

PART I

DESCRIPTION AND ANALYSIS

Chapter 1

The Legislative Framework

Patent Legislation

Section 41 of the Patent Act deals specifically with chemical processes intended for food or medicine, and for the purposes of this Report contains two major provisions: the protection of products only by way of their patented processes of manufacture,¹ and compulsory licences (the granting of a licence to allow a party not holding the patent to use the patent holder's processes prior to the expiry of the 17-year patent term) for the manufacture, import, use or sale of patented inventions capable of being used in the preparation or production of medicine.² The section also provides for payment of royalties to the patent holder, which have been set by the Commissioner of Patents, Foods and Medicine at "... 4% of the net selling price of the drug in its final dosage form or forms to purchasers at arms length."³

Medicine has been defined by Gibson, J. in *Imperial Chemical Industries Limited v. Commissioner of Patents* as "... a drug, a therapeutic agent, a biological agent, and a pharmaceutical specialty..."⁴ Because of the recent emergence of biotechnology as a major area seen for future medical advances, there is a current question of the applicability of Section 41 to discoveries in this field.

Brief History

Compulsory licensing for pharmaceuticals has existed in Canada since 1923.⁵ The Patent Act, until 1969, allowed for compulsory licences to be granted for the manufacture, use, and sale of patented processes. In 1969 the Act was amended to permit compulsory licences to import drugs.

Prior to the 1969 amendment to the Act, few applications for compulsory licences were made. The Economic Council of Canada⁶ reported that during

¹ *Patent Act*, R.S.C., c. P-4, s. 41(1).

² *Ibid.*, s. 41(4).

³ *Frank W. Horner v. Hoffmann-La Roche Ltd.* (1970) 61 C.P.R. 243, p. 262.

⁴ (1967) 1 Ex. C.R. 57, p. 61.

⁵ *Patent Act*, S.C. 1923, c. 23, s. 17.

⁶ Economic Council of Canada, *Report on Intellectual and Industrial Property* (Ottawa: Information Canada, 1971), p. 70.

the period between 1935 and June 27, 1969, 49 applications were made; of these, only 22 resulted in the granting of a licence, 4 were refused, and 23 were abandoned or withdrawn. Subsequent to the amendment, 559 licences to import and sell have been applied for; of these, 306 have been granted, 15 have been refused or terminated, 96 have been abandoned or withdrawn, and 142 are still pending (as of January 31, 1985; based on data provided by the Patent Office).

The amendment to the Patent Act to include compulsory licences to import came about as a result of a series of studies during the 1960s which concluded that Canadian drug prices were too high in comparison with those in other countries.⁷

The amendment resulted in the licensing of brand name products by firms, often referred to as "generic" firms, which could then produce and offer for sale their own brand of the basic generic drug, and the making available for sale of more than one of many of the commonly prescribed prescription drugs.

At the same time as the federal legislation was amended, various provinces enacted their own legislation to encourage price competition by enabling or requiring prescriptions of certain types to be filled by the dispensing pharmacist with the lowest-cost equivalent drug. The various provincial enactments dealing with "substitution" and reimbursement will be discussed later in this chapter.

More recently, the federal government has assessed the effects of Section 41 (4) on the pharmaceutical industry and engaged in discussions of possible changes in the Patent Act with interested parties, such as industry associations, consumer groups, professional organizations, and various levels of government.

General Provisions

In general, developed countries protect inventions by a government system of grants of patents which give the recipient exclusive use of the invention for a specified period of time. A country's patent provisions may protect the article or substance which is invented itself (a product patent), the process or processes by which the article or substance is made (a process patent), or the process and the product made by that process (a product-by-process patent), or any combination of the three with respect to different types of inventions.

Canada's patent protection with respect to chemical processes intended for food or medicine is for the process and the product by the process, and does not

⁷ The major reports were:

1. Canada. Department of Justice, Restrictive Trade Practices Commission, *Report Concerning the Manufacture, Distribution and Sale of Drugs* (Ottawa: Queen's Printer, 1963).
2. Canada. Royal Commission on Health Services, *Report of the Royal Commission on Health Services* (Ottawa: Queen's Printer, 1964).
3. Canada. House of Commons, Special Committee on Drug Costs and Prices, *Report of the Standing Committee on Drug Costs and Prices* (Ottawa: Queen's Printer, 1966).

allow a patent to be held for the chemical substance. Therefore, with respect to pharmaceuticals, patents will be granted in Canada not for the chemical compound itself, but for the way or ways in which the compound is made. The product will only be protected if it is made by a patented process. This protection by way of product by process is also to be found in Poland, Argentina, Mexico, and India, among others. Countries which provide for protection of the chemical compound itself include the United States, the United Kingdom, Switzerland, France, Italy, and Japan.⁸

There is an issue involving the "width" or "breadth" of protection which can be claimed in one patent. During the history of Canadian patent applications, policy and judicial pronouncement have varied the interpretation of the legislation and the procedures determining how broad or narrow a patent could be. Historically, patent claims were interpreted rather narrowly—if an applicant asked for protection for a broad classification of process claims, his claim would be restricted to what the applicant disclosed he had done. More recently the judicial interpretation⁹ has allowed the claim to be broader—it is possible to look at the disclosure of what has been done, add to this an element of prediction, and include in what is allowed to be claimed the class of things which can reasonably be predicted to be covered by the discovery in a relatively broad class of substances.

There are also differing provisions internationally for the length of time a patent holder is granted exclusive rights over the patented invention. Normally, any patent granted under the Patent Act¹⁰ in Canada is for a period of 17 years from the grant of the application.

The United States grants patents from the date of issue for a period of 17 years. Most of the European Economic Community countries' grants run from the date of filing for a period of 20 years, as do Japan's.¹¹

Exclusivity is not always absolute, and in Canada provision is made for non-exclusivity by various provisions of the Patent Act. The main provision is found in Section 67 of the Act which allows the Commissioner of Patents, if he is satisfied the patent is being abused, to revoke a patent¹² or to grant a licence to a party not holding the patent to use the patent holder's process. This type of provision, also found in Switzerland, West Germany, Japan, and the United Kingdom amongst other countries, is generally "more of theoretical than practical significance."¹³

⁸ Anne Marie Green, ed., *Patents Throughout the World* (New York: Clark, Boardman Co., 1984).

⁹ *Monsanto Co. v. Commissioner of Patents* (1979) 42 C.P.R. (2d) 161.

¹⁰ *Patent Act*, R.S.C., c. P-4, s. 48.

¹¹ Green, ed., *Patents Throughout the World*.

¹² *Patent Act*, R.S.C., c. P-4, s. 68(d).

¹³ Letter from Ciba-Geigy Canada Ltd., Mississauga, Ontario, December 7, 1984.

The Canadian use of Section 67 has been extremely limited. Of the approximately 90 applications under the section, only 11 have been granted, none in the area of pharmaceuticals.¹⁴ The nature of the pharmaceutical industry would seem to restrict the applicability of this section: licences may be granted for working of the patent; no provision exists for licences for importation of the patented product.¹⁵ Few patentees in Canada actually manufacture chemicals here; the economies of scale do not justify it.

