genome Canada's expertise in genomics to incorporate pharmacogenomic research units in successful genomics research groups and institutions.
- Canada should establish clear regulations for the use of pharmacogenomics in drug research and development.
- The Canadian government should establish clear regulations dealing with the treatment of personal genomic information.
- Canada should review the way personal information (genetic or not) is treated in a medical context.
- Finally, Canada should consider implementing legislation that would ensure that groups with genetic profiles that are too small to be of interest to pharmaceutical companies (orphan patients) have access to effective treatment for the conditions that affect them.

Key findings

Scientific issues

- Two theoretical models are being used in pharmacogenomics: the Genotype-to-phenotype (G2P) approach and the Phenotype-to-Genotype (P2G) approach.
- The G2P approach is advantageous for studying effects whose molecular mechanisms are well understood.
- The P2G approach is advantageous when studying pharmacogenomic effects whose significant phenotypical variations to drug response can be easily observed and measured.
- Genotype characterization of pharmacogenomically relevant portions of DNA is the most important scientific research subject in pharmacogenomics right now.
- Genotype characterization is accomplished principally through single nucleotide polymorphism (SNP) genotyping and haplotype characterization.
- SNP characterization is less demanding both economically and scientifically, therefore making it an excellent method of characterization when dealing with monogenic genotype-phenotype interactions.
- Haplotype characterization is considered to have a higher resolution when detecting polygenic associations, but it is also more costly and technically challenging.
- Most of the research done in pharmacogenomics studies the cytochrome P-450 gene family since it is important for the metabolism of a vast number of drugs on the market.
- The biggest challenges in pharmacogenomics are of technical nature and are often related to the amount of information that has to be processed rather than to the informative content itself.
- Finally, the main scientific challenge faced by pharmacogenomics is to change from a descriptive, anecdotal discipline to a predictive discipline, with a view to developing more efficient pharmacogenomic research programs.

Scientometric analysis

- The number of papers per year in pharmacogenomic research grew from 273 in 1991 to 1,671 in 2002 at the world level. Growth of Canadian scientific output was less important, the number of papers per year increasing from 17 in 1991 to 57 in 2002.
- The share of world papers in pharmacogenomic research by Canada was around 4% for the 1991-2002 period.
- Canada's growth rate per three-year periods was often inferior to that of other G7 countries and of the world as a whole during those periods. Canada experienced its greatest growth during the 1997-1999 period (129%).
- The United States largely dominate the field of pharmacogenomics, holding about 40% of the world's scientific output with 1,181 papers from 1991 to 2002.
- Canada, with an overall output of 130 papers, occupies the sixth position when it is compared to the other G7 countries.
- Among G7 countries, Canada is the fourth most specialized country in pharmacogenomic research (specialization index (SI) of 1.22), in front of the United States (which occupies the fifth place with an SI of 1.13).
- France is the most specialized country (SI of 1.27), and Japan and Italy are the only G7 countries that are specialized in pharmacogenomics (respective SIs of 0.92 and 0.54).
- The impact factor (IF) of pharmacogenomic articles at the world level (IF of 4.20) is higher than the general world average (IF of 3.02) of all articles in Medline.

- Between 1997 and 2002, two countries, the UK and the United States, stand out with IF values above 4.40. Nearly all the other countries show IF values between 3.50 and 4.00 (Canada has an IF of 3.82), the exception being France with an IF of 3.40.
- Within Canada, only two provinces, Ontario and Quebec, published more than ten papers between 1991 and 2002.
- Ontario has an SI of 1.61, and Quebec has one of 1.27, showing some degree of specialization.
- Ontario and Quebec's IFs (4.18 and 4.43) are comparable to the world IF of 4.20.
- Only two Canadian institutions produced more than ten papers during the 1991-2002 period: the University of Toronto and the Centre for Addiction and Metal Health, also located in Toronto.
- The four most prolific Canadian institutions are located in Toronto, making it the most important pharmacogenomic research centre in the country.
- Two of the most specialized Canadian institutions, the Centre for Addiction and Metal Health (SI of 15.06) and the Douglas Hospital in Montreal (SI of 13.14), are performing research in the fields of mental health, neurological disease and addiction.

Technometric analysis

- The number of pharmacogenomic patents issued each year at the world level grew from 2 in 1999 to 22 in 2003.
- The United States holds the lion share of patents in pharmacogenomics with about 91% (40 inventions) of the world's technological output (44 inventions). Germany is 2nd with 4 inventions, and the United Kingdom is 3rd with 2 inventions.
- Canada has one registered patent, filed by a biotech company (Signalgene) that has since closed.
- The leading assignee is an American corporation, Lexicon Genetics Inc, with 24 patents.

Pharmacogenomic technology and the healthcare industry

- Pharmaceutical companies, to this date, were slow to include pharmacogenomics in their research programs.
- Internal pressures such as the reduction of drug development time and the need to augment the number of new chemical entities (NCEs) on the market are pushing pharmaceutical companies to increase pharmacogenomics utilisation in their clinical research programs.
- External pressures such as the needs to reduce adverse drug reactions (ADRs) and costs for the healthcare system also favour the adoption of pharmacogenomic research programs by both enterprises and governments.
- Pharmacogenomics is therefore expected to rapidly gain importance in the industry.
- Ethical interrogations in pharmacogenomics revolve around questions of privacy and disclosing personal information.
- The question of genetic discrimination will also need to be addressed, especially since genetic stratification of populations may lead to the isolation of certain sub-groups, creating an "orphan patient" problem.
- The FDA is the most active regulatory agency in the field of pharmacogenomics. It has already published recommendations that address every situation and take into account the current status of development of pharmacogenomics in the area of diagnostics and drugs.
- Canada has yet to establish any regulations concerning the use of pharmacogenomics in the area of diagnostics and drugs.
- Pharmacogenomics is expected to bring numerous benefits to patients and the healthcare industry. It is expected to increase the number of new drugs and reduce the cost associated with drug development.

- Production cost will not be a deciding factor for pharmaceutical companies as to whether they should adopt pharmacogenomics or not.
- Most of the obstacles faced by pharmaceutical companies as to whether or not to include pharmacogenomic research programs are related to marketing issues.
- Pharmacogenomics is expected to have a market fragmentation effect and profound impacts on the marketing techniques that will need to be used for marketing pharmacogenomic drugs.
- Pharmaceutical companies will need to make far-reaching changes to their business models if they want to continue to grow. These changes will be necessary with or without pharmacogenomics, although pharmacogenomics will certainly be a catalyst for them.
- More than 25 deals were signed between large pharmaceutical and pharmacogenomics companies in the 2000-2002 period.
- Pharmacogenomics is expected to be beneficial for the Canadian healthcare system in that savings will be made by treating patients both more effectively and more efficiently (e.g. reduced ADRs, reduced treatment time, better diagnosis).
- Patients, the government and private partners (from private clinics to insurance companies) will benefit from these savings.
- Although these savings will be real, they will probably be difficult to evaluate precisely due to the administrative structure of the Canadian healthcare system.

SWOT analysis

- Canada's strengths in pharmacogenomic research and technology are (1) the presence of Genome Canada and its provincial counterparts, (2) the good quality of Canadian fundamental research and (3) Canadian expertise in genomics and clinical research.
- Canada's weaknesses in pharmacogenomic research and technology are (1) the absence of pharmacogenomic users in Canada, (2) the absence of pharmacogenomic regulatory guidelines, (3) the increasing gap between the Canadian and the world scientific output and (4) the absence of a Canadian pharmacogenomic portfolio of patents.
- Future opportunities for pharmacogenomic research and technology in Canada are (1) a rapidly growing pharmacogenomic market and (2) increasing interest by pharmaceutical companies.
- Future threats to pharmacogenomic research and technology in Canada are (1) a lack of dialogue between the public, social scientists and genomic scientists about ethical and social issues and (2) resistance on the part of pharmaceutical companies to pursue pharmacogenomic research.

Table of contents

Tables

Figures

1 Introduction

Pharmacogenomics and pharmacogenetics are now often used concomitantly to describe the discipline of pharmacogenomics, although some differences in meaning do exist between the two terms. The older term, pharmacogenetics, can be defined as the study of interactions between a defined gene or set of genes and pharmaceutical compounds. Pharmacogenomics can be defined as the study of the interaction between the whole genetic make-up of individuals (the genome) and pharmaceutical compounds (Grant, 2001). Even though, pharmacogenomics *stricto sensu* is the apex of research in the broad field of pharmacogenomics, there is still a lot of pharmacogenetic research left to be done, therefore explaining the simultaneous use of these terms to describe pharmacogenomics. The broad impacts this discipline will have both scientifically and economically are likely to be extremely important. The impact on how medicine is practiced and on the well-being of patients as well as the potential transformation of the pharmaceutical business model make a very strong case for trying to gain a better understanding of this discipline and its potential in Canada.

Although, nowadays, one often reads about pharmacogenomics and pharmacogenetics in the publicly available literature, it would be a mistake to think that these disciplines were just introduced in the past five years. Indeed, the term "pharmacogenetics" was first proposed by Friedrich Vogel in 1959 (Severino *et al.*, 2003). The term was first coined to characterize the study of the genetic basis for pharmacological responses. Pharmacogenomics has roots in various other disciplines such as biochemistry, chemistry, genetics and pharmacology, and researchers in these disciplines have been establishing bridges between them for a long time. Nonetheless, the recent development of genomics and the completion of the first part of the Human Genome Project (i.e. the completion of the complete rough draft of the human genome) have unleashed the real potential of pharmacogenomics, which explains the recrudescence of this term in the relevant literature.

Section 2 analyses the national and international context of pharmacogenomics, providing both a qualitative description of the scientific issues tackled by pharmacogenomics and a constitutive analysis of the field as well as describing the important players in this field. Section 3 presents scientometric and technometric measurements of the field of pharmacogenomics, thus quantitatively evaluating this field at the world, G7, provincial and institutional levels by benchmarking scientific production with known measurements and indices. The methods used for Sections 2 and 3 are briefly presented in the Appendix.

Section 4 will present a qualitative analysis of the potential impact of pharmacogenomics in the healthcare industry and will tackle all the issues relevant to this industry. This will lead to a concise SWOT analysis (Strengths, Weaknesses, Opportunities and Threats) that establishes the important elements that need to be taken into account when analysing the potential of pharmacogenomics in Canada.

These analyses will finally allow the formulation of specific recommendations for the optimal integration of pharmacogenomics in the Canadian healthcare landscape (Section 5).

2 International and national contexts

This section examines the international and national contexts with regards to the multiple scientific issues relevant to this field of study (Section 2.1). Section 2.2 will present a constitutive analysis of this field.

2.1 Scientific issues

Pharmacogenomic research aims to link differences in therapeutic effects and other pharmaceutical effects with genetic or genomic variations in target populations. This general research agenda raises a large number of questions (e.g., What is the most efficient way to characterize genomic variation for pharmacogenomic purposes? What family of genes is the most relevant to pharmacogenomics? What are the biochemical pathways involved in pharmacogenomic phenomena?). To answer these questions, researchers usually take two different approaches: the genotype-to-phenotype approach and the phenotype-to-genotype approach (Altman and Klein, 2002). The genotype is the sum of information contained in the genetic code. It is the blueprint of every living organism and differs from one being to another (with rare exceptions like identical twins and genetic clones). The phenotype is the sum of all physical characteristics, whether external or internal, of an organism. For example, height, eye colour, blood group and sensibility to acetaminophen are all part of the phenotype.

2.1.1 Theoretical models

The genotype-to-phenotype approach consists of tracking down sets of genes that are suspected of being important in modulating the response to drugs. Variation in the DNA sequences of those genes is then catalogued to allow an identification of the different phenotypes associated with this variation. Clinical studies are subsequently performed to establish the clinical relevance of the genotype-phenotype association (Altman and Klein, 2002). This approach is advantageous when studying effects whose molecular mechanisms are well understood. For example, the genotype-to-phenotype approach would be useful for studying gene families known to be important for pharmacokinetics (the study of how drugs are absorbed, distributed and cleared from the body), such as phase I metabolism enzymes (which control the toxicity, absorption and elimination of drugs) (Meisel *et al.,* 2000), phase II metabolism enzymes (which check if the new drug really does what it is supposed to) (Yan *et al.*, 1999), and membrane transporter molecules (Galtt *et al.*, 2001). Other systems amenable to the genotype-to-phenotype approach are those involved in pharmacodynamics (the study of how drugs achieve their therapeutic effect) and those whose mechanisms are well understood at the receptor and pathway levels. Examples might include the well-described pathways of asthma-related inflammation (Kuehl *et al.*, 2001; Israel *et al.*, 2001), the purine/pyrimidine biosynthetic pathways that are targeted by some anticancer agents (Ewesuedo *et al.*, 2001), and the enzyme cascade that controls blood clotting (Furuya *et al.*, 1995).

The phenotype-to-genotype approach is the mirror image of the preceding one. It consists of tracking down phenotypic variations in drug responses, which leads to the identification of genes that could explain these variations. The genotypic variation is then associated with the phenotypic variation so that the phenotype-genotype association and its clinical usefulness can be clinically confirmed (Altman and Klein, 2002). Since the genotype-to-phenotype approach necessitates a good knowledge of molecular mechanisms (which is not always the case), the phenotype-to-genotype approach may sometimes be the most appropriate method. There are, however, some important constraints inherent in this approach. Choosing the best phenotype for measuring is critical: it has to be clinically significant and measurable (e.g. drug elimination time, intensity of drug response, drug induced enzymatic response). Also, the search for genes explaining the phenotypic variation can be very arduous. Even though a large array of methods is available for detecting the genes responsible, the process remains essentially a statistical one, at least at the initial stages, and it is often hard to find a clinically interesting genotype-phenotype association.

Both methods have their own weaknesses and strengths. As a rule of thumb, however, it is safe to assume that when scientists have plenty of genetic information about the molecular mechanisms of a given drug, the genotype-to-phenotype approach would be more appropriate. The phenotype-to-genotype approach would be appropriate when a significant phenotypical variation to drug response can be easily observed and measured.

