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THE *PATENTED MEDICINES (NOTICE OF COMPLIANCE) REGULATIONS*

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TABLE OF CONTENTS

Page

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INTRODUCTION

This document deals with Parliament's attempt to strike a balance between effective protection of pharmaceutical inventions, in order to stimulate research and development (R&D), and keeping the cost of medicines down. Specifically, it examines the *Patented Medicines (Notice of Compliance) Regulations* (the Regulations),[1] which, along with the *Patent Act*,[2] attempt to achieve that balance by allowing the generic version of a medicine to be marketed once the patent for the original medicine expires.

However, the Regulations have been interpreted literally, and such stalling tactics as evergreening – which lead to delays in the marketing of certain generic medicines – have jeopardized the effectiveness of this system.

PATENTS AND MEDICINE PRICES: STRIKING A BALANCE

The pharmaceutical industry depends on innovation. While pharmaceutical firms have other ways of protecting their investments, patents give them a definite competitive advantage and are therefore a key tool.

However, R&D costs are rising faster than ever, and the length of the protection provided by pharmaceutical patents has been reduced, because the time needed for drug trials and regulatory approval must be taken into account, and this takes approximately 8 to 12 months.[3] That time is needed in order to ensure the protection of the public's health and safety.

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(1) SOR/93-133. Commonly referred to as the Linkage Regulations.

(2) R.S. 1985, c. P-4 ("LB").

(3) World Trade Organization, Report of the Panel, *Canada – Patent Protection of Pharmaceutical Products*, Complaint by the European Communities and their Member States, WT/DS114/R, 17 March 2000, p. 112.

Patents stimulate innovation and also have an impact on the cost of medicines, which is the most significant component of health care cost increases.(4) While patented medicine prices are now monitored by the Patented Medicine Prices Review Board (PMPRB),(5) the complete elimination of compulsory licences in 1993 made it necessary to adopt other methods of ensuring a fair balance between encouraging innovation and providing access to high-quality medicines at a lower cost, including bringing generic medicines onto the market as soon as possible.(6)

Two exceptions to patent infringement were therefore added to the *Patent Act*. The first, the "stockpiling exception,"(7) allowed manufacturers of generic medicines to stockpile their products for six months before a patent expired. This exception was held to be inconsistent with Canada's obligations as a member of the World Trade Organization(8) and was therefore abolished by legislation. The second, the "early working" exception,(9) which still exists,(10) allows generic medicine manufacturers to apply to Health Canada for approval of their product before the patent expires.

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(4) Expenditures on prescription medicines have doubled in 20 years, and in 2001 accounted for 12% of total health care costs, or $1.3 billion (Commission on the Future of Health Care in Canada (Commissioner Roy J. Romanow), Final Report, *Building on Values: The Future of Health Care in Canada*, November 2002, p. 215).

(5) Since the PMPRB was created in 1987, the annual increase in patented medicine prices has slowed, from 9% to 1.8%. In order to determine whether a price is excessive, the PMPRB reviews the average price of the medication in seven industrialized countries: France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States (*Patented Medicines Regulations, 1994*, para. 4(1)(*g*), *Canada Gazette II*, vol. 128, No. 24, 1994, p. 3851). In 2004, Canadian prices were about 9% below the median price in those seven countries (Patented Medicine Prices Review Board, *2004 Annual Report*, p. 24). However, the prices charted in those reference countries are among the highest in the world (House of Commons, 5th Report of the Standing Committee on Industry, *Review of Section 14 of the Patent Act Amendment Act, 1992*, Ottawa, April 1997).

(6) In 2004, the average retail price of a prescription for a brand name medicine was $62.06, while it was $23.33 for a generic medicine (IMS Health, "Average Cost per Prescription: Brand vs. Generic," http://www.imshealthcanada.com/htmen/3_2_19.htm).

(7) Former subss. 55.2(2) and (3) PA.

(8) More specifically, art. 30 of the *Agreement on Trade-Related Aspects of International Property Rights* (TRIPS), 1869 U.N.T.S. 332 (Annex 1C to the *Marrakesh Agreement Establishing the World Trade Organization*, 1867 U.N.T.S. 3), signed on 15 April 1994.

(9) Subsection 55.2 (1) PA.

(10) This is a reasonable exception under art. 30 of the TRIPS Agreement.