Furthermore, it is difficult to allege abuse of the patent on the basis of price alone, if the market demand is being met. Even though a number of applications have alleged price abuse, "We are not aware of any licence having been granted . . . by reason of the fact that the patentee was charging excessive prices."¹⁶

Even though provisions similar to Section 67 exist in other countries, use of these provisions is very low. For example, no licences have been granted under such provisions for non-working of the patent in Switzerland and Japan. There are also provisions in some countries for compulsory licences to be granted in the public interest, but again their use has been extremely limited (none in Japan or Switzerland; none since 1943 in West Germany).¹⁷

Regulation of Drug Use and Sale

In Canada, drugs must be approved by the Health Protection Branch of Health and Welfare Canada prior to being tested in human beings and again prior to being marketed. A drug is defined as "a substance or a mixture of substances that are manufactured, sold or represented for use in the diagnosis, prevention, treatment, mitigation, or cure of any disorder or disease in man or animal; or alternatively, a substance that produces a change in body organ functions."¹⁸ Regulations clearly expand this definition to mean a final manufactured formulation of a drug, not just the active ingredient. Therefore, the approval is for the finished product of the manufacturer.

Two types of drugs are dealt with differently by the Health Protection Branch (HPB). Old Drugs are those which were introduced to the Canadian

¹⁴ Submission to the Commission of Inquiry on the Pharmaceutical Industry from Hoffmann-La Roche Ltd., Etobicoke, Ontario, September 1984.

¹⁵ But see *E.H. Tate Company v. Lester Sweet Riley* 2 C.P.R. 53, when the Commissioner allowed the applicant to import one machine into Canada so as to provide the Canadian public with the product during the period prior to the licensee setting up the manufacture in Canada of the machines to produce the product.

¹⁶ Memorandum from the Pharmaceutical Manufacturers Association of Canada, Ottawa, Ontario, December 13, 1984.

¹⁷ Letter from Ciba-Geigy Canada Ltd.

¹⁸ Dr. Ian Henderson, "Clearance Procedures for New Drugs in Canada" in B.L. Strom, O.S. Miettinen, and K.L. Melonan, "Post Marketing Studies of Drug Efficacy : How?" *American Journal of Medicine* 77 (October 1984).

market prior to 1963, or those introduced since whose status has been changed from that of a New Drug because there are felt to be no further concerns with their side effects, efficacy, toxicity, stability, or manufacturing. New Drugs are required to be cleared prior to marketing.

The manufacturer of a New Drug must file a Preclinical New Drug Submission in order to obtain permission to commence clinical trials. Included with the application must be details about chemical composition and manufacturing and the results of all animal trials carried out. The purposes of the animal trials are to determine in so far as is possible prior to human exposure the efficacy of the drug, its lethal dosage, the side effects of effective dosage régimes, the potential for carcinogenicity, and the effects on reproduction. The approval for clinical trials considers all the above factors, and also examines the details of the methodology and expertise of the proposed clinical tests.

Clinical trials are in three phases: the first is a test among healthy humans; the second, among a small number of persons affected with the disease or disorder the drug is intended to affect; and the third, among a larger number of persons with the problem to be treated. No trial can be commenced without prior HPB approval. Specific types of drugs are dealt with by the division within HPB which is responsible for that area.

Prior to marketing a New Drug, the manufacturer must obtain an additional approval. This is done by filing a New Drug Submission consisting of all the previous manufacturing and test data, together with a Product Monograph. The Monograph is the official outline of the drug indications, dosages, side effects, and characteristics which will go to the prescribing professionals. Approval for marketing is called a Notice of Compliance.

If the New Drug is to be used for purposes differing from those in the original Notice of Compliance or if new side effects or difficulties are to be added to the prescribing information, additional submissions, called Supplementary New Drug Submissions (NDS/S), are required. These submissions generally contain new clinical test information, or observations gained during the use of the substance. The result of the successful NDS/S will be an updated Product Monograph.

If the New Drug is another formulation of a previously approved dosage form of a drug (i.e., a generic), the requirements are different. The applicant must prove the generic is chemically the same as a previously approved drug, and that the drug is bio-equivalent (i.e., it is absorbed and treated by the body in the same way). The required clinical testing is therefore restricted to these bio-equivalence studies.

Hospital and Medical Care Insurance

Almost without exception, Canadians have their hospital and medical costs covered by the national/provincial insurance plans.

The first provincial hospital insurance in Canada occurred in 1944 when the Alberta Program provided free hospital care for maternity patients.¹⁹ Saskatchewan and British Columbia also instituted public hospital insurance programs during the 1940s. Private hospital insurance expanded coverage in other provinces through Blue Cross and commercial insurance. In the six remaining provinces, 56 per cent of the population were covered by such hospitalization plans by 1955.

In 1957, the Hospital Insurance and Diagnostic Services Act was passed, which extended coverage by 1961 to 99 per cent of the Canadian population.

Coverage for medical care insurance (professional fees) was slower to develop, but by 1961 about 50 per cent of the population was entitled to benefits. And in 1967, the Medical Care Act²⁰ was introduced, so that by 1971 all provinces had joint federal-provincial medical care insurance plans in place.

Pharmicare

Third-party coverage by government or private industry of drug costs has been yet slower to develop than either hospital or medical care. Some costs are covered by federal and provincial schemes, some by private or group insurance plans.

Federal coverage for medication includes groups such as veterans and native peoples. There are also special programs organized by various volunteer groups including the Canadian Cancer Society, Planned Parenthood organization, the Victorian Order of Nurses, and The Canadian Cystic Fibrosis Foundation.²¹

In its brief to the Gordon Commission,²² Green Shield Prepaid Services estimated that 69 per cent of the population of Ontario has third-party insurance to cover drug costs. An additional 16 per cent receive benefits from the Ontario Drug Benefit plan. Blue Cross, which covers some "... five million persons ... through the eight Canadian Blue Cross Plans,"²³ estimates that 65 per cent of Canadians have some private drug plan benefits, with another 20 per cent covered by various provincial government plans.

¹⁹ The Canadian Pharmaceutical Association, *Pharmacy in a New Age: Report of the Commission on Pharmaceutical Services* (Toronto: The Canadian Pharmaceutical Association, 1971).

²⁰ *Medical Care Act*, S.C., 1966-67, c. 64.

²¹ Canadian Pharmaceutical Association, *Pharmacy in a New Age: Report of the Commission on Pharmaceutical Services*.

²² Submission to the Gordon Commission from Greenshield Prepaid Services, Windsor, Ontario, 1984, p. 29.

²³ Submission to the Commission of Inquiry on the Pharmaceutical Industry from Greenshield Prepaid Services, Windsor, Ontario, July 11, 1984, p. 5.

Private Insurance Schemes

Participation in private insurance plans can be arranged individually or on a group basis (usually employer related). The coverage for the vast majority of people is on a group basis and can be structured in two ways:

1. The risk for drug costs and variations in numbers and values of prescription cost claims is borne by the insurer and passed on to the payer of the insurance premium by way of fee rates. Fees are influenced by two opposing forces, competition among insurers for clients (which tends to decrease fees) and the risk from past cost experience that costs will increase over the coverage period (which tends to increase fees). The cost of the fees are borne either by the employer or by the employee (normally through payroll deductions), or a portion is borne by each.

2. The risk for drug costs and variations is borne by the payer of the drug costs, and the insurer administers the plan for a negotiated fee. Again costs may be allocated between employer and employee on any basis.