2.1.2 Genotype characterization

Mapping out the genomic differences between different phenotype-expressing groups is the central element of both the phenotype-to-genotype and the genotype-to-phenotype approach, and it is also the most important scientific research subject related to pharmacogenomics. The characterization of genotype-phenotype interactions is accomplished principally through single nucleotide polymorphism genotyping. Single nucleotide polymorphisms (SNPs, often also referred to as "snips") are naturally occurring variations of single nucleotides at given positions in a population's genome (Turyman and Primrose, 2003). To differentiate SNPs from rare, naturally occurring mutations, the least common genetic form must occur at a frequency of 1% or more. SNPs are often genetically linked and expressed together. When this is the case, researchers can characterize these associations, making genetic variations easier to detect. The characterization of SNPs by coherent packages (SNPs that are usually transmitted together), or haplotypes, could be more useful than the characterization of SNPs alone (Grant, 2001). Haplotype characterization is considered to have a higher resolution when detecting polygenic associations (Guiseppi-Elie, 2003) and is expected to accelerate the process of obtaining clinically relevant information from the complete human genome (Hood, 2003). On the other hand, it is easier, and less expensive, to detect a single SNP than to define a combination of several SNPs, i.e. defining an haplotype (Peet and Bay, 2001). When choosing a genotyping method (single SNP or haplotype), the type of genotype-phenotype interaction, whether monogenic or polygenic, should therefore be taken into account.

Many international organizations were created to stimulate international cooperation in genotyping activities, whether they were related to pharmacogenomics or not. The SNP consortium

(http://snp.cshl.org/) is an organization sponsored by a number of pharmaceutical companies. Its objective is to facilitate the public diffusion of SNPs for medical and pharmaceutical purposes. The International HapMap project is also relevant to pharmacogenomics (http://www.hapmap.org). The goal of the International HapMap Project is to develop a haplotype map of the human genome, the HapMap, which will describe the common patterns of human DNA sequence variations. Scientists from many countries, including Canada, are collaborating on HapMap. The SNP consortium also plays a role in the HapMap project, since it is one of the project's major funding organizations. Genome Canada is also a major funding agency of this project, which makes this body a potentially very important player for pharmacogenomics in Canada. The mapping of pharmacologically relevant SNPs and haplotypes being such a central issue for pharmacogenomics, an organization like Genome Canada is an essential player for pharmacogenomics in Canada. Its unifying and catalyzing effects on genomic research and development, as well as its expertise in facilitating the marketing of research products, could easily be used to stimulate pharmacogenomic research in Canada.

2.1.3 Pharmacogenomic research interests

A vast number of research subjects arise from the theoretical approaches presented above. The presentation of all the research subjects studied in pharmacogenomics is beyond the scope of this report; it is, nonetheless, essential to present the most important pharmacogenomic research fields to have a concrete image of this field.

Genetic polymorphisms influencing drug disposition

Pharmacogenomics began with a heavy emphasis on drug-metabolism-related research (Weinshilboum, 2003) but rapidly included the rest of the ADME (Administration, Distribution, Metabolism and Excretion) complex (Evans and Relling, 1999).

The cytochrome P (CYP)-450 gene family is one of the most studied gene families in pharmacogenomics (Rusnak *et al.*, 2001). These genes code oxidative metabolizing enzymes which are often important in the pharmacodynamics of drugs (Peet and Bey, 2001). A particular form of CYP, CYP2D6, is responsible for the metabolism of more than 25% of drugs available in the market (Severino *et al.,* 2003). Since genetic polymorphism was detected for at least six CYP-450 isozymes (Rusnak *et al.*, 2001), most of the research in pharmacogenomics revolves around the CYP family of genes.

The Human P-Glycoprotein Transporter Gene ABCB1 (or MDR1) codes P-glycoprotein (Evans and McLeod, 2003), whose principal function is to act as an energy-dependent cellular efflux of substrates, including bilirubin, several anti-cancer drugs, cardiac glycosides, immunosuppressive agents, glucocorticoids, human immunodeficiency virus (HIV) type 1 protease inhibitors (Choo *et al.,* 2000), and many other medication (Evans and McLeod, 2003).

A tangible example of this type of research is the association between treatment outcome and genetic variants in CYP3A4, CYP3A5, CYP2D6, CYP2C19, the chemokine receptor gene CCR5, and ABCB1

which has been studied in HIV-infected patients receiving combination antiretroviral therapy with either a protease inhibitor or a non nucleoside reverse transcriptase inhibitor (Fellay *et al.,* 2002).

Genetic polymorphisms of drug targets

Drug target (e.g. receptor) polymorphisms are known to have important effects on drug efficacy, with more than 25 examples already identified (Evans and McLeod, 2003). Examples of drug target polymorphisms with a direct effect on response were seen in the gene of the ß2-adrenoreceptor, affecting the response to ß2-agonists (Ligget, 2000). This polymorphism is known to be associated with bronchodilatation, susceptibility to agonist-induced desensitization and cardiovascular effects (Evans and McLeod, 2003). Effects were also linked to arachidonate 5-lipoxygenase (ALOX5) polymorphism. This polymorphism affects the response to ALOX5 inhibitors (Drazen, 1999), therefore modulating the response of certain asthma treatments. Another example of a pharmacogenomically relevant drug target polymorphism is the angiotensin-converting enzyme (ACE), which affects the renoprotective actions of ACE inhibitors (Jacobsen *et al,*. 1998), which, in turn, are known to have renoprotective effects, reduce blood pressure, reduce left ventricular mass and reduce endothelial function (Evans and McLeod, 2003).

Genetic polymorphisms with indirect effects on drug response

Pharmacogenomic effects have been seen with regards to the polymorphisms in genes encoding proteins that are neither direct targets of medication or involved in their disposition (Evans and McLeod, 2003). Where the first two research interests were more relevant to the G2P approach, this one is clearly more relevant to the P2G approach, since the molecular mechanisms explaining the observed pharmacogenomic effects are not always elucidated (Poirier *et al*., 1995). Examples of these effects include inherited polymorphisms in coagulation factors that are linked to the predisposition to deep-vein or cerebral-vein thrombosis of women taking oral contraceptives (Martinelli *et al.,* 1998) and polymorphisms in the gene of the cholesterol ester transfer protein that has been linked to the progression of atherosclerosis with pravastatin therapy (Kuivenhoven *et al,*. 1998).

Maybe more importantly, pharmacogenomic effects have been detected in relation to Alzheimer's disease. Indeed, genetic polymorphism in the apolipoprotein E (APOE) gene appears to have a role in predicting responses to therapy for Alzheimer's disease and to lipid-lowering drugs (Poirier *et al*., 1995). APOE also appears to have a role in predicting responses to therapy for cardiovascular problems (Gerdes *et al*., 2000). Obviously, the nature of the problems tackled by APOE research (Alzheimer's disease and cardiovascular problems) makes this a very important research subject in pharmacogenomics.

2.2 Scientific challenges

Pharmacogenomic challenges are more of a quantitative nature than a qualitative one. Pharmacogenomics' greatest challenges are, more often than not, related to the amount rather than its quality of the information the field has to process. Although it is more of a technological challenge, the main challenge facing pharmacogenomics will be to deal with the storing and

processing of vast amounts of data using bioinformatic tools (Altman and Klein, 2002). This challenge can be subdivided into nine categories:

1. Representing the diversity of pharmacogenomic data
2. Developing standards for data exchange
3. Integrating data from multiple data resources
4. Mining literature for knowledge
5. Using expression data to understand regulation
6. Understanding the structural basis of variability
7. Using comparative genomics
8. Managing laboratory information
9. Protecting sensitive patient information

As mentioned above, most of these challenges are technological rather than scientific. However, challenges 5, 6 and 7 are more of a scientific nature, since their objective is to create knowledge that will change pharmacogenomics from a descriptive, anecdotal discipline to a predictive one (Altman and Klein, 2002). This shift to a predictive discipline, if ever attained, will probably lead to more efficient pharmacogenomic research program, both scientifically and financially speaking. "Predictive" pharmacogenomics would therefore be more interesting to both research groups and private companies.

2.3 Constitutive analysis of the field

Pharmacogenomics is a complex field to characterize. To understand the players in this field, it is important to understand the larger picture of the pharmaceutical industry. Until the beginning of the 1990s, the big pharmaceutical companies (like Bayer, Novartis, Roche, Astra-Zeneca, etc.) controlled the lion's share of the pharmaceutical market, whether it was on the new drug front or the profit front (James, 2003). Although their FIPCO (fully integrated pharmaceutical company) model was highly successful, in that it concentrated all aspects of pharmaceutical activities into mega companies (from R&D through marketing to distribution), new forces (both economic and scientific) are bringing radical changes to this field. Big pharma's product pipelines are rapidly shrinking and its marketing strategies are steadily growing more costly while profits are stagnating (James, 2003).

As for biotechnology companies, even though many of the new chemical entities (NCEs) of the last two years were introduced by the biotechnology sector (20-25% of NCEs, a number that is predicted to grow (Drews, 2003)), biotech companies are also not delivering what they promised. Most biotech companies, with a few exceptions, did not respect their deal-making promises. Big pharmaceutical companies are therefore refusing to blindly jump on the "omics" train (In Vivo, 2001), because they believe that there is not enough evidence that all these new methods will work and are afraid of reducing their market by using them (this is especially the case for pharmacogenomics). As for the small biotech companies that bloomed in the early 90s, most of them are either being bought by bigger biotech companies or disappearing completely because of a lack of funding. This is due to

their inability to make the transition from being tool companies (producing new methods, platforms or research technologies) to product companies (producing marketable therapeutics) (Branca, 2003). Obviously, the trends observed in classical pharmaceuticals are also true for its younger sister-discipline, pharmacogenomics. Even if big pharma is presently investing in pharmacogenomics, mainly by taking genetic samples of their clinical trial test subjects so that they have access to this information in case of unsuspected adverse drug reactions (ADRs), therefore simplifying the process of relabeling a problematic compound, their contribution to the field is still limited (see Lesko and Woodcock, 2002). Most of the ground work in pharmacogenomics is presently being performed by genomic enterprises. Small biotech enterprises are mainly tool companies trying to establish themselves as reliable sub-contractors. It is important to note that although the majority of the work in pharmacogenomics seems to be being done by private enterprises, since the vast majority of the information available on the Internet comes from enterprises or persons employed by or involved in these enterprises, the inherent commercial nature of these activities makes them less visible in scientometric terms (as shown in Section 3.1). Often, the imperative of competition prevents small companies to publicly publish important research breakthroughs (in scientific publications), and they therefore lose the competitive edge gained by new knowledge. This phenomenon is exacerbated by the fact that pharmacogenomics has just begun to show its potential and that only a few companies and people are working in this field.

Although playing in a small and nascent playground, many players are involved in the field of pharmacogenomics: university researchers, private companies and regulatory bodies. The participants that have the most to lose or gain from the advent of pharmacogenomics are pharmaceutical companies. Pharmacogenomics is seen by many as the solution to a great number of the problems currently experienced by big pharmaceutical and biotechnology enterprises. The big pharmaceuticals are hoping that pharmacogenomics will reduce the cost of their pipelines and marketing, by enabling the development of more targeted drugs. This will augment the number of drugs that will reach approval and limit the cost of direct marketing campaigns by targeting specific clients. As for biotech companies such as genomics companies, pharmacogenomics is seen as a way of securing their future by making it easier to subcontract to larger pharmaceuticals. As a matter of fact, there have been many partnerships between big pharma and small genomics companies during the past few years (Branca, 2003). These development deals are supposed to replenish stretched-out big-pharma pipelines and provide genomics companies with much needed financing, with genomics companies acting principally as developers of new products that are to be scaled up by their bigger partners. Examples of these alliances include the 2001 US$150 million deal between Novartis and Immusol (Branca, 2003), by which Immusol used its proprietary gene inactivation platform technology, Inverse Genomics, to discover new oncology drug targets for Novartis. There is also the 2002 US$118 million deal between Syngenta and Diversa (Branca, 2003), by which the two companies combined their research activities in genomics and related technologies for new plant science applications, selected antibody generation and other biopharma product developments.

The American Food and Drug Administration (FDA) recently drafted guidelines for the voluntary submission of pharmacogenomic data prior to drug approval (FDA, 2003). Since these guidelines are

voluntary; companies are not obliged to submit pharmacogenomic data for product approval. This is part of an ongoing process that aims at a better understanding of the potential impacts, both positive and negative, of pharmacogenomics on drug development and regulations. As of now, no regulatory decisions about pharmacogenomics have been made. The FDA is looking at many options, like making pharmacogenomic data submission mandatory, and is continuing its study of the matter to determine the degree of importance to give to pharmacogenomic data when it comes to the approval or labelling of a drug. Other regulatory bodies, such as the Canadian, Japanese and European ones, are keeping relatively quiet on the subject. Little, if no, information about their point of view on pharmacogenomics is available.

As for university researchers and research groups, little information is available on the Internet and other public sources. This is strongly correlated with the fact that there is still a very small number of distinctively pharmacogenomic research articles published in scientific publications (see Section 3.1). This brings up the question of the "reality" of the pharmacogenomic field. Is pharmacogenomics a real field of research, or is it a combination of one established field with another. Many clues seem to lead to the second hypothesis. Although pharmacogenomics deals with specific scientific issues (see Section 2.1), it seems that these issues are approached by combining genomics techniques with pharmaceutical ones, rather than using uniquely pharmacogenomic techniques or knowledge. This absence of a properly defined research field creates a situation in which many researchers are contributing to pharmacogenomics with research from their own domain, either genomics or pharmaceutics, and a tiny minority of researchers are putting the different pieces together.

Finally, it is important to say that while many players have interests in pharmacogenomics, nearly no "pharmacogenomic" drugs have been produced and marketed. With exceptions like Genentech's Herceptin (trastuzumab), a product not developed using pharmacogenomics but that can only be used to treat breast cancer in women who over-express a specific protein (Nuffield Council on Bioethics, 2003), there are few, if any, real "pharmacogenomic" drugs on the market. This fact, above all others, shows that pharmacogenomics is only just starting to grow. It also explains why many organizations and companies are just starting to be interested in this field and are cautiously probing it to see if valuable research or profits can be made with it.

3 Scientometric and technometric measurements

This section presents scientometric and technometric analyses of pharmacogenomic science and technology with the aim of identifying Canada's strengths in the field.

3.1 Scientometric analysis

This section presents data on the rate of growth of scientific papers written in the field of pharmacogenomics at the world level (Section 3.1.1). It subsequently benchmarks the Canadian scientific output against that of the world as whole and against the other G7 countries. It also benchmarks scientific output at the Canadian, provincial and institutional (ten most active institutions) levels (Section 3.1.2).