THE PATENTED MEDICINES (NOTICE OF COMPLIANCE) REGULATIONS

A. 1993 to Date

The Governor in Council may make regulations governing the "early working exception and the prevention of patent infringement and abuses."(11) The adoption of the *Patented Medicines (Notice of Compliance) Regulations*(12) in 1993 was an exercise of that regulatory power.(13) Hoping to make, for the first time, the process for approving medicines dependent on the patent system, the government gave patent holders additional protection.

Given the complexity of the rules, and the concerns of the people involved, two amendments were made to the Regulations. In response to the Report of the House of Commons Committee on Industry, submitted in April 1997,(14) the first amendment came into force on 11 May 1998, making far-reaching changes to the Regulations.(15) The second amendment, which came into force on 1 October 1999, sought to prevent generic drug companies from circumventing the Regulations.(16) Subsequently, in a report submitted in 2001, the Senate Standing Committee on Banking, Trade and Commerce stated that the system needed to be changed so that stalling tactics could not be used to improperly extend the period of patent protection.(17) The Committee also recommended that any proposed changes to the Regulations be tabled in both houses of Parliament. In 2003, the House of Commons Standing Committee on Industry, Science and Technology began another review of the Regulations.(18)

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(11) Subsection 55.2(4) L.B.

(12) The Regulations were the culmination of the efforts of intense lobbying by the pharmaceutical giants, and in particular Merck, Eli Lilly and the Pharmaceutical Manufacturers Association of Canada, and came into force on 12 March 1993.

(13) The Minister of Consumer and Corporate Affairs prepared the Patented Medicines (Notice of Compliance) Regulations, *Canada Gazette II*, vol. 127, No. 6, 1993, p. 1383. Today, that responsibility belongs to the Minister of Industry.

(14) House of Commons (1997), Recommendation 4 – Regulatory Reform: With the complexities of these issues, the Committee recommends that the government re-visit the regulatory regime … .

(15) *Regulations Amending the Patented Medicines (Notice of Compliance) Regulations*, *Canada Gazette II*, vol. 132, No. 7, 1998, p. 1051.

(16) *Regulations Amending the Patented Medicines (Notice of Compliance) Regulations*, *Canada Gazette II*, vol. 133, No. 21, 1999, p. 2355.

(17) Senate of Canada, 3rd Report of the Senate Standing Committee on Banking, Trade and Commerce, Ottawa, April 2001, Appendix, Observations on Bill S-17.

(18) House of Commons, Standing Committee on Industry, Science and Technology, Study, *Automatic Injunction Provisions in the Patented Medicine (Notice of Compliance) Regulations of the Patent Act*, 2nd Session, 37th Parliament. The Committee did not write a report, given that no consensus was reached and the parliamentary session was prorogued.

On 11 December 2004, the Minister of Industry published proposed regulations clarifying the provisions of the Regulations, to achieve, once and for all the balance so long sought.(19) However, despite the Senate Committee's recommendation, the proposed regulations were not presented to both houses of Parliament. In the government's opinion, the amendments proposed by Industry Canada were part of a national pharmaceuticals strategy developed in September 2004.

B. Link Between Notice of Compliance and Patent

To ensure the safety and effectiveness of a drug, the federal Minister of Health examines and analyzes the detailed reports and clinical tests done by pharmaceutical companies. A firm may not market its product until it has been approved by the issuance of a notice of compliance (NC) under the *Food and Drug Regulations*.(20) The entire essential process obviously results in lengthy delays and substantial costs.

A generic drug manufacturer may file an abbreviated new drug submission for an NOC.(21) By establishing that its product is equivalent to a drug that has already been approved, the manufacturer can demonstrate its safety and effectiveness by comparison, without having to do extensive clinical studies,(22) thus saving time and money. The Minister of Health will issue an NOC only if the manufacturer also complies with the requirements of the Regulations.(23)

The link between the NOC and the patent system was made in order to prevent the infringement that would result if the generic medicines were marketed before the patent expired. The difficulty of obtaining an interlocutory injunction, and the delays associated with a traditional infringement action,(24) would enable generic drug companies to enter the market before the patent expired and to make huge profits. Those companies would therefore have every incentive to act with impunity, at least for a certain period of time.

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(19) *Regulations Amending the Patented Medicines (Notice of Compliance) Regulations*, *Canada Gazette II*, vol.. 138, No. 50, 2004, p. 3718 (not in force).

(20) C.R.C., c. 870, subs. C.08.002(1) and s. C.08.004.

(21) Section C.08.002.1 of the Food and Drug Regulations.

(22) Subsections C.08.002.1(2)(*a*) and C.08.002(2)(*g*) to (*i*) of the *Food and Drug Regulations*.