According to one insurer, the majority of the risk of increased drug prices in these schemes is borne by employers as part of wage and benefits packages.²⁴ Both private and public sector employers often bear the majority of the burden of these costs. The effect of the costs is to increase the operating costs of the private employer (and ultimately costs to the consumer) or to increase the tax burden in the case of the public employer.

The result of employers bearing the burden of such costs is to reduce the price sensitivity of the purchaser or recipient of the drug therapy, and therefore indirectly the price sensitivity of the prescriber.

Provincial Reimbursement Schemes

All provinces provide reimbursement schemes for costs of prescribed drugs to some extent. These vary from the universal coverage in British Columbia, Saskatchewan, and Manitoba (with co-payments from the recipient) to government provision of drugs to those on social assistance in Prince Edward Island (see Table 1.1). Most of the provinces with reimbursement schemes have tried to limit the costs in some form or another—reimbursement can be actual acquisition cost, in accordance with published formulary prices, wholesale plus a set markup, or any combination of the three.

Attempts to limit costs have also resulted in some provincial enactments which encourage the dispensing of the lowest-cost equivalent product. To protect the professional liability of the dispensing pharmacist, legislation which forces the pharmacist to substitute a lower-cost equivalent for a brand name drug found in a prescription may limit his legal liability for any health consequences of the substitution. Table 1.1 also sets forth the differing substitution provisions in each province.

²⁴ Submission to the Gordon Commission from Greenshield Prepaid Services.

Table 1.1

Provincial Legislation—Drug Reimbursement Programs

Province	Population Coverage	Formulary	Benefits	Administrative Body	Participation Fee	Amount Reimbursed	Basis for Reimbursement	Source of Listed Prices	Dispensing Fee	Pharmacy Competition
British Columbia	Universal	None	All Rx ^a plus few OTC ^b & some chronic supplies.	Pharmacare	65+ & SA & nursing home—none. Others—deductible & 20%.	Acquisition cost of pharmacy, wholesale and 12% of dispensing fee.	Actual cost of acquisition.	Wholesale list price (sometimes).	Average fee of pharmacy up to max. of 15% above province's prev. month's average overall max. of \$6.75.	No media advertising permitted. Can display price list in store.
Alberta	Social assistance, 65+ Others—voluntary	None	All Rx plus some OTC.	Dept. of Social Svcs & Community Health; Alberta Blue Cross; Ministry of Health	SA—none. 65+—20%. Others—deductible plus 20%.	Wholesale cost plus up to 25%.			Negotiated—\$5.50.	No advertising permitted of fees or prices.
Saskatchewan	Universal (some exceptions)	Yes	All Rx plus some OTC.	Prescription Drug Plan	Max.\$3.95/Rx. Some SA and special groups—nil.	Lower of formulary price or actual acquisition cost.	Standing offer contract drugs—6mth tenders for high volume multiple-source drugs. Others—man. list price.	Tenders. Manufacturers list price.	Negotiated (\$5.30 and \$4.80 over 20,000 Rx).	Pharmacy may charge less than maximum fees.

Manitoba	Universal	Yes—limited to high-selling multi-source drugs.	All Rx plus some OTC. Diabetic supplies.	Manitoba Health Svcs Commission; Dept. of Employment Services and Economic Security	Annual deductible +20% co-payment. SA & home-care—none.	Lesser of man. price or lowest wholesale price or MAC ^c in formulary or usual charge.	Manufacturers and wholesalers prices.	List prices by manufacturers & wholesalers.	Negotiated—\$5.05.	
Ontario	65+, social assistance, special groups	Yes		Drug Programs & Policy Branch, Min. of Health	None	Lesser of actual cost or lowest cost in inventory and disp. fee.	Manufacturers prices (some are negotiated).	Negotiated with manufacturers (some). Others are man. list.	\$5—negotiated.	
Quebec	65+, social assistance	Yes	Formulary drugs. Some OTC with permission.	Régie de l'assurance-maladie du Qué	None	Single-source—wholesale quotes + 9%. Multiple-source medium list price + 9% (max.).	Manufacturers wholesale quotes.	Manufacturers list.	Negotiated (\$3.62 for first 20,000, \$3.15 after).	Prices can be posted only inside pharmacy.
New Brunswick	65+, SA, cystic fibrosis, home care	Yes—limited to high-selling multi-source drugs	All Rx plus others.	Medicare, N.B. Dept. of Health	65+—\$3.00/Rx. SA—\$2.00/Rx Adult. \$1.00/Rx Child.	Price list & dispensing fee less co-payment.			Negotiated—\$5.55.	No ability to advertise prices.
P.E.I.	Social assistance, special groups	None			None	Actual cost of drugs to central dispensary.		Provincial dispensary buys products to be dispensed.		

Table 1.1 (continued)

Provincial Legislation—Drug Reimbursement Programs

Province	Population Coverage	Formulary	Benefits	Administrative Body	Participation Fee	Amount Reimbursed	Basis for Reimbursement	Source of Listed Prices	Dispensing Fee	Pharmacy Competition
Nova Scotia	65+, social assistance, disabled, diabetic, cancer, cystic fibrosis	Yes	65+—all Rx plus other.	N.S. Health Svcs Insurance Commission	65+ and SA—none.	65+—total costs.	OTC—SRP ^d or AAC* + 66.6%. Rx—Combination of: Usual and Customary cost + max. fee and lowest regular listed price, or AAC + fee.	Regular list price of manufacturers.	\$5.50—negotiated.	
Newfoundland	Social assistance, 65+ with GIS ^f	Yes—limited to high-selling multiple-source drugs	All Rx drugs, some OTC, vitamins & syringes.	Dept. of Health Policy	GIS—dispensing fee. SA—none.	SA—total cost. GIS—drug cost only (not dispensing fee).	Lowest price listed on formulary or MAC.	Manufacturers' quotes.	Bargained for (now \$5.25/Rx).	Can advertise lower fees.

Note: Substitution — In all provinces there is no substitution allowed if the prescribing physician so directs.

* Rx = prescription.

^b OTC = over the counter.

^c MAC = maximum allowable cost.

^d SRP = suggested retail price.

^e AAC = actual acquisition cost.

^f GIS = guaranteed income supplement.

Source: Submission to the Commission of Inquiry on the Pharmaceutical Industry from the Pharmaceutical Manufacturers Association of Canada and Paul K. Gorecki, "Compulsory Patent Licensing of Drugs in Canada: Have the Full Price Benefits Been Realized?," unpublished study, January 30, 1985.

Appendix 1: International Regulations

Patents

Introduction

Canada is one of the over 90 countries which are signatory to the Paris Convention for the Protection of Industrial Property (1883) as amended. The Convention is an international agreement which deals with patents among other aspects of industrial property. Its main provisions are national treatment of member inventions (each contracting state must provide the same protection to nationals of other states as they do to their own nationals), a right of priority (if a patent is filed in any member country, the date of that first filing will be protected for 12 months in all other member countries), and compulsory licensing to prevent patent abuse (only after three years from the date of issue of the patent and if the patentee is unable to justify himself with legitimate reasons).

The member countries agree to abide by these provisions, but are free to stylize their patent legislation outside the Convention areas in any way they see fit. The following is an overview of some of the main patent provisions in Canada and her main trading partners. Table A1.1 summarizes the provisions.