3.1.1 Scientific output at the world level

Pharmacogenomics can be considered as a slowly evolving field of research. In addition, it is still at a junction between two distinct fields: pharmaceutics and genomics. Little specifically pharmacogenomic research was done during the period studied, that is, between 1991 and 2002. Most of the fundamental research was done either in pharmaceuticals or genomics, and only a handful of researchers decided to combine them in a unique way. These characteristics make it very difficult to detect consistently pharmacogenomic research, since most of the research used in pharmacogenomics was done in its two parent disciplines. Nonetheless, our research revealed some purely pharmacogenomic research, and Figure 1 shows the Canadian and world output in this field.

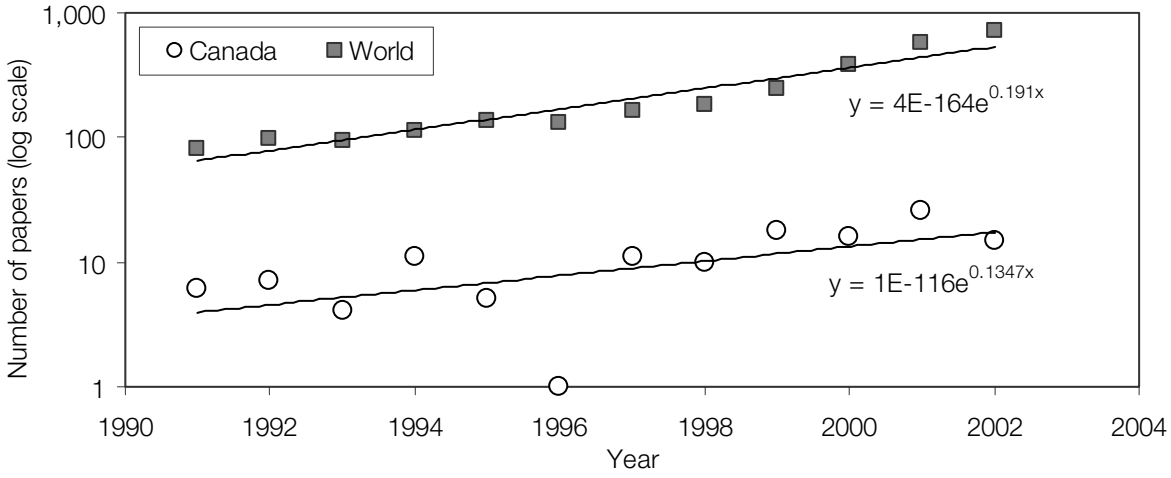


Figure 1 Pharmacogenomic papers by Canada and the world, 1991-2002
Source: Compiled by Science-Metrix from Medline

As we can see, not only Canadian output in pharmacogenomics seems minimal (a total of 130 publications), Canada is also losing ground to the world as a whole (a total of 2,968 publications, roughly the yearly total output of a large university biology department, such as that of the

University of Toronto). The world average yearly output in pharmacogenomics accounts for 0.06% of the total scientific output in the Medline database. These small numbers, at both the world and Canadian level, indicate that Canadian pharmacogenomic research is done by a small number of researchers and that pharmacogenomics is not always their only field of publication, the others probably being pharmaceutics and/or genomics.

Table I shows in detail the number of publications in pharmacogenomics at the Canadian, G7 and world levels from 1991 to 2002 as well as the growth rate by three-year periods.

Table I Number of papers and growth in the field of pharmacogenomics for Canada, the G7 countries and the world, 1991-2002

	1991-1993		1994-1996		1997-1999		2000-2002		1991-2002
Country	Papers	Growth	Papers	Growth	Papers	Growth	Papers	Growth	Papers
United States	124	-	144	16%	196	36%	717	266%	1,181
United Kingdom	18	-	26	44%	62	138%	166	168%	272
Japan	11	-	38	245%	48	26%	145	202%	242
Germany	16	-	24	50%	40	67%	142	255%	222
France	16	-	33	106%	44	33%	73	66%	166
Canada	17	-	17	0%	39	129%	57	46%	130
Italy	4	-	6	50%	12	100%	39	225%	61
World	273	-	384	41%	589	53%	1,671	184%	2,917

Source: Compiled by Science-Metrix from Medline.

The comparative study of the number of publications and the growth of pharmacogenomic scientific production by the G7 countries and the world yields some interesting results. The 1991-1993 period shows that the United States was already then the dominant country in terms of production. The United States published 45% of the world output in pharmacogenomics. Canada, France, Germany and the UK were at the same level (respectively 17, 16, 16 and 18 publications), Japan was trailing slightly with 11 publications, and Italy closed the march with only 4 publications.

The 1994-1996 period showed that, while France and Japan experienced tremendous growth (106% and 245% respectively), Canada experienced no growth at all, making it the only country in this study that did not grow during this period. Germany, Italy and the UK experienced growth of around 50% and the United States' number of publications grew by 16%. This sums up as a 41% world growth. In terms of publications, Canada fell from third to sixth position with only 17 publications. France took the third place with 38 publications, Germany remained in fifth place with 24 publications, and Italy stayed seventh with only six publications. As for Japan, its phenomenal growth put it in second place with 38 publications. The UK achieved a fourth position for this period (with 26 publications), while the United States remained first with 144 publications, even though its share of world publications dropped to 38%.

With 129% growth, Canada finally experienced a growth spurt during the 1997-1999 period; so did the UK, which improved its production by 138%. France, Japan and the United States experienced growth of around 30% to 40%. Germany experienced strong growth of 60%, and, finally, Italy

experienced 100% growth, for an overall world growth of 53%. Although it experienced significant growth, Canada remained in sixth position, with 39 publications for this period. France fell to fourth place with 44 publications, the third place being filled by Japan, which also dropped from its previous position, with 48 papers. Germany stayed in fifth place with 40 papers, while Italy also kept its previous position, still being seventh with 12 papers. The UK took the second place with 62 papers, and the United States held a strong first with 196 publications.

The 1999-2002 period was characterized by strong growth in pharmacogenomic production in many countries and in the world as a whole. Indeed, Germany experienced 255% growth, Italy 225% growth, Japan 202% growth, UK 167% growth and the United States a stunning 266% growth. These extraordinary growth rates translated themselves into 184% growth at the world scale. Canada and France are the only countries which did not experience growth rates superior to 100% for this period (Canada: 46%, France: 66%). Canada remained in sixth position with 57 papers, France fell to fifth place with 73 papers, and Germany came in fourth with 142 papers. Italy was still in seventh position with 39 papers, while Japan reached the third place (145 papers), England the second (166 papers) and the United States remained in first place (717 papers). For the total period spanning 1991 to 2002, the United States was obviously the leader in terms of publications (40% of the world's publications in pharmacogenomics). Then comes a leading pack formed by the UK, Japan and Germany (~9% of the world's publications). France (6%) and Canada (4%) come next, and Italy comes last (It published 2% of the world papers in pharmacogenomics).

Table II shows the specialization index (SI) in pharmacogenomics of Canada and the other G7 countries as well as the impact factor (IF) in pharmacogenomics of Canada, the other G7 countries and the world for the 1991-2002 period.

Table II Specialization index (SI) and impact factor (IF) in pharmacogenomics of Canada, the G7 countries and the world, 1991-2002

	1991-1993		1994-1996		1997-1999		2000-2002		1991-2002	
Country	SI	IF	SI	IF	SI	IF	SI	IF	SI	IF
France	1.30	-	1.87	-	1.63	4.01	1.01	2.91	1.27	3.40
United Kingdom	0.95	-	0.91	-	1.39	3.96	1.30	4.70	1.26	4.44
Germany	1.01	-	1.06	-	1.07	4.06	1.32	3.91	1.24	3.95
Canada	1.65	-	1.19	-	1.82	3.77	0.97	3.86	1.22	3.82
United States	1.23	-	1.01	-	0.94	5.63	1.26	4.41	1.13	4.74
Japan	0.45	-	1.08	-	0.90	4.16	0.98	3.54	0.92	3.73
Italy	0.37	-	0.40	-	0.53	4.07	0.61	3.54	0.54	3.68
World	1.00	-	1.00	-	1.00	4.56	1.00	4.03	1.00	4.20

Source: Compiled by Science-Metrix from Medline.

Canada started out strong when it comes to the SI. It occupied the first place in 1991-1993 with an SI of 1.65 (meaning that it produced 65% more articles in pharmacogenomics than what could have been expected). France and The United States came next with SIs between 1.20 and 1.30. Germany and the UK were not specialized, their respective SIs hovering around a value of one. Finally, Italy

and Japan were clearly underspecialized with values between 0.35 and 0.45. During the 1994-1996 period, Canada's SI fell to 1.19, while France's grew to a strong 1.87. Germany, Italy and the UK's respective SIs remained relatively stable Japan's experienced phenomenal growth, with its SI reaching 1.08, jumping from being greatly underspecialized to producing the expected output for this discipline. Canada attained an SI of 1.82 during the 1997-1999 period, making it the period where it was the most specialized. The UK's SI also improved visibly, reaching 1.39. France's SI decreased slightly to 1.63 and that of the other countries remained relatively stable. Finally, the 2000-2002 period saw another decrease for Canada's SI, which fell to 0.97. The small number of publications is probably responsible for this boom-and-bust pattern since the small number of publications was probably produced by a handful of researchers, which often can not maintain a regular rhythm of publication from one year to the next. France and Japan's SI were around 1.00, while Germany reached its highest SI with 1.32. Italy had an SI of 0.61. Although relatively stable from one period to the next, Italy's SI experienced a slight but regular augmentation during the 12-year period. Finally, the UK and the United States had SIs of around 1.30. For the 12-year period as a whole, all the differences between countries tend to smooth themselves out. Indeed, all countries, except Italy and Japan, had SIs between 1.10 and 1.30. Japan had an SI of 0.92 and Italy 0.54.

As for the impact factor, it is interesting to note that nearly all of the countries' IFs in pharmacogenomics presented here are higher than the general world average of 3.02 (all Medline). The only exception is France with an IF of 2.91 during the 2000-2002 period. The impact factor of Canadian publications in pharmacogenomics is lower than that of the world in this field. Canada's IF was 3.77 for the 1997-1999 period and 3.86 for the 2000-2002 period, for a total IF of 3.82. In contrast, the world's IF dropped from 4.56 in 1997-1999 to 4.03 in 2000-2002, for a total IF of 4.20 for the total period. As for the other countries, France, Germany, Italy, Japan and the UK's respective IFs were near the 4.00 value, and the United States' IF was 5.63, making Canada the country with the smallest impact during this period. The 2000-2002 period was characterized by a generalized drop in IF for most countries, except Canada, which was the only country that experienced a growth in IF. During this period, the United Kingdom was the clear leader with an IF of 4.70, surpassing the United States' IF of 4.41. France came last with an IF of 2.91. When we look at the 12-year period as a whole, two countries, the UK and the United States, stand out with IF values above 4.40. Nearly all the other countries had IFs between 3.50 and 4.00, the exception being France with an IF of 3.40.

3.1.2 Scientific output at the Canadian level

Table III presents Canadian publications according to province over three-year periods. Ontario is the only province to have published every period during the 12 years covered by this study, publishing a total of 72 publications. With 30 publications, Quebec follows in terms of publications and is also the only other province to have published more than ten papers during at least two consecutive three-year periods. Nova Scotia and Prince Edward Island tie in third place with six publications each, followed by Alberta and British Columbia in fourth place with five publications each. Saskatchewan comes in fifth with four publications and Manitoba sixth with one publication. Newfoundland and New Brunswick are last, since they did not publish at all in pharmacogenomics.

Table III Number of papers in pharmacogenomics by Canadian provinces, 1991-2002

Country	1991-1993	1994-1996	1997-1999	2000-2002	1991-2002
Ontario	15	12	17	28	72
Quebec	2	0	14	14	30
Alberta		1	1	3	5
British Columbia				5	5
Manitoba				1	1
Saskatchewan		3	1		4
Nova Scotia		1	2	3	6
Newfoundland					0
New Brunswick					0
Prince Edward Island			3	3	6

Source: Compiled by Science-Metrix from Medline.

Growth was measured only for Ontario, Quebec and Prince Edward Island, since they were the only three provinces to have published more than 3 publications for at least two consecutive three-year periods. The very small number of publications involved in these measurements indicates that they must be interpreted with caution. Ontario experienced a decrease in publications between the 1991-1993 and 1994-1996 periods, as shown by the 20% decline between those periods. It then experienced 42% growth between the 1994-1996 and 1997-1999 periods and 65% growth between the 1997-1999 and 1999-2002 periods. Quebec and Prince Edward Island maintained a stable number of publications between the 1997-1999 and 1999-2002 periods (0% growth).

Table IV shows each province's specialization index (SI) by three-year periods for the 12-year period covered by this study. It also shows Ontario, Quebec and Prince Edward Island's impact factor for the 12-year period. Only these three provinces are included in the IF analysis, since they are the only ones for which we can look at IF data for more than five publications.

Table IV SI and IF in pharmacogenomics by Canadian provinces, 1991-2002

Country	1991-1993	1994-1996	1997-1999	2000-2002	1991-2002	IF (Total)
Ontario	3.34	1.92	1.79	1.06	1.61	4.18
Quebec	0.84		2.74	1.07	1.27	4.43
Alberta		0.59	0.45	0.45	0.45	
British Columbia				0.76	0.47	
Manitoba				0.46	0.23	
Saskatchewan		5.82	1.53		1.15	
Nova Scotia		2.50	2.98	1.51	1.90	
Newfoundland						
New Brunswick						
Prince Edward Island			46.73	14.94	20.21	1.48

Source: Compiled by Science-Metrix from Medline.

As far as the specialization index is concerned, Ontario's performance does not reflect the dramatic boom-and-bust pattern observed at the national level, but, instead, a gradual decline in specialization. Its SI spans from 3.34 during the 1991-1993 period to 1.06 during the 2000-2002 period, generally showing smoother variations from year to year than what was seen at the national level. For the total period spanning 1991 to 2002, the Ontario SI was 1.61, slightly higher than the general Canadian specialization index. Quebec's specialization index was relatively lower, falling from 3.75 in 1999 to 0.55 in 2002, with an SI of 1.19 for the period as a whole. As for the other provinces, it is hard to interpret their SI because of their few publications during the time span studied. This is the case for Prince Edward Island in particular (which extravagantly scores above ten), probably because it has only a small number of publications indexed in the Medline database since it possesses no medical school.

Ontario and Quebec's IFs are higher than the Canadian one (4.18 for Ontario, 4.43 for Quebec). They are very close and, in the case of Quebec, even slightly higher than the world's 4.20 impact factor for the total period. Even though Prince Edward Island's SI was extravagantly high, its IF, 1.48, was relatively low.