(23) If the manufacturer wants only to export its product, it is not required to apply for an NOC under the Regulations. We would point out, however, that obtaining an NOC may be of significant benefit for marketing a product in another country.

(24) Patent holders may still bring an infringement action, since the Regulations merely provide additional protection.

C. Automatic 24-Month Waiting Period

Section 5 of the Regulations requires that a manufacturer that compares its generic medicine to a drug for which there is a patent on the Health Canada register include "Form V" in its application for an NOC. The generic drug manufacturer must then make a choice. It may state that it agrees to wait until the patent expires before receiving its NOC[(25)] or allege, essentially, that the patent is invalid or that there is no patent infringement, and say that the Minister should not be prevented from issuing an NOC to it.[(26)] In the latter case, it must also send a notice of allegation to the brand name drug manufacturer, stating the basis for the allegation.

Within 45 days of receiving the notice of allegation, the brand name drug manufacturer may apply to the Federal Court for an order prohibiting the Minister from issuing an NOC to the generic manufacturer until after the expiration of the patent.[(27)] Once the application for an order is filed, and for the 24 months prescribed by the Regulations,[(28)] the Minister may not issue an NOC to the generic manufacturer unless one of the following two situations occurs:

- a decision by the court in favour of the generic drug manufacturer;[(29)] or
- the expiration of the patent.[(30)]

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(25) Subsection 5(1)(*a*) of the Regulations. According to Health Canada statistics for 2004, this accounted for about 27% of cases, or 51 statements out of a total of 189 Form Vs (Therapeutic Products Directorate, *Statistical Report 2004 Patented Medicines (Notice of Compliance)*, Department of Health, 2004, p. 17).

(26) Paragraph 5(1)(*b*) of the Regulations. The 2004 statistics also show that this option accounted for about 67% of cases, or 127 allegations out of a total of 189 Form Vs (*ibid.*).

(27) Subsection 6(1) of the Regulations.

(28) The waiting period was 30 months before the 1998 amendments. It was shortened to take into account the time the courts need to dispose of litigation. The time needed for processing prohibition applications was 7 to 58 months in 1993 and 21 to 24 months in 2003, not counting appeal proceedings (Therapeutic Products Directorate (2004), p. 35). The waiting period in the United States is still 30 months (*Federal Food, Drug, and Cosmetic Act*, 21 USCS § 355 (2005), (j) (5) (B) (iii).)

(29) Paragraphs 7(1)(*e*) and 7(2)(*b*) and subs. 7(4) of the Regulations.

(30) Paragraph 7(2)*a*) of the Regulations.

Otherwise, the Minister may issue the NOC to the generic manufacturer only once the 24-month stay has expired.(31) Thus an interlocutory injunction is granted automatically, regardless of the merits of the application made by the brand-name manufacturer.

D. Evergreening(32)

Because the automatic 24-month waiting period can delay the entry of generic medicines into the market by being applied repeatedly, it is a subject of some controversy. In some cases, the 24-month rule may be abused, and lead to what is called "evergreening." This refers to the situation when a brand-name manufacturer adds new patents while a regulatory "waiting period" is in effect, so that the generic manufacturer is then obliged to serve fresh notices of allegation. The brand-name manufacturer may then apply to the Federal Court for a prohibition. The fresh prohibition application gives rise to a further 24-month waiting period.(33) Some brand-name manufacturers also register new patents shortly before, or even after, the expiration of the initial patent.(34) Because an innovative pharmaceutical company can control the timing of the issuance of its various patents, these strategies can be very effective in delaying the arrival of generic medications on the market.

E. Delays

Despite the fact that delays average 12 months in some cases,(35) the system instituted by the government seems to function well, in general. Because a large majority of medicines are covered by only one or two patents,(36) most litigation is dealt with in a reasonable time, and the 24-month regulatory waiting period ends before the time needed for approving the

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(31) The Minister never has an obligation to issue an NOC, because the Minister must always ensure that the medicine is safe and effective.

(32) In French: "renouvellement continu de brevet" or "perpétuation des brevets."

(33) The Romanow Commission considered this technique to be "a particular concern" (Final Report, p. 209).

(34) One example is Prozac, for which a new patent was added 12 hours before expiration of the patent.

(35) House of Commons study: *Automatic Injunction Provisions in the Patented Medicine (Notice of Compliance) Regulations of the Patent Act*, Meetings, *Evidence*, No. 049, 2nd Session, 37th Parliament, 2 June 2003, 1710, testimony of Éric Dagenais (Acting Director, Patent Policy Directorate, Department of Industry).