Canada

Prior to 1923, Canada's Patent Act contained no provisions specific to pharmaceuticals. It was in 1923 that the Act was amended to add Section 17¹ which provided for compulsory licensing of food and drug patents. This amendment was basically a duplicate of the compulsory licensing provision of the English Patents and Designs Act. The amendment provided for licensing:

"2. In the case of any patent for an invention intended for or capable of being used for the preparation or production of food or medicine, the Commissioner shall, unless he sees good reason to the contrary, grant to any person applying for the same, a licence limited to the use of the invention for the purposes of the preparation or production of food or medicine but not otherwise; and, in settling the terms of such licence and fixing the amount of royalty or other consideration payable the Commissioner shall have regard to the desirability of making the food or medicine available to the public at the lowest possible price consistent with giving to the inventor due reward for the research leading to the invention."²

¹ *Patent Act*, S.C. 1923, c. 23, s. 17.

² *Ibid.*

Table A1.1

International Patent Provisions for Pharmaceuticals: Selected Countries

Country	Type of Patent*	Length of Protection (years) A-from application G-from grant	Compulsory Licensing Provisions	Remarks/ History
Argentina	Process	15 G	None	15-year term is at option of Commissioner. Working must be carried out within 2 years of grant or patent cancelled. ^a
Australia	Product ^b	16 A	After 3 years from grant. Public requirements not met.	
Brazil	None	15 A	After 3 years from grant for non-working in Brazil. Discontinuance of working for 1 year.	
China	None ^c			
France	Product ^c	20 A	After 3 years from grant or 4 years from application. Non-working in France. Government licences for public need.	Until 1960, full ban on pharmaceutical patents. ^b Until 1978, partial ban on pharmaceutical patents. ^b
India	Process	7	After 3 years from grant. Non-working in India. Medicine licensed as of 3 years from grant.	
Spain	None	20 G		
Sweden	Product ^c	20 A	After 3 years from grant or 4 years from application, if in public interest or of extreme importance.	Prior to joining EPC no <i>per se</i> protection for pharmaceuticals and term was 18 years. ^a

United Kingdom	Product ^c	20 A ^c	On grounds of inadequate working, demand in U.K. not being met or met by imports or on unreasonable terms.	1949— <i>per se</i> protection of chemicals restored ^c as it had existed in 1919. Prior to EPC term was 16 years. ^a Compulsory licensing provision for manufacture of medicines in place since 1923 was repealed in 1977.
United States	Product ^c	17 G ^d		Additional grants for new uses before 1984 was 17 years from filing.
West Germany		20 A	On grounds of non-working after 2 years from grant if invention exploited elsewhere. Public interest.	<i>Per se</i> protection since 1968. ^a Prior to EPC was 18-year term. ^a

**Product* — Protection of the chemical compound itself.

Process — Protection only of the patented manufacturing process or process by which the chemical is created.

Product by Process — Product is protected if manufactured by patented process. Reverse onus clause assumes process used unless demonstrated otherwise.

Source: Information is from Anne Marie Green, ed., *Patents Throughout the World* (New York: Clark, Boardman Co., 1984) unless otherwise noted (see below).

^a Dr. E. Jucker, *Patents and Pharmaceuticals*, Basle, 1980.

^b Association of British Pharmaceutical Industry, *Memorandum of Evidence to the Committee to Examine the Patent System and Patent Law*, March 1968.

^c Dr. E. Jucker, *Patents—Why 1982*, Basle, 1982.

^d Consumer and Corporate Affairs Canada, *Compulsory Licensing of Pharmaceuticals: A Review of Section 41 of the Patent Act*, 1983.

and limitation of the type of patent protection to process and product by process, together with a reverse onus clause:

"(17)(1) In the case of inventions relating to substances prepared or produced by chemical processes and intended for food or medicine, the specifications shall not include claims for the substance itself, except when prepared or produced by the methods or processes of manufacture specially described and claimed or by their obvious chemical equivalents.

"In an action for infringement of a patent where the invention relates to the production of a new substance, any substance of the same chemical composition and constitution shall, in the absence of proof to the contrary, be deemed to have been produced by the patented process."

The latter half of the subsection

"... was intended to alleviate the task of the patentee in discharging the *onus* of proving infringement, which is always on the patentee in such an action. As the product was now protected only when made by the patented process, a patentee would have to prove not only that the alleged infringer had the product, but also that the product in question had been made by the patented process. As such proof is extremely difficult, if not impossible, to adduce, the law provided the patentee in such cases with the benefit of a statutory presumption in his favour, leaving it to the infringer, if he could do so, to prove that the otherwise infringing substance had not been made by the infringer process, and thus escape the charge of infringement."

A minor amendment occurred in 1935 when the Statutes of Canada were revised. The word "specially" was replaced by "particularly" in the opening lines of the section. The interpretation of this amendment was tested in the Supreme Court of Canada.³ The contention that the amendment was intended to allow claims directed toward a process which was not patentable, so long as the product met the tests of patentability, was rejected. It was held that the process must be a patentable process. No further changes were made to the provision until 1969.

*Parke-Davis and Co. v. The Comptroller General et al.*⁴ was a House of Lords decision which found the compulsory licensing requirements in the Paris Convention applied only to cases of alleged abuse. Therefore, compulsory licensing provisions for public health or public interest reasons did not have to comply with Article (5) of the Convention setting forth the "three year after" rule and the legitimate reasons for refusal.

Notwithstanding the existence of this legislation, few successful uses of the section were made. The Economic Council of Canada has stated⁵ that during the 34-year period between 1935 and June 27, 1969, only 49 applications for compulsory licence had been made. Of these, 22 resulted in the granting of a

³ Ibid.

⁴ I. Goldsmith, "Drugs in Canadian Patent Law," (1967) 13 *McGill Law Journal* 232, at 233.

⁵ *Commissioner of Patents v. Winthrop Chemical Inc.* (1948) 7 C.P.R. 58.

⁶ Economic Council of Canada, *Report on Intellectual and Industrial Property* (Ottawa: Information Canada, 1971), p. 70.

⁷ *Parke-Davis and Co. v. The Comptroller General et al.* (1954) 71 R.P.C. 169 (H.L.).

compulsory licence, four applications were refused, and 23 applications were abandoned or withdrawn. It must be noted that these statistics do not reflect the number of licences which were granted by companies under the threat of this legislation.

Many of the applications under this section were hard-fought by the patentees and hard-won by the applicants, so much judicial interpretation exists of the provisions. *Aktiebolaget Astra etc. v. Novocol Chemical Manufacturing Co. of Canada Ltd.*⁸ determined that the scope of the Commissioner's powers to interpret whether good reason exists for the refusal of an application for compulsory licence was not subject to interference by the Court unless the Commissioner was manifestly wrong or had made an error of law. The powers of the Commissioner were held to be wide enough for him to limit a licence to domestic production only and not to production for export.⁹ Finally, it was decided that the Commissioner's refusal to hold a hearing if requested was not a denial of natural justice.