In terms of most active institutions, Table V presents the total number of publications in pharmacogenomics for the 1991-2002 period. It also shows the SI and the IF of all institutions that published five or more publications in pharmacogenomics.

Between 1991 and 2001, only ten institutions published five or more papers (Table V). With 30 publications, the University of Toronto is clearly the leading institution in Canada. It is followed by the Centre for Addiction and Mental Health with 13 publications, Toronto Public Health with nine publications and, in fourth place, the Hospital for Sick Children with eight publications. All four institutions are located in Toronto, making the Queen's city the closest thing Canada has to a pharmacogenomics hub. The other important centre is Montreal with two top-ten institutions, McGill University and the Douglas Hospital, each with five publications.

Table V Most active Canadian institutions in the field of pharmacogenomics: publications, SI and IF, 1991-2002

Institution	Paper	SI	IF
University of Toronto	30	3.75	3.41
Centre for Addiction and Mental Health	13	15.06	2.80
Toronto Public Health	9	3.02	3.14
Hospital for Sick Children	8	2.25	
CHUQ	7	4.41	3.72
University of Western Ontario	7	1.88	
Prince Edward Island University	6	20.70	1.48
Dalhousie University	5	2.06	
Douglas Hospital	5	13.14	
McGill University	5	1.01	

Source: Compiled by Science-Metrix from Medline.

As for the SI, the strong performances of the Centre for Addiction and Mental Health (15.06) and the Douglas Hospital (13.14), both institutions dealing with mental health and addiction issues, denote an important degree of research intensity in the field of pharmacogenomics in these two institution. In addition to clinically used drugs, researchers of the Pharmacogenetics Section, led by Drs. Rachel F. Tyndale and Edward M. Sellers of the Centre for Addiction and Mental Health (CAMH), explore the role that genetic variation in drug-metabolizing enzymes can have on the metabolism of drugs of abuse. As for the Douglas Hospital, pharmacogenomic research is being conducted on the treatment of Alzheimer's (Schappert *et al.,* 2002) and on pharmacogenomic effects in the treatment of depression and schizophrenia (Turecki *et al.,* 2001). A clinical and pharmacogenetic study of attention deficit/hyperactivity disorder (ADHD) is also being conducted at the moment.

Prince Edward Island University also has a high SI, probably an artifact because of the very small number of Prince Edward Island publications indexed in the Medline database (this is in part attributable to the fact that Prince Edward Island does not have a faculty of medicine). The totality of Prince Edward Island's publications comes from. Dr. Alastair Cribb's Laboratory of Comparative Pharmacogenetics at the Atlantic Veterinary College. The objective of this laboratory is to understand the molecular basis of pharmacogenetic variation within and between species, with a view to improving the safety of drugs in human and veterinary medicine, avoiding drug- and chemical-induced toxicity and increasing the exchange of information between human and veterinary pharmacogenetics.

Finally, the five institutions whose IF was measured had an IF that was slightly lower than or equal to their respective provincial scores. The slight differences are probably due to some well-published articles that came from institutions that are not in the top ten in terms of number of publications.

3.2 Technometric analysis

This section presents data on intellectual property at the world level. Table VI presents the total number of pharmacogenomic patents filed at the USPTO since its implementation and the total growth of patenting in this field.

As one can easily see, very few patents were clearly filed with pharmacogenomics in mind. The first identifiable pharmacogenomics patents were filed in 1999, and, since then, the number gradually grew from 2, reaching 22 in 2003. Although the growth rates are somewhat high (jumping from 4 to 14 between 2001 and 2002), it is important to keep in mind that the 44 pharmacogenomics patents are but a speckle on the total patenting picture. Indeed, more than 900,000 patents were filed at the USPTO from 1999 to 2003, giving pharmacogenomics a share of world patents smaller than one half of a percent.

Table VI Total world growth, number of inventions and intellectual property (IP) assignation in pharmacogenomics for the world and the patenting countries, 1999-2003

	1999		2000		2001		2002		2003		1999-2003	
Country	Invention	IP	Invention	IP	Invention	IP	Invention	IP	Invention	IP	Invention	IP
United States	1	1	2	2	2	2	14	14	21	21	40	40
Germany							4				4	
United Kingdom	1	1							1		2	1
Canada					1	1					1	1
France									1	1	1	1
Italy					1						1	
Norway	1										1	
Sweden					1	1					1	1
World*	2	2	2	2	4	4	14	14	22	22	44	44
World Growth	-		0%		100%		250%		57%		-	

Source: Compiled by Science-Metrix from the USPTO.
* IP and invention are always the same at the world level

As expected, the near totality of pharmacogenomic inventions, 40 of 44, are attributed to the United Sates. The United States also owns all its inventions. In terms of invention, Germany comes in second with four inventions, but it does not own its inventions. The United Kingdom comes in third with two inventions and one IP assignation. Canada, France and Sweden come next with one invention and one IP assignation each. Finally Italy and Norway have one invention each, of which they do not hold the intellectual property.

This small number of pharmacogenomic patents could also be a consequence of pharmacogenomics being a field that is still strongly influenced by its two parent disciplines, genomics and pharmaceutics. It is probable that most of the technology presently used in pharmacogenomics was developed for genomics or pharmaceutics, which would explain the small number of specifically pharmacogenomic patent. Moreover, pharmacogenomically relevant SNPs are often not patented but publicly distributed through a non-profit organization, the SNP Consortium, made up of

academic centers and industry members that wish to accelerate pharmacogenomic research and minimize pre-product competition and monopoly (Branca, 2002). However, the regular growth of pharmacogenomic patenting lets us foresee the implementation of specifically pharmacogenomic technologies that will come with the establishment of pharmacogenomics as a scientific discipline.

Table VII lists the different pharmacogenomic patent assignees (i.e. owners of intellectual property). The most important assignee is clearly Lexicon Genetics with more than half of the patents. Lexicon Genetics is a biopharmaceutical company that uses proprietary gene knockout technology to identify new drug targets. It is important to specify that their patents are said to have *potential* uses in the field of pharmacogenomics and, like most of the patents presented here, there are no indications that these inventions are presently being used in pharmacogenomics. The sole Canadian patent was held by a Montreal-based company called Signalgene and was filed in 2001. Since then, the company was sold and transformed into an oil and gas company called Signalenergy. Signalenergy is absolutely not implicated in pharmaceutical research, and it is unclear if it still holds the right to the original patent.

Table VII Pharmacogenomic patents assignees, their type of organization, country and number of patents, 1993-2003.

Institution	Sector	Country	Papers
Lexicon Genetics Incorporated	Enterprise	US	24
DNA Sciences Laboratories, Inc.	Enterprise	US	4
Arch Development Corporation	Enterprise	US	2
The USA Dept. of Health and Human Services	Government	US	2
Affymetrix, Inc.	Enterprise	US	1
Genaissance Pharmaceuticals, Inc.	Enterprise	US	1
Genset, S.A.	Enterprise	France	1
Imperial Cancer Research Technology Limited	Enterprise	UK	1
Integriderm, Inc.	Enterprise	US	1
Buddhiraja Vijaya Kumar and Louis G. Lange, III	Individuals	US	1
Pyrosequencing AB	Enterprise	Sweden	1
Rosetta Impharmatics, Inc.	Enterprise	US	1
Sangamo BioSciences, Inc.	Enterprise	US	1
Signalgene	Enterprise	Canada	1
Vanderbilt University	University	US	1
Whatman, Inc.	Enterprise	US	1

Source: Compiled by Science-Metrix from the USPTO.

Pharmacogenomic patenting is still a marginal field of patenting, but current data shows that it is a growing activity, and it is reasonable to think that it will continue to grow in the future since the number of patents in the field gradually grew from 2 to 22 in 2003. Moreover, the actual development of pharmacogenomic drugs and test kits will inevitably lead to a growth in patenting.

4 Pharmacogenomics and the healthcare industry

In Section 1, it was mentioned that even if the term pharmacogenetics was first proposed in 1959 by Friedrich Vogel (Severino, 2003), it is really only once the Human Genome Project was completed in June 2000 that its real potential became evident. It is also in this time frame that its use by pharmaceutical companies became more important.

Nevertheless, it is generally agreed upon that pharmaceutical companies have been slower than predicted in adopting pharmacogenomics in their drug development programs. It is felt that genomics' market impact is still ten years away (Branca, 2003). Pharmaceutical companies' lack of enthusiasm for this promising technology could be explained by the following reasons:

- Pharmaceutical companies' belief that there is not enough evidence that all of these new methods will work (In Vivo, 2001);
- Pharmaceutical companies' fear of reducing their market by using pharmacogenomics (In Vivo, 2001);
- Genomics having proved itself to be better at finding new drug targets than at validating them (Branca, 2003);
- The fact that the anticipated quick and substantial impact on drug development pipelines did not occur (Branca, 2003);
- The traditional conservative and slow responsiveness of big pharmaceutical companies;
- The important and substantial changes it will impose on the big pharma model (James, 2003) as well as on the way medicine is practiced (Lesko and Woodcock, 2002).

On the other hand, there are many more reasons why the pharmaceutical industry may have no other option than to adopt pharmacogenomics in their drug development plans and marketing strategies. Among them, the following are the most important:

- The lack of new compounds. The annual number of new chemical entities for the top 24 pharmaceutical companies in 2000 was 1.8 (Drews, 2003);
- The steady decrease of the number of approved breakthrough drugs since 1996 (Murphy, 2000);
- The fact that pharmaceutical companies are suffering from an innovative deficit and are looking for new ways to improve their productivity (Norton, 2001);
- The need to reduce development time and cost (Murphy, 2000);
- The FDA's favorable position toward using pharmacogenomics in drug development (Murphy, 2000).

In addition to these "internal" factors, external (social) elements will also put pressure on the pharmaceutical industry to increase its adoption of this relatively new technology. The most important of these external incentives are that most drugs typically work in 40% to 70 % of patients (Maggio *et al.,* 2002), that adverse drug effects among hospitalized patients may be as high as two million patients a year, of which up to 100,000 die (Norton, 2001), that the cost associated with drug morbidity and mortality could be as high as $76 billion a year (Wertz, 2003) and that adverse drug reactions are between the fourth and sixth leading cause of death in the US (Murphy, 2000).

The main question is whether the pharmaceutical industry will abandon its current business model to adopt a new model that would fit better the use of pharmacogenomics not only in drug development and marketing but also in new ways practicing medicine. Will the advantages offered by pharmacogenomics be sufficient to overcome the disadvantages that will come with it? Will the pharmaceutical industry jump on the pharmacogenomics band wagon or will it sit on the side lines and be outflanked by biotechnology companies? Could the pharmaceutical industry eventually prevent pharmacogenomics from becoming a new tool in the armamentarium of technologies used to develop new therapeutic agents?

While early adoption was rather slow and disappointing for the reasons already mentioned, most of the literature seems to indicate that pharmacogenomics will rapidly gain importance. Some experts believe that it will become an essential tool to the industry within the next three to five years (Norton, 2002). Others state that personalized medicine is one of the most seductive lures of the genomic revolution (Branca, 2003). Even so, some pharmaceutical companies, such as Bristol Myers Squibb, are reportedly stating that "individualized medicine doesn't play to our core interests". (Wertz, 2003).

While there are a small number of experts that believe that pharmacogenomics will not enjoy the popularity predicted, most of them believe it will (Murphy, 2000). Two products using pharmacogenomics have already been approved by the FDA and are currently being marketed. They are Herceptin™ (Amgen) and Gleevec™ (Novartis). Herceptin™ was the first pharmacogenomic drug to be approved (1998), followed by Gleevec™ in 2001. Evidently, the number of drugs using pharmacogenomics in their development and currently being marketed is not very impressive. But, we should not be misguided by this small number. A number of other facts found in the literature indicate a very high level of interest and activity. Below are a few examples illustrating this fact:

- Covance Inc. (an international contract research organization) reports that 80% of its large pharmaceutical clients are banking DNA from patients enrolled in clinical trials (Branca, 2003);
- The FDA has received 50 or so pharmacogenomics related New Drug Applications (NDAs) in recent years (Branca, 2003);
- At least one dozen clinical trials are underway using DNA microarrays (Branca, 2003);
- 30% of Astra Zeneca's Phase I trials now set out a genetic hypothesis to be pharmacogenomically confirmed in Phase II and III trials (In Vivo, 2001);
- The financially important high-value genomics-based drug discovery and development deals (25) made by pharmaceutical companies in the 2000-2002 period (Branca, 2003);
- The important number (almost 1,800) genomics deals signed in the 2000-2002 period (Branca, 2003);
- The purchase of Rosetta Inc. by Merck and its recent deal with deCode Genetics (LifeSciences World, 2003);
- The strong involvement of top pharmaceutical companies such as Merck, Glaxo Smith Kline and Novartis and of the most important biotechnology companies such as Amgen;
- The compound annual growth rate (CAGR) of the pharmacogenomics market will be 22% for the 2004-2007 period (Fontline Strategic Consulting Inc., 2003);

- The pharmacogenomics market is forecasted to reach in excess of US$1.5 billion in 2008. Big pharma companies will continue to drive the industry towards personalized medicine (Mindbranch, 2003).

This evidence seems to point to the fact that pharmacogenomics is probably here to stay and that its use will significantly increase in the years to come. Pharmacogenomics is already being used by organizations like Genome Canada[1] to encourage financial and scientific support for genomic research, thus highlighting the importance that some players give to this discipline.

In the next pages of this report we will discuss the ethics and privacy issues that need to be dealt with (Section 4.1), the current and future direction of regulatory affairs (Section 4.2), the current and future impact of pharmacogenomics on pre-clinical and clinical drug development (Section 4.3), the impact of pharmacogenomics on the production of drugs (Section 4.4), marketing (Section 4.5), the current pharmaceutical business model (Section 4.6) and the Canadian healthcare system (Section 4.7).

4.1 Ethics and privacy

Ethics and privacy are very sensitive issues not only for pharmacogenomics but for any –omics technology. There are many reasons that could explain the concerns expressed not only by individuals but also by the medical and ethical community: the type of information collected, i.e. individuals' genetic data including their future morbidity and, in extreme cases, their mortality (Kaplan and Junien, 2000), the impact this information could have on an individual's self-perception and his/her attitudes (Hood, 2003), and the potential impact that it could have on his/her insurability and employment (Vaszar *et al.*, 2002). Other concerns such as research integrity, informed consent and access to information are also important (Hood 2003).