(36) As of 5 April 2005, out of a total of 419 medicines, 233 (56%) had one patent listed against them and 89 (21%) had two patents. One medicine had 16 patents listed against it (Therapeutic Products Directorate (2004), p. 14).

generic medication expires. However, the waiting period could be reduced to about 18 months, to more closely reflect the average time for approving a generic medicine, which was 17 months for the period from 2000 to 2004.(37)

Cases in which serious problems arise are the exception. However, brand-name manufacturers use stalling tactics to preserve their monopoly on important medicines, which are of considerable commercial value. Omeprazole, for example, which is marketed under the name Losec, was the subject of a legal battle that went on for 11 years, and in the case of Paxil, patents were filed on five different occasions, thus delaying the entry of the generic version onto the market by about four years.(38)

In the United States, President Bush realized that delays on the order of 40 months in getting a generic version on the market were the result of successive prohibition periods, and was afraid of the harmful effects this might have on competition. Acting on the recommendations of the Federal Trade Commission, he declared that he was putting an end to evergreening by instituting a single 30-month waiting period. That change in the American system, which took effect on 18 August 2003, is expected to save consumers $35 billion over 10 years.(39) In Canada, the government has not favoured that solution, and has preferred instead to limit the application of the Regulations.

F. Leading Court Decisions

The Regulations were made in a hurry, in an “emergency” situation, and without the traditional consultation process. They were then fleshed out as time went on, and as numerous cases made their way through the courts. In some cases, there is a significant gap between what the courts have said and the policy objectives of the Regulations.(40) This paper examines some major examples of this situation.

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(37) Health Canada, *Annual Drug Submission Performance Report – Part I, Therapeutic Products Directorate (TPD)*, 2004, p. 31.

(38) In the United States, legal tactics are said to have made it possible for GlaxoSmithKline to make over $1 billion more in sales of Paxil (Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, July 2002, p. 49).

(39) *Ibid*., p. iv.

(40) Regulatory Impact Analysis Statement, *Canada Gazette II*, vol. 138, No. 50, 2004, p. 3722.

1. Adding a Patent When a Medicine is Changed

When Bristol-Myers Squibb inadvertently forgot to apply for an important patent within the prescribed time, it adopted a strategy, on its fourth attempt, of persuading the Minister of Health to enter its patent on the register.(41) The company asked to change the name of its drug "Serzone" to "Serzone-5HT2," and attached a list to its application that included the patent in question. The Federal Court refused to allow the application, which would have made the time requirements ineffective and unduly delayed the entry of the generic medicine onto the market.

The courts will therefore not allow a patent to be added when an application is made regarding technical or administrative changes or when the application relates to the firm itself, because the government wants to encourage only progressive, legitimate and substantial innovation, by protecting only those changes that have a direct therapeutic application.

2. Requirement That the Medicine be Marketed

In another case,(42) the innovative company had stopped marketing omeprazole capsules (Losec 20 mg) in 1996. It subsequently added two patents to the register in relation to Losec 20 mg. A majority of the Federal Court of Appeal was of the opinion that the generic manufacturer, Apotex, had to take those patents into account even though the comparison drug, Losec 20 mg, was no longer on the Canadian market.

The Court of Appeal found that the Regulations require only that the reference drug have been marketed at some point, under any NOC. However, the dissenting judge argued that the balance struck required that the public be truly able to benefit from the invention, in order for the pharmaceutical company to be able to take advantage of the exceptional protection offered by the Regulations.

3. Indirect Comparison

In another case,(43) a generic manufacturer, Nu-Pharm, compared its product to a generic medicine already on the market, Apo-Enalapril, hoping that it would thus be able to work around the Regulations. Apo-Enalapril had received an NOC based on bioequivalence with a

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(41) *Bristol-Myers Squibb Canada Inc.* v. *Canada (Attorney General)*, (2001) 10 C.P.R. (4th) 318, 2001 CarswellNat 85 (F.C.), aff'd (2002) 16 C.P.R (4th) 425.

(42) *AstraZeneca Canada Inc.* v. *Canada (Minister of Health)*, 2005 FCA 189, 2005 CarswellNat 1399, leave to appeal to the Supreme Court granted (20 October 2005).