"As the Commissioner correctly pointed out in this case, he was entitled to set the procedures, and he did so. It was for him to decide whether or not the circumstances required an oral hearing, cross-examination upon affidavits, or oral submissions. In my opinion, his decision not to require any of these things cannot be considered to be a denial of natural justice to the appellant."¹⁰

In sum,

"As to what is 'good reason to the contrary', the matter is one for the discretion of the Commissioner, and unless, on the evidence, his decision is manifestly wrong, or he acts on a wrong principle of law, his decision will not be reversed on appeal. Generally speaking, if the applicant has a reasonably permanent organization, if he is qualified to work the patent, the Canadian market is not already over-supplied with the product and the public interest will benefit, or at least will not suffer, the Commissioner must grant a licence."¹¹

The rate of royalty under the section which was set by the Commissioner was generally in the range of 10 to 15 per cent of the net price of the bulk medicine before being encapsulated or tableted.¹² *Hoffmann-La Roche Ltd. v. Delmar Chemicals Ltd.* determined that the rate of "...12½% on the sale price of bulk product from the time of the granting of the licence to the end of the year 1965, and ... 15% on the sale price of the bulk product thereafter"¹³ was not manifestly low, and did not overturn the procedures of the Commissioner, even though he did not set forth reasons for the rate.

⁸ *Aktiebolaget Astra etc. v. Novocol Chemical Manufacturing Co. of Canada Ltd.* [1964] 44 C.P.R. 15.

⁹ *Rhône-Poulenc S.A. v. Micro Chemicals Ltd.* (1964) 44 C.P.R. 208.

¹⁰ *Per Martland, J., Hoffmann-La Roche Ltd. v. Delmar Chemicals Ltd.* (1965) 45 C.P.R. 235, at 242.

¹¹ I. Goldsmith, "Drugs in Canadian Patent Law," p. 240.

¹² *Ibid.*, p. 241.

¹³ *Hoffmann-La Roche Ltd. v. Delmar Chemicals Ltd.* (1967) 51 C.P.R. 11, p. 13.

Beginning in about 1960, Section 41 came under the scrutiny of several different commissions. In 1960, the Ilsley Commission recommended that, *inter alia*, pharmaceutical companies be permitted to patent product claims to pharmaceuticals while at the same time being subjected to compulsory licence.¹⁴ In 1963, however, the Restrictive Trade Practices Commission recommended the complete abolition of patents for pharmaceuticals.¹⁵ In 1964, the Hall Report recommended retaining pharmaceutical patents with a streamlined procedure, standard royalty, and expansion to permit licensing of imports.¹⁶

Finally, after the report of the Harley Committee, Parliament amended the compulsory licensing provisions of Section 41 of the Act. This Committee concluded that

"... the price of drugs in Canada is at least higher than it need be; ... that no significant change has taken place in the drug-cost structure since the recommendations of the Hall Commission which were primarily based on the recommendations of the Restrictive Trade Practices Commission ... [and that] s. 41(3) of the Patent Act of Canada should be amended to include applications for compulsory licences to import drug products in all forms."¹⁷

After the June 27, 1969, amendment of the Act, Section 41 reads in part as follows:

"(1) In the case of inventions relating to substances prepared or produced by chemical processes and intended for food or medicine, the specification shall not include claims for the substance itself, except when prepared or produced by the methods or processes of manufacture particularly described and claimed or by their obvious chemical equivalents.

"(2) In an action for infringement of a patent where the invention relates to the production of a new substance, any substance of the same chemical composition and constitution shall, in the absence of proof to the contrary, be deemed to have been produced by the patented process.

"(4) Where, in the case of any patent for an invention intended or capable of being used for medicine or for the preparation or production of medicine, an application is made by any person for a licence to do one or more of the following things as specified in the application, namely:

"(a) where the invention is a process, to use the invention for the preparation or production of medicine, import any medicine in the preparation or production of which the invention has been used or sell any medicine in the preparation or production of which the invention has been used, or

¹⁴ Canada. Royal Commission on Patents, Copyright and Industrial Design, *Report on Patents of Invention*, (Ottawa: Queen's Printer, 1960), pp. 92-97.

¹⁵ Canada. Department of Justice, Restrictive Trade Practices Commission, *Report Concerning the Manufacture, Distribution and Sale of Drugs* (Ottawa: Queen's Printer, 1963), pp. 516-24.

¹⁶ Canada. Royal Commission on Health Services, *Report of the Royal Commission on Health Services* (Ottawa: Queen's Printer, 1964), Vol. 1, pp. 701-9. See in particular, Recommendations 67-69, pp. 42-43.

¹⁷ Canada. House of Commons, Special Committee on Drug Costs and Prices, *Report of the Standing Committee on Drug Costs and Prices* (Ottawa: Queen's Printer, 1966).

“(b) where the invention is other than a process, to import, make, use or sell the invention for medicine or for the preparation or production of medicine,

“the Commissioner shall grant to the applicant a licence to do the things specified in the application except such, if any, of those things in respect of which he sees good reason not to grant such a licence; and, in settling the terms of the licence and fixing the amount of royalty or other consideration payable, the Commissioner shall have regard to the desirability of making the medicine available to the public at the lowest possible price consistent with giving to the patentee due reward for the research leading to the invention and for such other factors as may be prescribed.

“(5) At any time after the expiration of six months from the day on which a copy of an application to the Commissioner pursuant to subsection (4) is served on the patentee in prescribed manner, the applicant may, if the Commissioner has not finally disposed of the application, request the Commissioner to grant to him an interim licence to do such one or more of the things specified in the application as are specified in the request, and the Commissioner shall, upon receipt of such request, forthwith serve upon the patentee a notice stating that he may, within such period as is specified by the Commissioner in the notice, not exceeding twenty-one days from the day the notice is served on the patentee, make representations with respect to the request.

“(6) Upon the expiration of the period specified by the Commissioner in the notice to the patentee referred to in subsection (5), the Commissioner shall, if he has not finally disposed of the application, grant an interim licence to the applicant to do the things specified in the request except such, if any, of those things in respect of which he sees good reason not to grant such an interim licence.

“(7) Subsection (4) applies, *mutatis mutandis*, in settling the terms of an interim licence granted pursuant to subsection (6) and fixing the amount of royalty or other consideration payable.

“(8) The Commissioner shall not grant an interim licence pursuant to subsection (6) unless the applicant has filed with the Commissioner a guarantee bond satisfactory to the Commissioner, payable to Her Majesty in right of Canada, to secure the payment by the applicant of the royalties or other consideration that may become payable to the patentee under the interim licence.

“(9) Subject to subsection (10), an interim licence granted pursuant to subsection (6) shall have effect according to its terms for an initial period, not exceeding six months from the day on which the interim licence is granted, specified by the Commissioner in the licence and may, in prescribed circumstances, be renewed by order of the Commissioner for a further period or periods not exceeding six months in all.

“(10) An interim licence granted to an applicant pursuant to subsection (6) ceases to have effect

“(a) where the Commissioner grants a licence to the applicant pursuant to his application made under subsection (4), on the day on which such licence becomes effective; or

“(b) where the Commissioner rejects such application, on the expiration of the period for which the interim licence is then in effect.

"(11) Any decision of the Commissioner under this section is subject to appeal to the Federal Court, except that a decision of the Commissioner with respect to an interim licence is final for all purposes and is not subject to appeal or to review by any court.

"(12) Notwithstanding subsection 67(2), where the importation from abroad of an invention or medicine by a licensee pursuant to a licence or an interim licence granted under a patent pursuant to subsection (4) or (6), or by the patentee while the licence or interim licence is in effect, is preventing or hindering the working within Canada on a commercial scale of the invention to which the patent relates, the exclusive rights under the patent shall not be deemed to have been abused in any of the circumstances described in paragraph 67(2)(a) or (b).