The degree of sensitivity may depend, in some part, on the type of information sought by the pharmacogenomic test. If the purpose of the test is treatment and not primarily diagnosis of a disease, the ethical issues connected to pharmacogenomics are less urgent (Hood, 2003) and likely less sensitive. The same could be true if a test is used by a physician to confirm a diagnosis or to select the best drug for a patient. In these cases, genetics tests may not be any different from other biological tests (as reported by Dr. Janice Kurth[2]).

At the other end of the spectrum, genetic screening, the issues of ethics and privacy become very important. Ensuring the privacy of an individual's genetic data has been a major obstacle to genetic screening (Gatto, 2003). The potential of misuse of this information by insurance companies and employers as well as the potential for "genetic race discrimination" are real and will need to be dealt with by stakeholders. Situations in which employers tested employees without their full and

[1] http://www.genomecanada.ca/GCprogrammesRecherche/projets/projectDetail.asp?id=c2p54&l=e (visited in March 2004)

[2] http://www.aacc.org/access/pharmacogenomics/qanda.stm (visited in March 2004)

knowledgeable consent have already occurred (Gatto, 2003). In this case, the government will need to impose very strict guidelines on the industry to ensure that the privacy of individuals (they are not patients in this situation) is fully protected and that information is used within specific boundaries. Incidentally, insurance companies are expressing interest in the field of genetic screening, and at least one of them (Aetna) is ready to work on establishing national guidelines to promote genetic testing as a tool for disease prevention and management (Gatto, 2003). They believe that personalized medicine could reduce the cost of healthcare, therefore their expenditures and eventually the premiums paid by their clients. One could easily imagine that such a position has raised a number of critical issues that will need to be dealt with before this happens.

Genetic screening done exclusively for prophylactic reasons also needs to be addressed. Why profile if we cannot prevent a specific disease from occurring? Will it provide more negative impacts such as patient anxiety and depression, unnecessary medical procedures, suicide etc.? The example of women being screened for breast cancer in a family with a high incidence of breast cancer clearly illustrates the dilemma posed by genetic screening done for prophylactic reasons or for any reason other than the treatment of disease.

Somewhere along this spectrum is the use of genetic information collected during clinical trials. Generally speaking, this information is collected to differentiate the different types of patients from a pharmacodynamic and pharmacokinetic point of view. Usually, genetic information is stored and used in the design of other clinical trials or, when rare and unpredicted adverse effects occur, once the product has been commercialized. Evidently, measures will need to be taken to ensure that this information is not accessible and, if it is, that it is used for the right reasons. Pharmaceutical companies will need to fully inform patients enrolled in clinical trials that their genetic information will be collected and stored. They will also have to inform them of the potential use of this information. They will need to do this in order to obtain full and informed consent from patients. Patients should have the right to withdraw their DNA samples from the research project (Vaszar *et al.*, 2002). Two different methods could be used to ensure this privacy. The first one consists of stripping the information of any information that could be used to identify an individual (Martin *et al.*, 2003). The second one consists of unlinking the information that could be used to identify the donor from his/her biological sample and keep the codes in separate locations (Vaszar *et al.,* 2002).

Moreover, the concept of informed consent can be blurred further. Since an individual's genetic make-up is composed of half of each of his/her parents' genetic make-up, an individual's genetic information also reveals information about the individual's parents. This phenomenon can also be extended to the rest of the immediate family (brothers, sisters, grandparents, etc.), then to the community and finally to the population. If some kind of consent is to be asked of members of these groups, then the private relationship between a doctor and his/her patient can be severely modified or even eliminated (Vaszar *et al.*, 2002). Tough questions of "property" of one's genes necessarily need to be addressed if pharmacogenomics is to be widely used. One could argue that genetic information is no different from medical family history information, but the same concerns are also

already raised with respect to the use of this type of information[3], further indicating that the concept of private information in a medical context urgently needs to be addressed.

Finally, another issue that legislators will have to look at is what is called the "orphan patient concept". Patients belonging to groups with genetic profiles that are too small to be of interest to pharmaceutical companies and to make it financially worth developing drugs for them are less profitable to treat, which could eventually affect their future care, insurability and even employment. The government may have to adopt anti-discrimination legislation coupled with patent and other incentives to encourage companies to develop drugs suited to this population (Vaszar *et al.*, 2002). Such a law has been implemented in the United States for an analogous situation: the orphan drug problem. The *Orphan Drug Act*[4] was passed to foster and facilitate the development and approval of pharmaceutical products for the treatment of rare diseases (Rohde, 2000). The act provides mainly economic incentives for the production of such drugs. It provides drug researchers and manufacturers with three primary incentives[5]: 1) federal funding in the forms of grants and contracts for clinical trials of orphan products; 2) tax credits to the value of 50% percent of clinical testing costs; and 3) an exclusive right to market the orphan drug for seven years from the date of FDA marketing approval (Rohde, 2000). Until now, the *Orphan Drug Act* has succeeded in bringing to market drugs to treat rare diseases. More than 100 products have received FDA approval and are currently available to the affected patient populations (Rohde, 2000). Similar legislation could certainly be applied to the orphan patient concept, therefore encouraging production of cures for small populations of afflicted individuals and helping to reduce genetic discrimination.

In order for pharmacogenomics to realize its full research and medical applications, these ethical and privacy concerns will need to be addressed by the federal government.

4.2 Regulatory affairs

One of the impediments to the more rapid development of pharmacogenomics in the pre-clinical and clinical development of new drugs has been the lack of clear guidelines from the different regulatory agencies. It is only recently (November 2003) that the FDA has issued a consultation

[3] http://genetics.faseb.org/genetics/ashg/policy/pol-38.htm (visited in April 2004)

[4] Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa - ee (1998))

[5] Incentive 1 significantly reduces the approval costs of new drugs. Incentive 2 continues where incentive 1 left off, virtually eliminating approval costs, and since it is a tax credit and not a reimbursement, even giving back more money than what was actually spent. Incentive 3 provides for a patent-like protection of intellectual property that was not admissible for patent protection. This is especially useful for drug uses that were discussed in public scientific journals, which, under normal patent regulations, would not be patentable.

document[6]. Other regulatory agencies, both in Canada and in Europe, have not yet provided any guidance in terms of what they would look for when it comes to using pharmacogenomics in clinical trials and new or supplementary drug submissions. Because of the importance of regulatory requirements before a drug is approved, it is not surprising that pharmaceutical companies have not been overly enthusiastic in using pharmacogenomic information in their new drug applications.

On the other hand, the FDA signified its interest in using genetic applications in drug development as early as April 1997, when it published its *Guidance for Industry* document, describing the use of genetics in the study of drug metabolisms and safety (Mehr, 2002). Furthermore, in the guidance document released more recently by the FDA, the Agency has stated its objective of developing its internal expertise in the field of pharmacogenomics and that it intends to "champion the field" (Branca, 2003).

The use of pharmacogenomics will affect the three FDA's regulatory departments (Drugs, Biologics and Medical Devices) depending on how it is used and for what purpose. If it is used in drug development, it will be reviewed by the department responsible for approving new drugs. If it used in diagnostic tests (mainly *in vitro*) to assist physicians in selecting the most appropriate drug, it will be classified as a Medical Device and reviewed by the appropriate department. Finally, if a diagnostic test is done in a "Central Lab", it will not be covered by any regulatory requirements even if the FDA could regulate these private labs but has not done so up to now (Bristol, 2003). On the other hand, central labs will still need to prove that the tests are reliable and reproducible and guarantee the analytical and clinical validity of genetic and *in vitro* tests (Bristol, 2003). Furthermore, American private labs have to meet GLP (Good Laboratory Practice) norms by law (*Clinical Laboratory Improvement Act* (CLIA)) which a type of quality "guarantee". In Canada, our private labs do not have to meet GLP norms, but most important labs meet the GLP norms set by the FDA. We will not discuss this situation any further but will elaborate more on the first two situations mentioned.

The regulatory framework for genetic testing (or diagnostic kits) is quite straightforward. In the US, it would be classified as a Class III medical device and would require an IDE. In Canada, it would also be classified as a medical device and would have to follow a similar regulatory approval process that varies according to the type of *in vitro* test and body fluid used. It should be noted that these procedures apply to any type of *in vitro* testing and no modifications to the guidelines will be required to cover genetic testing. As for the European Agency for Evaluation of Medical Products, it does currently regulate *in vitro* genetic testing. It has no current guidelines but it wants a harmonized approach to pharmacogenomic protocols in clinical trials (Bristol, 2003).

The area that will be most affected by regulatory requirements is the pre-clinical and clinical development of drugs and eventually their therapeutic use. The recent FDA's *Guidance for Industry* represents the Agency's current thinking on pharmacogenomics and should only be considered as

---

[6] FDA. 2003. *Guidance for Industry: Pharmacogenomic Data Submissions*. November 2003. http://www.fda.gov/cder/guidance/5900dft.pdf (visited in March 2004)

recommendations on which the Agency wants drug developers' comments and suggestions. The document was issued in November 2003, and it is still too early to report on the comments of the various stakeholders. However, because these guidelines will eventually become the Agency's policy and because other regulatory officials around the world will harmonize their requirements with those of the FDA, it is expected that drug developers will carefully review this document and definitely come up with recommendations. In not making these guidelines a policy at this time, the FDA, in addition to obtaining the industry's comments, wants to improve its internal expertise in this area by allowing companies the flexibility of submitting or not pharmacogenomic data in some situations.

These guidelines address every situation and take into account the current development status of pharmacogenomics in the area of diagnostics and drugs. For example, they differentiate between valid and non-valid biomarkers and consider whether tests will be used in conjunction with a particular drug or if the tests to be used will be submitted for an Investigational New Drug (IND), for a new NDA or supplement or for an approved NDA or supplement. Once approved, these guidelines will have an important impact on labeling (or, as it is called in Canada, indications), on the requirements as to whether to use a specific genetic test before prescribing a drug, on the way of practicing medicine and on the healthcare system (Hurko, 2001).

As for the situation in Canada, a spokesperson for Health Canada stated that they will issue their own guidelines in the near future (based on personal correspondence). Hopefully, they will be harmonized with the American guidelines because pharmaceutical companies are always hesitant to produce drugs for market without clear regulation out of fear of unforeseen regulatory obstructions. It would therefore be essential that Canada equips itself with compatible, yet personalized, regulations for pharmacogenomics. This would create a stable situation that would enable pharmaceutical companies to develop pharmacogenomic drugs with all the necessary regulatory characteristics for the Canadian market.

4.3 Pre-clinical and clinical drug development

Pharmacogenomics is the technology that will allow personalized medicine to happen. The objective of personalized medicine is to administer the right dose of the right drug to the right patient at the right time. Pharmacogenomics is a combination of two sciences, as stated in Section 2. It combines studying the effects of genes on enzymes and enzymatic systems to explain the impact they have on the ADME (Administration, Distribution, Metabolism and Excretion) of drugs and on clinical drug development. From pharmacogenomics, some researchers have developed new terms such theragenomics (Gut, 2002) and chemical genomics (Ilag *et al.,* 2003). This later field of research is a very promising evolution of pharmacogenomics *per se*. The subject will be discussed in more detail later in this section.

The two objectives of personalized medicine are to increase the efficacy of drugs and to reduce the incidence and severity of adverse effects by allowing pre-screening patients predisposed to toxicity before prescribing a. It is therefore not surprising that pharmaceutical companies have used this

technology in the early phases of their drug development efforts. Initially, pharmacogenomics was used in Phase I clinical trials to explain variations in individuals' abilities to metabolize drugs (Norton, 2001). As researchers became more familiar with the advantages offered by the technology, they started using it in Phase II clinical trials. Eventually, they will use the knowledge acquired in Phase I and II clinical trials to design improved Phase III clinical trials, which will remain pivotal (Mehr, 2000). This current situation as well as its evolution, both upstream and downstream, is well illustrated in figure 2.

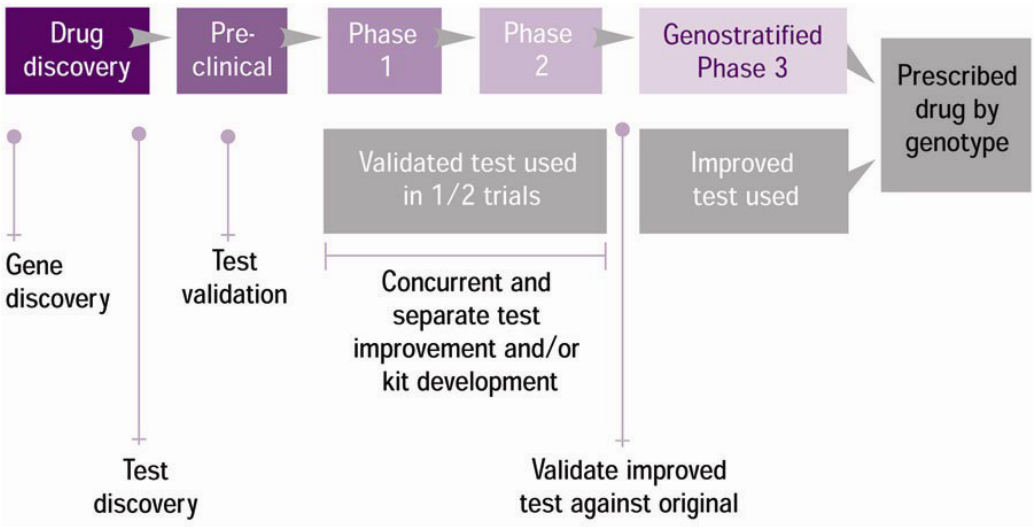


Figure 2 Current and future uses of pharmacogenomics in pre-clinical and clinical drug development

Source: Mehr (2000)

At this time, pharmaceutical companies are using pharmacogenomics in the development of new drugs to identify the phenotype of patients that best respond to a particular drug. Patients can be classified as slow responders, rapid responders, non-responders and adverse reactants (Naik, 2002). Using pharmacogenomics, pharmaceutical companies can identify the genetic profile of each type of responder and eventually identify the "ideal" responder.

But pharmacogenomics could also be used to rescue drugs that have been or, in some cases, will be withdrawn from the market because of adverse effects. Some rare and sometimes serious adverse effects have an incidence so low that they will not be detected in clinical trials which involve only a few thousand patients. In this case, the company would have to have banked the DNA of patients enrolled in clinical trials to compare it to the DNA of patients experiencing the adverse effect. Therefore, pharmacogenomics could be used in Phase IV (also called post-marketing) clinical trials. This is what could be called the upstream evolution of pharmacogenomics. Rezulin™ (Warker-Lambert, now Pfizer) is an excellent example where the use of pharmacogenomics in a Phase IV trial would have been very useful. It is believed that the company would have been able to increase sales more rapidly if it had identified beforehand patients who were susceptible to liver problems and that had taken the drug; instead, it lost US$200 million in potential sales while investigating the problem

(Naik, 2002). Many other examples can be found of drugs that were withdrawn from the market because of serious adverse effects (for a list of recent withdrawals, see Gut, 2002).