(43) *Merck & Co.* v. *Canada (Attorney General)*, (2000) 5 C.P.R. (4th) 138 (F.C.A.).

patented drug, Vasotec (marketed by Merck). The Federal Court of Appeal held that Nu-Pharm had to take the patent listed against Vasotec into account by serving a notice of allegation on Merck. A generic manufacturer cannot avoid the Regulations by hiding behind an NOC that in fact refers to an innovative drug.

That was certainly not the case in *Biolyse Pharma Corporation* v. *Bristol-Myers Squibb Company*, which was heard by the Supreme Court of Canada.(44) In fact, Biolyse had done independent clinical trials, at the request of Health Canada, because it could not rely on the Bristol-Myers Squibb drug, Taxol,(45) since the two products were different in origin and in specific uses.(46) Both drugs contained the same medication, paclitaxel, but a majority of the Court stressed the fact that paclitaxel was not patented. Biolyse therefore had not benefited from Bristol-Myers Squibb's invention. The majority held that the Regulations applied only to generic drug manufacturers who rely, directly or indirectly, on an innovative drug, which meant that Biolyse had not violated the Regulations.

A MITIGATED SUCCESS

In conclusion, can we say that the *Patented Medicines (Notice of Compliance) Regulations* have helped to strike the balance sought between protecting patents and getting medicines on the market as soon as possible? There is no clear answer. The one thing that is certain is that these are very important issues and the Regulations are a formidable weapon for those who know how to use them. In fact, the Minister of Industry said, in 2003:

> Are we ever going to get agreement between generics and brand names on what the right balance is between patent and competition? Are we ever going to get unanimity on whether the NOC regulations are right or should be adjusted more? I predict not.(47)

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(44) [2005] 1 S.C.R. 533.

(45) We would note that the product was very successful commercially. As well, Bristol-Myers Squibb took advantage of a tax reduction in the United States. Taxol, which can be used to treat a rare disease that accompanies AIDS, Kaposi's sarcoma, is classified as an "orphan drug."

(46) Both products are used to treat different forms of cancer.

(47) Quotation taken from House of Commons study: *Automatic Injunction Provisions in the Patented Medicine (Notice of Compliance) Regulations of the Patent Act*, Meetings, *Evidence*, No. 049, 2nd Session, 37th Parliament, 2 June 2003, 1545.

In 2004, nearly half of all notices of allegation resulted in judicial proceedings.(48) On the other hand, the proportion of court orders prohibiting the Minister of Health from issuing an OAC to a generic manufacturer fell from 26% to 9% after the 1998 amendments.(49) This significant decrease seems to favour – in 9 cases out of 10 – the argument of generic manufacturers that their NOC applications are legitimate. However, the 24-month regulatory period continues to be triggered automatically in all cases in which a brand-name manufacturer applies to the Federal Court for an order. This suggests that the Regulations have created an imbalance in the scheme in a way that is unduly favourable to brand-name manufacturers.

It must not be forgotten, however, that the Regulations were initially made to prevent abuses that might result from use of the "early working exception." In fact, that objective is still one of the primary justifications for the system that the government instituted in 1993. That exception to patent infringement would, if it were not regulated to some degree, allow generic companies to obtain precious years of marketing of its products.(50) It is therefore easy to put into perspective the 24-month regulatory period and the drawbacks it may create.

In fact, the problem may lie less in the system itself, or its underlying principles, than in the literal interpretation of its provisions by all parties – pharmaceutical firms and courts – and the contentious results, and strategies like evergreening, that arise out of it.

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(48) Fifty-three out of a total of 127 (42%). From 1998, when the amendments were made, to 31 December 2004, the figure was about 45%: in 203 cases proceedings were instituted, out of a total of 454 notices of allegation (Therapeutic Products Directorate [2004], pp. 17 and 28).

(49) From 1993 to 1998, 40 orders were made out of a total of 151 cases taken to court. From 1998, when the far-reaching amendments were made, to 31 December 2004, 18 out of 203 cases were taken to court (*ibid.*, pp. 27 and 28).

(50) Two to five years is the range commonly mentioned (Regulatory Impact Analysis Statement, *Canada Gazette II*, vol. 138, No. 50, 2004, p. 3718; John H. Stewart, "Issues in Canadian Pharmaceutical Patent Legislation: R & D Investments, Drug Prices, and Growth of the Generic Sector," *Canadian Intellectual Property Review*, Vol. 14, No. 2, 1998, pp. 141 and 145). We would note, however, that under this statutory exception, the patent holder's monopoly would in fact be extended artificially. See the decision of the United States Supreme Court in *Eli Lilly & Co.* v. *Medtronic Inc.* 496 U.S. 661, 670 (1990).