"(13) Where an application is made pursuant to subsection (4) or a request is made pursuant to subsection (5), the Commissioner shall forthwith give notice of such application or request to the Department of National Health and Welfare and to any other prescribed department or agency of the Government of Canada.

"(14) The Governor in Council may make rules or regulations

"(a) prescribing anything that by this section is to be prescribed;

"(b) regulating the procedure to be followed on any application made pursuant to subsection (3) or (4), including, without limiting the generality of the foregoing, the information to be contained in any such application and the making of representations to, and the adducing of evidence before, the Commissioner with respect to any such application;

"(c) respecting the form and manner in which an applicant or patentee may make representations to, and adduce evidence before, the Commissioner with respect to any application or request referred to in this section;

"(d) respecting the manner in which any application, request, notice or other document referred to in this section or in any regulation made under this subsection may or shall be made, served, forwarded or given;

"(e) providing for the making of representations to the Commissioner on behalf of the Government of Canada with respect to any application or request referred to in subsection (13); and

"(f) generally, for carrying the purposes and provisions of this section into effect.

"(15) Any rules or regulations made under paragraph 14(b) regulating the procedure to be followed on any application made pursuant to subsection (4) shall include provision for the final disposal by the Commissioner of such application not later than eighteen months after the day on which a copy of the application is served on the patentee in prescribed manner.

"(16) Nothing in this section or in any licence or interim licence granted pursuant to this section shall be construed as conferring upon any person authority to prepare, produce, import or sell any medicine contrary to, or otherwise than in accordance with, the requirements of the *Food and Drugs Act* and the regulations thereunder and of any other law applicable thereto."¹⁰

¹⁰ *Patent Act*, R.S.C., c. P-4, s. 41.

The essence of the amendment was to extend the compulsory licensing provisions relating to medicine to permit licensees to import medicines into Canada, and to provide for interim licences to applicants six months after application.

The Commissioner set forth extensively in *Frank W. Horner v. Hoffmann-La Roche Ltd.* (1970) 61 C.P.R. 243 the principles that would apply in granting licences and determining royalties under the new Section 41:

"... the principles determined by the Courts in the interpretation of the former s. 41(3) still remain applicable ... it is clear that s. 41(4) ... is mandatory in that the Commissioner of Patents 'shall grant to the applicant a licence to do the things specified in the application except such, if any, of those things in respect of which he sees *good reason* not to grant such a licence....'

"The policy underlining the section before the amending legislation was stated succinctly by Rand, J., in *Parke, Davis, and Co. v. Fine Chemicals of Canada Ltd.*," "...namely, that new medicines prepared from patented processes, are, in the public interest, to be free from legalized monopoly."

"It is also well settled that the principal purpose of former s. 41(3) was to bring about competition, and the change in the section only makes abundantly clear the express authority of the Commissioner of Patents to issue compulsory licences to applicants wishing to import medicinal substances manufactured under patented processes or substances produced by patented processes used in the preparation or production of medicine.

"One other point of principle. It is also well settled that the Commissioner's decision to grant a licence under the subsection must not depend on whether or not the patentee's prices for its product are reasonable....

"In short, compulsory licences applied for under s. 41 of the *Patent Act* leave little discretion to the Commissioner of Patents. These licences, in fact, amount almost to licences of right."²⁰

With respect to fixing the amount of royalty, the Commissioner also gave notice that the section did not guarantee a patentee a reasonable advantage from its patent rights.

"The Commissioner's responsibility in fixing the royalty or other consideration payable to the patentee is that such royalty is 'consistent with giving to the patentee due reward for the research leading to the invention'; and thus the Commissioner is not required to take into consideration such further elements as the cost of obtaining and maintaining medical acceptance of the drug, return on the capital employed in research and promotion and any other elements other than 'research leading to the invention'"²¹

The Commissioner then went on to set the royalty at 4 per cent of the net selling price of the drug in its final dosage form to purchasers at arm's length.

¹⁹ Rand, J., in *Parke-Davis and Co. v. Fine Chemicals of Canada Ltd.* 30 C.P.R. 59 in *Frank W. Horner v. Hoffmann-La Roche Ltd.* (1970) 61 C.P.R. 243.

²⁰ *Frank W. Horner v. Hoffmann-La Roche Ltd.* (1970) 61 C.P.R. 243.

²¹ *Ibid.*, p. 258.

This amount was deemed sufficient to maintain research incentive and reflect the importance of the pharmaceutical.

The above 4 per cent royalty rate became a rough and ready rule of thumb which was applied by the Commissioner in subsequent cases.

The section has more recently been the subject of jurisprudence with respect to its constitutionality. In *American Home Products Corp. v. Commissioner of Patents*,²² the claim was made that Section 41(4) constituted a denial of the patentee's normal rights of ownership. It was alleged that the rights were guaranteed by Section 1 of the Canadian Bill of Rights which reads in part:

"1. It is hereby recognized and declared that in Canada there have existed and shall continue to exist... the following human rights and fundamental freedoms, namely,

"(a) the right of the individual to ... enjoyment of property, and the right not to be deprived thereof except by due process of law;"²³

The claim was rejected on the basis

"... that title to a Canadian patent for medicinal products is granted subject to the restrictions contained in s. 41(4).... Compulsory licensing does not therefore constitute subsequent interference with title. It is a qualification of the title as and when granted pursuant to the *Patent Act*."²⁴

It was additionally alleged that the procedure of the Commissioner infringed Section 2 of the Canadian Bill of Rights which reads in part:

"2. Every law of Canada shall ... be so construed and applied as not to abrogate, abridge or infringe ... any of the rights or freedoms herein recognized and declared, and in particular, no law of Canada shall be construed or applied so as to

"(e) deprive a person of the right to a fair hearing in accordance with the principles of fundamental justice for the determination of his rights and obligations."²⁵

This additional allegation was rejected with the following explanation by Jerome A.C.J.:

"I am not satisfied, however, that a decision under the compulsory licensing provisions without guarantee of oral hearing can be equated to a determination of the owner's rights without a fair hearing. Acting in the public interest, Parliament has declared that inventors of medicinal products are granted patent rights in Canada, subject to the compulsory licensing provisions. Consistent with those priorities, Parliament has set out procedures which afford the owner of the patent the opportunity to make written submissions to the commissioner and to seek an oral hearing. There is, of course, no suggestion by counsel that a hearing cannot be fair unless it is oral.

²² *American Home Products Corp. v. Commissioner of Patents* (1982) 69 C.P.R. (2d) 257.

²³ *Canadian Bill of Rights*, R.S.C. 1970, Appendix 3.

²⁴ *American Home Products Corp.*, p. 261.

²⁵ *Canadian Bill of Rights*.

In assessing the fairness of the hearing given to the applicant in this matter, I must bear in mind the justification on the part of Parliament for causing the title to patent for medicinal products to be subservient to the assurance of reasonable access to the products by the Canadian consumer. These two legitimate interests must be reconciled and Parliament has authorized the commissioner to do so under the directions contained in the last paragraph of s. 41(4). The applicant has not persuaded me that the opportunity given to the owner to present submissions, whether written or oral, falls below the standard of fairness to which owners of patents for medicinal products are entitled in this process of reconciliation of their rights with those of the public."²⁶

Another recent decision has examined the reverse onus clause found in Section 41(2). In *Hoffmann-La Roche Ltd. v. Apotex Inc.*, the applicability of the clause was confirmed:

"... the plaintiff contends that quite apart from s. 41(2) of the *Patent Act*, at common law the rule has always been that when the subject-matter of an allegation lies particularly within the knowledge of one of the parties that party must prove it, whether it be of an affirmative or negative character.