On the downstream side of drug development, we could talk about chemical genomics. The impetus for the development of chemical genomics was the expensive failure of genomics-focused drug discovery (Wallace, 1999). Chemical genomics will resurrect fallen angels - drugs dropped from development because of a lack of understanding of their modes of action (MOAs) (Wallace, 1999). By using small molecules it will also be very useful to elucidate biological functions allowing the identification of several interesting molecules and their corresponding targets. Chemical genomics will help companies choose the right target, therefore avoiding costly mistakes further down the pipeline. In other words, chemical genomics finds target for drugs, a key problem faced by all the -omics technologies and a frequent complaint against pharmacogenomics, which is perceived to be of little value in this area. It is expected that the true value of the chemical genomics approach cannot be assessed for another five to ten years (Ilag *et al.*, 2002). Chemical genomics will also be a key technology in validating targets and solving the problems associated with target validation, now that genomics has facilitated target identification (Hurko, 2001). Furthermore, pharmacogenomics, through the identification and development of appropriate surrogate markers, can improve the predictive accuracy of animal models to humans allowing an earlier and more rapid triage of compounds (Riniger *et al.*, 2000).

The final therapeutic application of pharmacogenomics could be in the presymptomatic genetic diagnosis which would allow prophylactic treatment (Hurko, 2001). This could be particularly useful for mental disorders and other disease states such as diabetes, cancer, neurodegenerative disorders, under the condition that we are able to develop effective prophylactic drugs. This is different from genetic profiling in which the genomic "map" of an individual is established to identify the individual's future morbidity and mortality without being associated with either a therapeutic or prophylactic measure. The type of pharmacogenomics that is not associated with a drug, that is, using the understanding of an individual's genome to better prescribe a treatment, is beyond the scope of this report and falls outside the field covered by this study.

For some scientists, pharmacogenomics has numerous benefits both for the patient and for healthcare companies. They are:

- Provides a new tool for drug discovery (Murphy, 2000);
- Reduces drug-development time and cost (Murphy, 2000);
- Allows for personalized medicine with less side-effects and better efficacy (Murphy, 2000);
- Improves therapeutic indexes of many drug interventions (Lesko and Woodcock, 2002);
- Allows for more precise diagnosis (Lesko and Woodcock, 2002)
- Allows for better management of post-approval risks (Lesko and Woodcock, 2002);
- Reduces incidence of drug-induced morbidity and mortality (Lesko and Woodcock, 2002).

There are also significant business benefits to pharmacogenomics such as:

- Reduction of the development cost in the range of US$60 to US$85 million per approved drug according to Naik in 2002, and up to US$300 million according to the Boston Consulting Group (Hood, 2003);
- Reduction of the development time by as much as two years according to the Boston Consulting Group (Hood, 2003);
- Improvement of companies' success rates (Hood, 2003);
- Creation of between US$200 and US$500 million in extra revenues (Norton, 2001).

Other business benefits will be discussed in Section 4.5.

If pharmacogenomics is going to meet its scientific and business promises, it will have to resolve a few outstanding issues. Pharmacogenomics will need to convince the scientific and business community that identifying slow metabolizers using genetic identification is more beneficial than using other direct methods of measuring drug levels in individual patients (Hurko, 2001). The field will need to fully convince pharmaceutical companies that it minimizes risk while increasing productivity and efficiency (Hurko, 2001), that regulatory guidelines have been clarified and approved by both regulatory agencies and pharmaceutical companies (see Section 4.2 for more information), that ethical and privacy issues will be dealt with to the satisfaction of all parties involved (see Section 4.1), and that the cost of genotyping is substantially reduced (Martin *et al.*, 2003).

4.4 Production

Pharmacogenomics will lead to personalized medicine' which could in turn lead to patient stratification and market fragmentation (Murphy, 2000). The different functions (marketing, R&D and production) of the pharmaceutical industry will be affected by the changes brought about by the increased use of pharmacogenomics. We have already discussed the impact of this technology on R&D (Section 4.3), and this section will discuss its impact on production. The following section will focus on marketing.

Most of the cost of modern pharmaceuticals results from research and development and not from manufacturing (Hurko, 2001). This is especially true for solid forms (tablets, caplets and capsules). Even the production cost of injectables is not an important component of the cost of developing and marketing a drug. Nevertheless, the adoption of pharmacogenomics will influence production of pharmaceuticals and require changes within the pharmaceutical industry.

The greatest concern of pharmaceutical executives related to the advent of pharmacogenomics is the impact pharmacogenomics will have on the economies of scales they enjoy with their current production levels. While most experts agree that there will be a negative impact on production costs, the magnitude of the additional cost has not been calculated. It is expected that the additional production costs will be completely recovered by the economies that the companies will enjoy in their R&D programs and maybe even by the additional revenues that could be generated by marketing "pharmacogenomic niche drugs" that could either have a premium price and/or a more

important market share in the niche. These issues will be discussed in more depth in the following two sections.

Pharmaceutical companies could modify their current business to at least partly reduce the impact pharmacogenomics will have on their production costs. One of these strategies would be to concentrate the worldwide manufacturing of a specific drug in one location. Many pharmaceutical companies are already using this approach. For example, Montreal's Merck facility is the worldwide supplier of Zocor™. The second strategy that they could use is to contract out their manufacturing function to specialized companies that could produce their products at a lower cost than they would do.

To summarize, the production cost issue will not be a key factor in pharmaceutical companies' decision to adopt pharmacogenomics or not. The cost savings in R&D and the potential additional revenues that personalized medicine could generate far outweigh the additional production costs.

4.5 Marketing

This section and the one following on the pharmaceutical business model are interrelated, and a certain level of overlapping could occur. In this section, we will focus our discussion on "pure" marketing issues that, to a certain extent, affect the business model. This is not surprising considering the importance of the marketing function in the overall operations of a pharmaceutical company. After all, pharmaceutical companies spend more money on marketing than on R&D (Murphy, 2000).

Pharmacogenomics will have important effects on how pharmaceutical products will be marketed. Some of these will be negative. For example, the market fragmentation caused by pharmacogenomics will result in market share loss and therefore decrease revenues and bring an end to the so-called "blockbuster" drugs. The reality may be quite different because drugs that benefit a majority of the patient population and stand in the marketplace with little or no competition may still have the potential to become blockbusters (Murphy, 2000). In addition, drugs using pharmacogenomics in their clinical development programs would tend to exclude "me-too" competition and be highly valuable to patients (Norton, 2001). As a result, pharmaceutical companies could justify the costs or ask for premium prices for their drugs (Murphy, 2000). The benefits of these two effects are that companies could generate more revenues per unit and for longer periods and add US$200 to US$500 million extra revenues per drug (Norton, 2001).

On the other hand, pharmacogenomics will also have beneficial effects. Currently, pharmaceutical companies spend more than $US7 billion per year on marketing and sales overall, and anywhere between US$300 and US$600 million on marketing and selling each new approved drug. Companies cannot afford spending these amounts on drugs that they bring to the market only to find out that a subset of the population suffers from life-threatening or serious adverse events that negatively affect revenues or, even worse, require that the product be withdrawn from the market (Murphy, 2000). Furthermore, we have not yet mentioned the important amounts they would have to pay to affected

patients. Pharmacogenomics will enable the marketing of safer drugs, which will give these products a competitive advantage (Roses, 2001).

Also, pharmaceutical companies will need to deal with important new obligations in the development process. The first one is that they will need to develop more and better class drugs that will fit the largest fraction of patient population that could command the most important market share (Maggio *et al.*, 2002). This will force them to select the best class drugs in pre-clinical trials (Maggio *et al.*, 2002). They will also need to contemplate co-development and approval of pharmacogenomics drugs with the accompanying diagnostic tests (Murphy, 2000). Pharmaceutical companies will need to partner with pharmacogenomics and diagnostic companies to develop panels of tests that will need to be submitted for regulatory approval in parallel with their new drug application (Murphy, 2002). We saw in the introduction to this section that deal-making is already occurring. It could be expected that the type of deals being done will eventually evolve and that pharmaceutical companies will eventually acquire pharmacogenomics companies (more on this subject in the next section). This trend is so important that some experts believe that pharmacogenomics will become an essential tool to the industry within the next three to five years (Norton, 2001).

Pharmacogenomics will not only change the way that medicine will be practiced, it will also change the way companies promote their products. The high level of patient specificity for pharmacogenomic drugs will concentrate diagnosis and treatment in small numbers of specialists, which will require sales teams to have a high level of consultative skills. In addition, the higher level of patient involvement in therapy and the small numbers of physicians and patients for specific drugs and diseases will change the patterns and the media approaches for both education and promotion (James, 2003). Will it be the end of Direct to Consumer promotion? Will it reduce the size of the sales team? Those questions will need to be answered.

Pharmacogenomics will also create a few barriers that the industry will need to deal with. For example, to limit the potential for abuse with pharmacogenomic testing, companies may have to have limits on the amount of advertising and promotion for such tests, in the same manner that limits are imposed on the advertising and promotion of drugs (Vaszar *et al.*, 2002). Companies will also need to develop drugs for the less important "genetic" niches in order to avoid (or benefit from) legislative measures (see Section 4.1).

While some companies are still skeptical as to the positive effects that pharmacogenomics could have on their revenues, the following facts could help to reassure them:

- Herceptin™ commands a premium price (Datamonitor, 2001);
- First-year sales of Herceptin™ were US$280 million (Datamonitor, 2001);
- The compound Annual Growth Rate for the pharmacogenomics market is forecasted to be 22% over the next three years (2004-2007) (Frontline Strategic Consulting, Inc., 2003);
- The worldwide pharmacogenomics market is expected to reach US$1.5 billion by 2008 (Mindbranch, 2003).

4.6 Pharmaceutical business model

The current pharmaceutical business model was created in the late 1960s and based on two interrelated concepts:

- A value proposition built around offering superior value through product innovation. This value proposition was defined by a set of core capabilities: a deep and unique set of skills and assets, a cache of relationships with customers and competitors and a fully integrated infrastructure that internalized the value chain from drug discovery through marketing to physicians (James, 2003);
- A volume market opportunity centered on delivering a steady stream of new primary care products for highly prevalent diseases with chronic treatment profiles that addressed the demand for new and better drugs backed up by the ability of public and purchaser to pay (James, 2003).

It is quite evident that pharmacogenomics does not fit within these concepts and that, if it was only for this technology, one might expect that pharmaceutical companies would not modify their business model. On the other hand, other events are clearly demonstrating that this model may not meet the needs of the future. The following are some of the events demonstrating that this model is not effective anymore and that it has done its time:

- There is a lack of new compounds in big pharma (Drews ,2003);
- Development time is longer (Drews, 2003);
- The number of drugs from biotech companies in relation to the total number of drugs is increasing (Drews, 2003);
- R&D in pharmaceutical companies has produced only a handful of validated targets (Drews, 2003);
- The costs of R&D are rising (James, 2003);
- An impossible number of NCEs (three to five) must be approved each year to maintain an annual growth rate of 10% (Norton, 2002);
- Pharmaceutical companies are unable to deliver the growth rates delivered in the past (James, 2003);
- The low average peak sales do not allow for an acceptable return on investment (James, 2003);
- The costs of marketing and sales are increasing (James, 2003);
- The number of breakthrough drugs approved has declined steadily since 1996 (Murphy, 2000);
- Pharmaceutical companies need to improve productivity and their success rate in bringing new products to market (Murphy, 2000).

Other external events are also contributing to the dismantling of the current pharmaceutical model. The consolidation of biotech companies to offer more complete solutions to drug discovery will, if carefully targeted mergers are done, create small pharma companies that will be more productive than most big pharma companies (Drews, 2003). Finally, increasing healthcare costs are also a key factor in putting enormous pressure on the current business model.

The first way by which the industry tried to solve the problems mentioned above was to merge big pharmaceutical companies together. Rather than solving the problem, this strategy has made the situation even worse (James, 2003). Therefore, the big innovative pharmaceutical companies are looking for solutions.

While pharmacogenomics could contribute to making this problem worse, it could also be the solution:

- Pharmacogenomics could provide pharmaceutical companies with the opportunity to develop proprietary pharmacogenomic markers allowing them to position their products apart from others while still operating under the old drug development paradigm (Murphy, 2000);
- The high efficacy and low adverse effects expected in those populations (pharmacogenomically defined) will translate into high clinical utility and shorter and easier development (Norton, 2001);
- Genotyping will identify many new disease-related genes and provide an explosion of new targets to pursue (Peet and Bey, 2001);
- Drugs derived from using pharmacogenomics can achieve blockbuster sales, while targeting smaller populations (Datamonitor, 2001);
- Pharmacogenomics could replace "blockbuster" drugs by a subset of compounds that, together, comprise a blockbuster drug class (Peet and Bey 2001).

The numerous commercial advantages offered by pharmacogenomics as well as the potential savings in pre-clinical and clinical development were already presented in previous sections.

While it is safe to assume that pharmacogenomics would not change the current big pharmaceutical model by itself, we could reasonably assume that its direct effects on the industry as well as its effects on the way medicine will be practiced in the future will make it a driving force in this process. In fact, a trend can already be identified. More than 25 deals were signed between pharmaceutical and pharmacogenomics companies in the 2000-2002 period (Branca, 2003). Even if there was a slight decrease in the last year of this period, activity seems to have picked up again in 2003. We have also mentioned that over 1,800 deals were signed in genomics during the same period (Branca, 2003). A scenario that is likely to happen is that, initially, pharmaceutical companies will sign co-development deals with pharmacogenomics companies. This will allow pharmaceutical companies to fully evaluate the technology developed by pharmacogenomics company. If the technology is promising from a scientific and commercial point of view, the pharmaceutical company will purchase the pharmacogenomic company. Already two examples of this strategy exist. Merck has bought Rosetta and Novartis Immusol. Eventually, pharmaceutical may do a "reverse integration" to be able to offer both the diagnostic kit and the corresponding drug. Not only will they control the development of the kit but they will also control its production while generating additional revenues and setting up an entry barrier to competitors.