"Therefore, in a case such as this where the plaintiff holds a process patent and the defendant is granted a compulsory licence, the onus shifts to the defendant to show that the supplier he selects abroad does not use the plaintiff's patented process. The defendant of the two parties involved is the only one having any real opportunity of determining the actual foreign process being employed."²⁷

Because it was concluded that Apotex was the only party with an opportunity to determine the true nature of the foreign process, the onus shifted to Apotex to show that the patented process was not being used.

The Patent Act provides for limitations on the general exclusivity given all patentees pursuant to Sections 67 and 68 of the Act (dealing with abuse of rights under patents) and Section 19 (dealing with the use of a patented invention by the Government of Canada).

Section 19 gives the federal government the right to use any patented invention. Provision is made of payment of "a reasonable compensation" set by the Commissioner and subject to appeal.

Section 67 gives the right to interested persons, after three years from the grant of a patent, to ask the Commissioner to find there has been abuse of the exclusive rights of a patent. Grounds for abuse include non-working of the patent on a commercial scale (with no satisfactory reason), hindrance of working in Canada because of importation of the patented item, failure to meet Canadian demand to a reasonable extent and on reasonable terms, prejudice to Canadian industry to trade because of the patentee's refusal to grant a licence, and prejudice to the manufacture, use, or sale of materials not protected by the patent.

²⁶ *American Home Products Corp.*, p. 262.

²⁷ *Hoffmann-La Roche Ltd. v. Apotex Inc.* (1983) 71 C.P.R. (2d) 20.

If the Commissioner finds abuse, he can grant licences to the applicant, refuse patent licensees the right to import goods, allow licensees to prosecute infringements of patents, grant exclusive licences, revoke patents, or refuse the application. The considerations for granting of licences include allowing the widest possible Canadian use consistent with the "...patentee deriving a reasonable advantage from his patent rights..."²⁸ and give the patentee the maximum advantage consistent with allowing the licensee to work the invention at a reasonable profit. He must also endeavour to ensure equality between licensees, taking into account work done to test the commercial value of the product or to ensure commercial-scale working. An exclusive licence may only be granted by the Commissioner if he is satisfied commercial working requires such capital expenditure that exclusive rights are necessary. The section clearly directs that revocation of the patent is only to be used on a limited basis (if it does not contravene any international arrangement) and as a last resort if no other solution would solve the abuse problem.

There have been approximately 90 applications pursuant to Section 67 of the Act. Of these the great majority were withdrawn or abandoned, only 11 have been granted, and 13 were refused.²⁹ These figures do not take into consideration, however, the number of voluntary licences granted by patentees with the threat of this remedy hanging over them.

Judicial interpretation of Section 67 has been quite extensive. For the purposes of the pharmaceutical industry in Canada, though, the section has proved to be of limited value. Rarely has there been allegation in Canada that a patentee of a pharmaceutical process has abused the patent privilege by failing to meet market demand. The avenue for abuse alleged would more likely have to deal with abuse because of high pricing. Though there is no specific legislative provision saying this would not be abuse, this allegation has never been used successfully by the Commissioner of the Courts under this section of the Act.

United States

Of all the countries which the Commission surveyed, the United States has the most extensive (or the strongest) patent protection.

Originally, the Patent Act of 1861 gave a patent protection for a term of 17 years. This term ran from the date on which the patent was actually granted, and not, as in many other countries (for example Canada and members of the EEC) from the date of filing. The length of protection provision remained unchanged until last year. At that time legislation was passed with respect to pharmaceutical patents guaranteeing patentees certain minimum patent protection for their products or processes. The justification for this change had been the lengthy time required for conducting tests and receiving market approval for sale of a drug.

²⁸ *Patent Act*, R.S.C., c. P-4, s. 68(a)(i).

²⁹ Submission to the Commission of Inquiry on the Pharmaceutical Industry from Hoffmann-La Roche Ltd., Etobicoke, Ontario, October 1984.

Each patent application, whether for a product or a process to manufacture a product (both are available in the U.S., and there is no specific provision with respect to pharmaceuticals) may cover only one product or one method of manufacture. There can also be patents covering the medical use of a drug. This has resulted in many patents being applied for and issued for one product: there will be a patent for the product itself, others for the methods of making it, and others for its medical uses. The result of this legislation and the procedure followed for approvals and the time it takes between the application and the grant is that not all of the patents will be issued at one time, and the 17-year term will run from and expire at differing dates. There may also be an early application made for a broad scope of compounds, which is eventually abandoned in favour of one or another of continuation or continuation-in-part applications.³⁰

The United States has no compulsory licensing provisions for patented products or processes, although some have been granted as a result of anti-trust provisions.³¹ There are also no requirements under the Act for working of the patent in the United States.

New legislation, the Drug Price Competition and Patent Term Restoration Act, was introduced in the fall of 1984. This has two effects. Firstly, there is an abbreviated procedure for approval of generic drugs. Secondly, patented drugs can have their patent terms extended to make up for the time it has taken to have the FDA approve them in the first place. Under the new bill, brand name manufacturers would have up to a five-year exclusive marketing extension for new chemical entities if the drug has undergone regulatory review. The maximum period is five years, but the actual period of extension is calculated on the time that was required for the FDA approval process up to this maximum. There is also an overall maximum period of patent life beyond which an extension will not be granted: the total of the unexpired patent period after the approval when added to the extension period pursuant to the amendment may not exceed a maximum of 14 years. This extension provision is only available to drugs which have not yet been patented or tested. If the drug has been patented and tested, but not yet approved by the FDA, the possible maximum extension is two years.

Generic drug manufacturers can now use the patented item for testing in preparation for making an application for marketing approval of their generic products at the end of the patent period, and for making an application for approval to market if that marketing is not intended for the time prior to patent expiry.³²

³⁰ Alfred B. Engelberg, "Patent Term Extension: an Overreaching Solution to a Nonexistent Problem," *Health Affairs*, Spring 1982.

³¹ F. M. Scherer, *The Economic Effects of Compulsory Patent Licensing* (New York: New York University Press, 1977), p. 41.

³² U. S. House of Representatives, *Drug Price Competition and Patent Term Restoration Act of 1984* Rept. 98-857, Part 2.

European Countries

Pursuant to the European Patent Convention signed at Munich on October 5, 1973, a centralized patenting office has been set up; filing in this office protects patented products and processes in all member countries. The centralized system does not mean that the individual patenting systems of the member countries cease to be effective. The effect of filing with the European Patent Office "...leads to a bundle of national patents, each being governed by the same provisions as a national patent granted directly in the country concerned...."³³ Certain time-limited reservations (10-year limitation from the date of the Convention, which may be extended for five years) dealing with the right to limit pharmaceuticals to process protection are possible. (Austria made this reservation.) The various member communities who have had varying patenting provisions in the past have recently enacted amending provisions to bring their patenting provisions in line with the centralized system.

The term under the Convention for patent protection is 20 years. Protection is afforded both to products and processes, and no compulsory licensing provisions or other restrictions are specifically applied to pharmaceutical products (except for the transitional reservation mentioned).