4.7 The Canadian healthcare system

The Canadian healthcare system is a public system, even if some of its components are private. There is no universal coverage for drugs, and diagnostic testing could be done in public or private facilities. Most Canadians have their drugs reimbursed totally or partially either by a government program or by a private insurer. The role of the government as a third-party payer has been increasing steadily over the last few years, gradually covering more and more Canadians. Combined with an aging population, it is not surprising that public healthcare costs are increasing year after year.

Another issue with the Canadian system is that it uses a “silo” approach, which makes it difficult to find out how a new technology or a new system of patient care or management affects the whole healthcare budget. It becomes very difficult to implement a new technology in one sector if it increases the budget of this sector even if it could generate substantial economies in another “silo”. Changes such as ambulatory care, day surgery, outpatient treatment and keeping the elderly at home programs have probably been more economical than it looks, even if the total healthcare budget has still increased substantially. The questions that are rarely if ever asked are, "How high would the healthcare budget have been without these measures? How much more money would we have needed for the hospitalization silo without these new strategies?" Difficult questions to answer but they definitely need to be asked and at least tentatively answered.

These are important issues in the case of pharmacogenomics because, as in the case of many new technologies, it could be expected that the field might initially increase healthcare costs and then, eventually reduce them in the future (Hood, 2003). The rationale behind this situation is the following. Currently, one or two general approaches are typically used for the pharmaceutical management of diseases. The first approach is trial and error, and the second one is the treatment protocol approach. Pharmacogenomics will introduce a third approach by predicting those patients likely to experience the desired therapeutic effect from the drug under consideration. Figure 3 illustrates the decision diagram that could be used by physicians using pharmacogenomics in their practice.

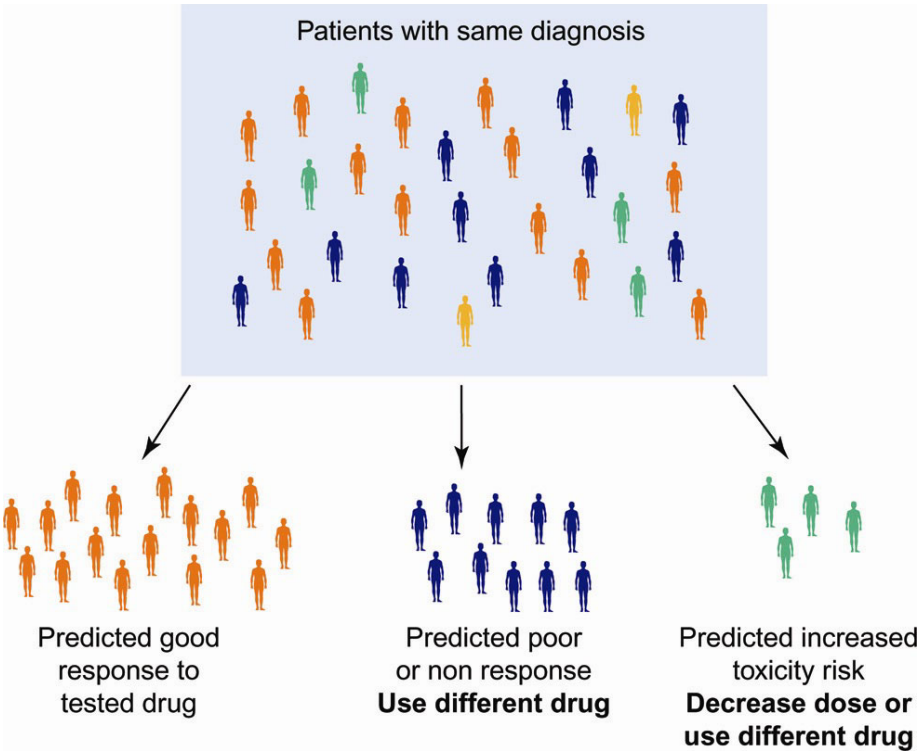


Figure 3 Clinical potential of pharmacogenomics
Source: Johnson 2003

Using pharmacogenomics in this way provides significant important economies by:

- Reducing the length of uncontrolled diseases, which will reduce the number of visits to physicians and decrease the number of negative outcomes (Johnson, 2003);
- Avoiding the use of ineffective drugs, therefore reducing the cost associated with adverse effects and with administering the drug (Johnson, 2003);
- Providing better diagnoses (Lesko and Woodcock, 2002);
- Improving the therapeutic index of many drugs (Lesko and Woodcock, 2002);
- Offering better management of post-approval risks (Lesko and Woodcock, 2002);
- Decreasing the incidence of drug related morbidity and mortality (Lesko and Woodcock, 2002).

Even insurance companies may experience cost savings due to the reduction of prescribing non-effective medications to their clients (Wieczorek and Tsongalis, 2001). The interest expressed by Aetna, mentioned previously in this report, confirms that insurance companies believe that pharmacogenomics will help them reduce their costs.

The key to this debate is not if personalized medicine and therefore the use of pharmacogenomics will occur but rather when it will happen. Many experts believe that personalized medicine will have a tremendous impact on health by 2010 (Branka, 2003; Lesko and Woodcock, 2002). Francis Collins, head of the NIH Human Genome Project, predicted at the American Society of Human Genetics

Annual Meeting in 2001 that "primary care providers would practice genetic medicine" by 2010 and that pharmacogenomics would be commonly used in 2020 (as reported by Dr. Janice Kurth[7]).

The impact of public funded systems like the Canadian one is important. The use of resources for genetic testing may mean fewer resources for other health needs. Privately financed, genetic testing will have an impact on the public sector (Caulfield *et al.*, 2001). If a test is reimbursed by the public sector and also available in the private sector but not covered by a third-party payer, waiting lists in the public sector could grow (Caulfield *et al.,* 2001).

If a genetic test provides a genuine net health benefit at a reasonable cost, it should be included in the public health insurance system (Caulfield *et al.*, 2001). The key will be to document this health benefit.

On the other hand, some useful and safe genetic tests may be available only through private arrangements. The danger in this case is that the discretionary assessment of the gate keepers (health professionals, mainly physicians) may be influenced by additional incentives in favor of testing (Caulfield *et al.*, 2001). A number of different strategies could be used to prevent this situation from occurring. We have already mentioned some type of control of advertising and promotional activities similar to the ones in place for prescription drugs. Another measure that could be adopted by the government is to request economic studies (like pharmacoeconomic studies done for prescription drugs) to be submitted by companies for the approval of a genetic test from Health Canada.

As for the price of pharmacogenomically developed drugs, the Canadian system already has in place a group that could ensure that this product is not overly priced. It is the Patented Medicine Price Review Board.

Pharmacogenomics will eventually become a fact of life in the Canadian healthcare system. Its impact on our healthcare system will be important. It is generally agreed that its overall impact should be positive and eventually reduce healthcare costs. It is recommended that the Canadian authorities anticipate this new treatment paradigm and put in place the necessary guidelines to ensure that the economies generated by the use of pharmacogenomics to treat Canadians are more important than some of the incremental costs related to the additional diagnostic procedures required to institute personalized medicine.

[7] http://www.aacc.org/access/pharmacogenomics/qanda.stm (visited March 2004)

5 SWOT analysis

Prior to making recommendations, it is important to assess Canada's strengths and weaknesses in pharmacogenomics. This evaluation is based mainly on the contents of this report. To fully benefit from this competitive analysis, it is also important to consider the opportunities and threats offered by this technology. The overall picture provided by this analysis will allow decision makers in Canada to develop an action plan for which it has the resources in the areas where it could establish itself as a strong achiever.

5.1 Strengths

- **Presence of Genome Canada and its five provincial counterparts:** The creation of Genome Canada in 2000 has allowed Canadian researchers to benefit from important investments in the field of genomics. In its two first contests, it has distributed almost CDN$200 million for 50 large-scale products. It recently received an additional CDN$60 million from the Canadian government.
- **World-class fundamental research by Canadian researchers:** Research performed by Canadian researchers in –omics fields, including genomics, are recognized as being of top quality. Our researchers are leading many international collaborations. With the recent addition of the Montreal Genome Centre, directed by Dr. Thomas Hudson, a world-renowned researcher in genomics, Canada now has the required infrastructure it was missing.
- **Expertise in two fields, genomics and clinical research:** In addition to its expertise in the field of genomics, Canadian physicians have the reputation of performing good clinical research at a competitive price. Furthermore, our public healthcare system is an important advantage in the recruitment of patients for clinical trials.

5.2 Weaknesses

- **Absence of decision centers:** The most important users of pharmacogenomics are pharmaceutical and large biotechnology companies. Only two or three of these companies conduct basic research in Canada. Furthermore, none of these companies have their head office in Canada. Generally, companies using new technologies, such as pharmacogenomics, prefer making deals with companies close to their research facilities. In addition, decisions made on the geographic distribution of clinical trials are made at the head office.
- **No current regulatory guidelines:** Clinical development of a new drug is an expensive undertaking. Companies cannot afford mistakes. The current lack of guidelines from Health Canada on the use of pharmacogenomics creates a risk that pharmaceutical companies would prefer not to have. The fact that the FDA has issued clear guidelines for discussion with the stakeholders puts Canada at a significant disadvantage to our neighbors.
- **Losing ground to other G7 countries:** Figure 1 (Section 3.1.1, page 9) and Table 1 (page 10) show that the number of papers published by Canadian researchers is not following the world trend. In addition, our specialization index decreased between the 1991–1993 and 2000–2002 periods (Table II, page 11). The only other G7 country that has seen its specialization decrease for the same time periods is France.

- **No portfolio of patents:** Of the 44 patents assigned to pharmacogenomics, the United States has 40 and Canada only one, which is owned by Signalgene (Table VI, page 16) a company recently transformed into an oil and gas company.

5.3 Opportunities

- **Rapidly growing market:** Sections 4.5 and 4.6 list a number of facts that clearly demonstrate that the pharmacogenomic field is rapidly growing and that it will continue to enjoy an important growth rate for a number of years to come.
- **Increased interest by pharmaceutical companies:** In the 2000–2002 period alone, 25 deals were concluded between pharmaceutical and pharmacogenomics companies, with the number of deals increasing between 2002 and 2003. Furthermore, almost all major pharmaceutical companies, including the most important ones such as Merck and Smith Kline Glaxo, have signed deals with pharmacogenomics companies and are using pharmacogenomics in their clinical research program.

5.4 Threats

- **Lack of dialogue between the public, social scientists and genomic scientists about ethical and social issues:** Ethical and social issues are difficult to deal with because they involve individual and society values. Concerns about the potential abuse or inappropriate use of information provided by pharmacogenomics exist and will need to be dealt with by the public, the ethical community and the scientific community if pharmacogenomics is to be used to its full potential.
- **Resistance from pharmaceutical companies:** While many facts mentioned in this report seem to indicate that pharmaceutical companies are in the process of adopting pharmacogenomics, some industry observers remain skeptical. They do not believe that companies are ready to modify their business model. They believe that pharmaceutical companies are interested in using pharmacogenomics in their pre-clinical and clinical development programs because of the important benefits offered. The observers also believe that companies are not very enthusiastic about having constraints imposed on their labeling. Furthermore, they are also concerned about the market fragmentation that pharmacogenomics will cause and the impact this will have on their revenues.

6 Conclusion & recommendations

Pharmacogenomics is still in its infancy, and this is reflected by the fact that large pharmaceutical companies are hesitant to invest massively in it. Moreover, very little proper pharmacogenomic research is being done in the world. Although pharmacogenomics shows some significant promises for many applications, its present high cost and potentially disruptive economical effects are greatly impeding its development. This is further exacerbated by the fact that the different players in this field are not aiming for the same goal. Pharmaceutical companies want to create more marketable, cheaper drugs; regulatory bodies want to better protect the public; and scientists want to publish more cutting-edge research. Although these goals are not necessarily opposed, they contribute to preventing the rapid crystallization of a homogeneous pharmacogenomic field.

Since, the most important pharmacogenomics users, pharmaceutical and large biotechnology companies, are situated outside of Canada, Canada should focus its efforts on the realm of pharmacogenomic research. It is important that Canada financially supports fundamental research in this field; otherwise, it could rapidly be outdone.

Scientometric data showed that Canadian pharmacogenomics is a very small field of research and that it was losing ground when compared to the world as a whole. Although this delay could seem alarming, it is still feasible for Canada to become competitive at the world level, especially since pharmacogenomics is such a small field of publication. To do this, it would be preferable for Canada to specialize in a few fields of pharmacogenomic research. It seems that there is already a small concentration of research in the fields of mental health and neurological disease. It would be wise to continue developing these fields.

It would also be interesting to integrate pharmacogenomic research branches in already strong genomic research units. Genome Canada's expertise in genomics would be invaluable since it already has extensive knowledge of the genomic research being done in this country. It could certainly be helpful in promoting pharmacogenomic research in fields where Canada is excelling already. The specialization in pharmacogenomic research would then be a catalyst for other fields of pharmacogenomics since it would facilitate collaboration between research groups, which often leads to collaboration between institutions and sectors.

Also, since pharmacogenomics is not a discipline studied exclusively in universities and research centers, but often by pharmaceutical and biotech companies, it is imperative that Canada equips itself with a set of specific regulations to deal with the specificity of this field of research and its development. Companies often see a lack of guidelines as a sign that a field is not yet ready to be developed. Moreover, a lack of governmental guidelines puts the total amount of the risks to be taken in the hands of the private companies developing it. Clear guidelines give companies, and the scientists working for them, unequivocal information on what is needed for new products to be approved and distributed and limits the risks that they have to take, therefore making investment in this field more interesting.

The establishment of a strong research network and of realistic and clear regulations would make Canada a much more competitive country to perform research in pharmacogenomics. This would probably lead to an increase in the participation of pharmaceutical and large biotechnology companies, either in the form of actual laboratories or, more likely, in the form of scientific, technological and commercial cooperation with Canadian researchers in this field.

Not only should Canada equip itself with commercial, technical and scientific regulations, it should also establish clear regulations dealing with the treatment of personal genomic information. The protection of one's personal information is the most important ethical question faced by pharmacogenomics because of way this information could be misused by various organizations, like insurance companies or the government itself. Moreover, the fact that a portion of genomic data is shared between different individuals (family, community and even "racial" or ethnic groups) further complicates the question of the protection of personal information and exacerbates the need for clear regulations.

This brings up the necessity for Canada to seriously reevaluate the way personal information (genetic or not) is treated in a medical context. The discussions that would be generated by this line of questioning should involve the public, social scientists and physical scientists. Only when a workable consensus is reached, could pharmacogenomic methods be widely applied.

Finally, Canada should consider the possibility of implementing legislation that would ensure that groups with genetic profiles that are too small to be of interest to pharmaceutical companies have access to effective treatment for conditions that affect them. Such legislation could be based on the American *Orphan Drug Act* and give economic incentives to both companies and researchers that develop and produce treatments for small pharmacogenomic populations, therefore facilitating these populations' access to effective drugs and preventing genetic discrimination in a pharmaceutical context.

References

Altman R.B. and T. E. Klein. 2002. Challenges for Biomedical Informatics and Pharmacogenomics. *Annual Review of Pharmacological Toxicology*. 42: 113–133.

Branca M.A. 2002. The new, new pharmacogenomics. *Bio-IT Worlds*. September 9 2002: 11p.

Branca M.A. 2003. Genomics Deal Making: Finding Value in the Post-Genomics Era. *SPECTRUM Pharmaceutical Industry Dynamics*. May 21 2003: 5-1-5-17.

Bristol L.A. 2002. A regulatory protocol for pharmacogenomics. *The Pharmacogenomics Journal*. 2: 83-86.

Caulfield T.A., Burgess, M.M. and Williams-Jones B. 2001. Providing genetic testing through the private sector – A view from Canada. *Canadian Journal of Policy Research*. 2(3):72-81.

Choo EF, Leake B, Wandel C, et al. 2000. Pharmacological inhibition of P-glycoprotein transport enhances the distribution of HIV-1 protease inhibitors into brain and testes. *Drug Metabolism and Disposition*. 28:655-660.

Datamonitor. 2001. *Will pharmacogenomics revolutionize clinical trials?* Press release (11/1/2001). Available online at: http://www.eyeforpharma.com/pharma/papers/datamonitor.pdf (visited on March 2004)

Drazen J.M., Yandava C.N., Dube L., *et al.* Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nature Genetics*. 22:168-170.

Drews J. 2003. Strategic trends in the drug industry. *Drug Discovery Today*. 8 (9): 411-420.

Evans W.E. and McLeod H.L. 2003. Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects. *New England Journal of Medicine*. 349(6):538-549.

Evans W.E. and Relling M.V. 1999. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science*. 286:487-491.

Ewesuedo R.B., Iyer L., Das S., Koenig A., *et al.* 2001. Phase 1 clinical and pharmacogenetic study of weekly TAS-103 in patients with advanced cancer. *Journal of clinical Oncology*. 19: 2084-2090.

Expert Access Online. 2003. *Pharmacogenomics: A Prescription for Industry?* Interview with Janice Kurth, M.D., Ph.D.

FDA. 2003. *Guidance for Industry: Pharmacogenomic Data Submissions*. November 2003.

Fellay J, Marzolini C, Meaden ER, et al. 2002. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. *The Lancet*. 359:30-36.

Frontline Strategic Consulting Inc. 2003. *Pharmacogenomics: A Strategic Market Outlook and Business Analysis.*

Furuya H., Fernandez-Salguero P., Gregory W., *et al.* 1995. Genetic polymorphism of CYP2C9 and its effect on warfarin maintenance dose requirement in patients undergoing anticoagulation therapy. *Pharmacogenetics*. 5: 389-392.

Gatto J.G. 2003. The changing face of bioinformatics. *Drug Discovery Today*. 8 (9): 375-376.

Gerdes L.U., Gerdes C., Kervinen K., *et al.* 2000. The apolipoprotein epsilon4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction: a substudy of the Scandinavian Simvastatin Survival Study. *Circulation*. 101:1366-1371.

Glatt C.E., DeYoung J.A., Delgado S., *et al.* 2001. Screening a large reference sample to identify very low frequency sequence variants: comparison between two genes. *Nature Genetics*. 27: 435-438.

Grant, S.F.A. 2001. Pharmacogenetics and pharmacogenomics: tailored drug therapy for the 21st century. *TRENDS in Pharmacological Sciences*. 22 (1): 3-4.

Guiseppi-Elie, A. 2003. Biochip Platforms for DNA Diagnostics. *Business Briefing: Pharmatech 2003.* 1-6.

Gut J. 2002. *Severe Adverse Drug Reactions and Theragenomics. Business Briefing: PharmaTech*. Business Briefings Ltd (London) UK: 1-5.

Hood E. 2003. Pharmacogenomics: The Promise of Personalized Medicine. *Environmental Health Perspectives*. 111 (11): 1-9.

Hurko O. 2001. Genetics and genomics in neuropsycopharmacology: the impact on drug discovery and development. *European Neuropsychopharmacology*. 11: 491-199.

Ilag L.L., Ng J.H., Beste G. and Henning S.W. 2002. Emerging high throughput drug target validation technologies. *Drug Discovery Today*. 7 (18): S136-S142.

In Vivo. 2001. *The Business & Medicine Report*. 15 (11): 18.

Isarel E., Drazen J.M., Liggett S.B., *et al.* 2001. Effect of polymorphism of the beta(2)-adrenergic receptor on response to regular use of albuterol in asthma. *International Archives of Allergy and Immunology*. 124: 183-186.

Jacobsen P., Rossing K., Rossing P., *et al.* 1998. Angiotensin converting enzyme gene polymorphism and ACE inhibition in diabetic nephropathy. *Kidney International*. 53:1002-1006.

James B.G. 2003. Big Pharma: The Beginning of the End or the End of the Beginning? *SPECTRUM Pharmaceutical Industry Dynamics*. May 5 2003: 4-1-4-18.

Johnson J.A. 2003. Pharmacogenetics: Potential for individualized therapy through genetics. *Trends in Genetics*. In Press.

Kaplan JC. and Junien C. 2000. Genomics and medicine: An anticipation. *Life Sciences.* 323: 1167-1174.

Kuehl P., Zhang J., Lin Y., *et al.* 2001. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nature Genetics*. 27: 383-391.

Kuivenhoven J.A., Jukema J.W., Zwinderman A.H., *et al.* 1998. The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. *New England Journal of Medicine.* 338:86-93.

Lesko L.J. and Woodcock J. 2002. Pharmacogenomic-guided Drug Development: Regulatory Perspective. *The Pharmacogenomics Journal.* 2: 20–24.

Liggett S.B. 2000. Beta(2)-adrenergic receptor pharmacogenetics. *American Journal of Respiratory and Critical Care Medicine*. 161:S197-S201.

Nuffield Council on Bioethics. 2003. *Pharmacogenetics: Ethical Issues*. London: Nuffield Council on Bioethics. 132 p.

Maggio E.T., Shenderovich M., Kagan R., Godette D. and Ramnaryan K 2002. Structural pharmacogenomics, drug resistance and the design of anti-infective super-drugs. *Drug Discovery Today*. 7 (24): 1214-1220.

Martin M., Kochan J. and Babiss L. 2003. *Use of Single Nucleotide Polymorphisms in Support of Integrated Healthcare.* In *Business Briefing: Future drug Discovery*. Business Briefings Ltd (London) UK. pp. 44-49.

Martinelli I., Sacchi E., Landi G., *et al.* 1998. High risk of cerebral vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *New England Journal of Medicine.* 338:1793-1797.

Mehr I.J. 2000. Pharmacogenomics and Industry Change. *Applied Clinical Trials*. 9(5): 34-36.

Meisel C., Roots, I., Cascorbi I., *et al.* 2000. How to manage individualized drug therapy: application of pharmacogenetic knowledge of drug metabolism and transport. *Clinical chemistry and laboratory medicine* 38: 869-876.

Mindbranch. Inc. 2002. *The Global Pharmacogenomic Market*.

Murphy M.P. 2000. Pharmacogenomics: a new paradigm for drug development. *Drug Discovery World*. Fall 2000: 1-7.

Naik N. 2002. *Brave New Biotechnology World Revisited.* In *Business Briefing: Future Drug Discovery*. Business Briefings Ltd (London) UK: 1-7.

Norton R.M. Clinical pharmacogenomics: applications in pharmaceutical R&D. *Drug Discovery Today*. 6 (4): 180-185.

Peet N.P. and Bey P. 2001. Pharmacogenomics: challenges and opportunities. *Drug Discovery Today*. 6 (10): 495-498

Poirier J., Delisle M.C., Quirion R., *et al.* 1995. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. *Proceedings of the National Academy of Sciences U.S.A.* 92:12260-12264.

Rininger J.A., DiPippo V.A. and Gould-Rothberg B.E. 2000. Differential gene expression technologies for identifying surrogate markers of drug efficacy and toxicity. *Drug Discovery Today*. 5 (12): 560-568.

Rohde D.D. 2000. The orphan drug act: An engine of innovation? At what cost? *Food and Drug Law Journal*. 55: 125-144.

Roses A.D. 2001. How rill pharmacogenomics impact the future of research and development. *Drug Discovery Today*. 6 (2): 59-60.

Rusnak, J.M., Kisabeth, R.M., Herbert, D.P. *et al.* 2001. Pharmacogenomics: A Clinician's Primer on Emerging Technologies for Improved Patient Care. *Mayo clinic Proceedings*. 76:299-309.

Schappert, K., Sevigny, P., and Poirier, J. 2002. Apolipoprotein E: A pharmacogenomic marker used in the treatment of Alzheimer's disease. In B. Lerer (Ed.), *Pharmacogenetics of psychotropic drugs*. Cambridge, UK; New York: Cambridge University Press. pp. 358-369.

Severino G., C. Chillotti, M.E. Stochino and Del Zompo M. 2003. Pharmacogenomics: State of the Research and Perspectives in Clinical Application. *Neurological Science*. 24: S146–S148.

Szymkowski D.E. 2003. Chemical genomics versus orthodox drug development. *Drug Discovery Today*. 8 (4): 157-159.

Turecki, G., Grof, P., Grof, E., *et al*. 2001. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. *Molecular Psychiatry*. 6(5): 570-578.

Turyman R.M. and Primrose S.B. 2003. Techniques Patents for SNP Genotyping. *Pharmacogenetics*. 4(1): 67-79.

Vaszar L.T., Rosens G.D. and Raffin T.A. 2002. Pharmacogenomics and the challenge to industry. *The Pharmacogenomics Journal*. 2: 144-147.

Wallace R.W. 1999. Pharmacogenomics - the next logical step. *Drug Discovery Today*. 4(3): 105-107.

Weinshilboum R. 2003. Inheritance and drug response. *New England Journal of Medicine*. 348:529-537.

Wertz D.C. 2003. Ethical, social and legal issues in pharmacogenomics. *The Pharmacogenomics Journal*. 3: 194-196.

Wieczorek S.J. and Tsongalis G.J. 2001. Pharmacogenomics: Will It Change the Field of Medicine? *Clinica Chimica Acta.* 308: 1-8.

Yan L., Otterness D.M. and Weinshilboum R.M. 1999. Human nicotinamide N-methyltransferase pharmacogenetics gene sequence analysis and promoter characterization. *Pharmacogenetics.* 9: 308-316.

Appendix: Scientometric and technometric methods

Scientometric analysis

The scientometric analysis uses data from the Medline database, produced by the US National Library of Medicine (NLM). The database has been conditioned by Science-Metrix with a view to producing statistics on scientific publications in the biomedical and clinical medicine sectors. This database has one limitation: entries comprise only the affiliation of the first author of the papers indexed. This makes it difficult to perform studies on collaborations, although one could foresee developing methods to associate most authors with specific affiliations and, thus, providing a walk-around way to computing statistics on collaboration. Nevertheless, this limitation is more than made up for by the power of the keywords used in Medline, the Medical Subject Headings (MeSH), which constitute a controlled vocabulary used for indexing articles in Medline.

The construction of the dataset for the scientometric analysis is essentially based on an advanced search method using a combination of MeSH Terms and title/abstract keywords. A MeSH Term is a term from the National Library of Medicine's controlled vocabulary thesaurus and is composed of a "descriptor" and a "qualifier" that pinpoints a specific aspect of the concept represented by the descriptor.

The following datasets were used to produce detailed statistics on the following indicators:

- Number of papers - Number of scientific papers written by authors located in a given geographical, geopolitical or organizational entity (e.g. countries, cities or institutions).
- Percentage of papers relative to total output, specialization index - The specialization index is an indicator of the intensity of research in a given geographic or organizational entity relative to the overall output for a given reference. For example, if the percentage of Canadian papers (the geographic entity) in the field of pharmacogenomics is greater than the percentage of papers in this field at the world level (the reference), then Canada is said to be specializing in this field.
- Impact factor - This indicator is a proxy for the quality of the journals in which papers are published. It is based on a calculation of citations received by journals. An average is calculated by assigning a journal impact factor to each paper belonging to a given geographic or organizational entity.

Technometric analysis

Patents are widely used to compute statistics despite several well-known disadvantages associated with their use:

- incompleteness: many inventions are not patented since patenting is only one way of protecting an invention;

- inconsistency in quality: the importance and value of patented inventions vary considerably;
- inconsistency across industries and fields: industries and fields vary considerably in their propensity to patent inventions;
- inconsistency across countries: inventors from different countries have different propensities to patent inventions, and countries have different patent laws.

Despite these disadvantages, inventions are widely used to compare the level of technological development of different geographic locations. This report uses the United States Patents and Trademark Office (USPTO) database. Its data are widely used to measure invention since the USPTO is one of the largest repositories of patented inventions in the world. Because the USA is the largest market in the world, the most important inventions tend to be patented there. Although the USPTO database presents an obvious bias towards the USA, it is a potent tool for comparing other countries.

The delineation of the field of pharmacogenomics was performed iteratively. A set of patents was selected using keywords in the titles and abstracts of patents and using US patent classes. Subsequently, all selected patents were verified one by one in order to discard irrelevant patents.

Unlike scientific publications, patents possess two fields that contain bibliographic information relevant to the calculation of where the patent originates: the inventor field and the assignee field. An inventor is necessarily a physical person whereas an assignee can be a physical person and/or an institution. These fields are used to compute statistics on two different indicators, namely, invention and intellectual property (IP).

The inventor field contains data on the name of the inventor(s) and where he or she resides. The assignee field contains the name of the entity that owns the IP of the patent. When this field is empty, the inventor is the owner of the intellectual property and, in this case, the addresses contained in the inventor field are used to compute where the IP is owned. In some cases, where an individual is the owner of the IP, the address of this owner is used to compute the location of the IP. The majority of patents are owned by corporations, and their addresses, which appear in the assignee field, are used to compute the geographical location of IP ownership.

This report presents data on invention and IP and also distinguishes institutional IP from total IP. The location of inventors provides a proxy for the creativity of regions, whereas the location of IP ownership, particularly of institutional IP, provides an indicator of the potential economic impact of inventions.