The Community Patent Convention was entered into at Luxembourg on December 15, 1975. By its provisions "...European patents ... have a unitary and autonomous character."³⁴ The effect of the Community Patent is that the patent filed will be effective in respect of all the territories covered. One of the transition provisions of this convention allows member states to reserve the right to provide for compulsory licences in the event of non-working within the state. The transition period is again 10 years, with extension of up to five additional years. After the transitional period, compulsory licences within the laws of each contracting state are possible, but not for non-working within that state if manufacturing is done within another state with sufficient quantities to supply the first state.

There are, however, contained within the other European Economic Community agreements, provisions for parallel importing which have a lowering effect on prices in member countries by providing competitive sourcing of products.

Prior to the United Kingdom becoming party to the European Patent Convention and amending its patent legislation, patent protection existed for products and "matters of manufacture" for 16 years from the date of grant of the patent. A provision similar to Section 67 in Canada existed as well, providing for compulsory licensing in the case of abuse. As in Canada,

³³ *Manual for the Handling of Applications for Patent Designs and Trademarks Throughout the World* (Amsterdam: Registered Patents and Trademark Agents, 1980). Supplement No. 40 (February 1980), p. 1.

³⁴ *Ibid.*, Supplement No. 36 (April 1978), p. 1.

applications pursuant to this abuse provision were very rare.³⁵ Special provisions also existed for the compulsory licensing of food and medicines. This section was in fact the one upon which the early Canadian section was modelled. There was also provision for patents to be used by the Crown, again similar to the Canadian provision. The specific section dealing with compulsory licensing of pharmaceuticals and food was repealed in 1977. The abuse provision remains. There is also a specific provision allowing the Crown to sell medicines pursuant to Section 55(1)(c) of the Patent Act. [An additional historical note: *per se* protection of chemicals in the United Kingdom was abolished in 1919 and restored in 1949.]

Prior to becoming a party to the Convention, Sweden also restricted product patent protection to stated uses excluding pharmaceuticals, and the length of patent protection was 18 years. The Netherlands also had no *per se* protection until 1976. In Italy the length of protection had been 15 years and medicines had been unpatentable before 1979. Before the 1978 Swiss amendment, medicines had been non-patentable, and the term was 18 years from the date of filing. There were also provisions for compulsory licences, in the case of abuse, in the case of a junior (or more recent) patent not being usable without infringement of a previous patent, and in the case of public interest. Before 1978 the provisions with regard to pharmaceuticals in West Germany were essentially the same as those in Sweden.

Compulsory licensing with respect to junior patents, non-working, and public interest still exist in many of the European countries, including Sweden and the Netherlands. France and West Germany still provide for compulsory licences on the grounds of non-working and public interest. In Italy, compulsory licences may be granted to junior patents and in the case of non-working.³⁶

The situation with respect to price competition is different from that in either Canada or the United States, however, because of the existence of parallel imports (where a marketer will bring in product at a lower price from another member country) and also because of price controls exerted over products in various forms in many member countries. These price controls stem from the many differing forms of drug reimbursement programs found in these countries.

The United Kingdom has recently published a limited list of drugs for which the health authority will pay. This is a restricted list of drugs which a doctor can prescribe under the National Health Service in certain therapeutic classes. There is also in the United Kingdom a Pharmaceutical Price Regulation System which provides for NHS reimbursement of pharmacists at certain levels (depending upon certain negotiated returns to pharmaceutical companies, and discounts offered by wholesalers to pharmacists).

³⁵ C.T. Taylor and Z.A. Siberston, *The Economic Impact of the Patent System* (Cambridge: Cambridge University Press, 1973), p. 16.

³⁶ Anne Marie Green, ed., *Patents Throughout the World* (New York: Clark, Boardman Co., 1984).

Many other European countries have negotiated prices which will be allowed to companies for their products. France controls prices by entering into contracts with individual companies. Part of the contract negotiations for rises in prices are commitments on research and development, investment, exports, and employment.³⁷

"In order to be reimbursed at all a drug must be on the Ministry's approved list. New drugs can be added only if they are either medically more effective or equally effective but less costly than already reimbursed drugs."³⁸

In Belgium,

"A five-category system provides for different levels of patient contribution to the cost of medicines: category A, life-saving medicines—fully reimbursed; category B, therapeutically useful—patient pays 25% up to a limit which varies by patient category; categories C, CS, less useful—patients pay 50%, or 60% with a higher limit than B; category D, others—non-reimbursable."³⁹

Italy, through its pricing commission (the CIP) determines the price of medicines taking into account the cost of raw materials, packaging, scientific and medical information, manufacturing, marketing, and research and development expenditure.⁴⁰

"About 1,400 priority drugs on an approved list are supplied for a prescription fee of 1,000 lire. For other drugs on the list the patient pays in addition 20% [*Italian sources suggest the level is nearer 15%.—Ed.*] of the retail price subject to an upper fixed limit. Drugs not on the approved list are not reimbursed."⁴¹

Spain also controls prices to the Spanish pharmaceutical industry.⁴²

"Contraceptives, dietary products and over the counter products are non-reimbursable. For the vast majority of reimbursable medicines, the patient pays a contribution of 40% of the cost. For a small number of priority drugs, the patient contribution is 10%."⁴³

West Germany is discussing setting forth a "positive" list of drugs to be permitted to be prescribed.⁴⁴ "There is a negative list of drugs, ... for which all adults have to pay in full For other drugs patients pay a prescription charge."⁴⁵

³⁷ *Scrip*, No. 958 (December 17, 1984).

³⁸ *Scrip*, No. 970 (February 4, 1985).

³⁹ *Ibid.*

⁴⁰ *Scrip*, No. 951 (November 21, 1984).

⁴¹ *Scrip*, No. 970.

⁴² *Scrip*, No. 944 (October 29, 1984).

⁴³ *Scrip*, No. 970.

⁴⁴ *Scrip*, No. 963 (January 9, 1985).

⁴⁵ *Scrip*, No. 970.

In Ireland,

"Patients on lower incomes are entitled to free health care under the state scheme, within which doctors may prescribe only from a limited list of some 900 drugs. Patients with higher incomes must join a voluntary (i.e., charitable or private) insurance scheme meeting certain minimum requirements."⁴⁶

Japan

Japan protects patents for a term of 15 years from the date of grant but not exceeding 20 years from the date of application. Patents of addition are granted only for the unexpired term of the original patent. Before 1976 only product-by-process protection for chemicals was available; *per se* protection now exists.

Compulsory licences may be granted after three years of consecutive non-working of the product in Japan, in the case of necessity for the public interest, and in the case of a junior patent.

Health insurance schemes also influence Japan to exercise price controls on listed drug products. For example the list price reductions have recently (See *Scrip*, January 9, 1985) been set at an average 6 per cent, to come into effect in March 1985.

⁴⁶ Ibid.

Drug Regulatory Requirements

Canada

Regulation of drugs has existed in Canada since 1875. The current legislation has existed in basically the same form since the Food and Drug Act was enacted in 1953. It deals with general principles regarding the requirements of food, drugs, cosmetics, and devices. The body which oversees the regulation of drugs is the Health Protection Branch (HPB) of the Department of Health and Welfare.

The main provisions of the original Food and Drug Act were:

1. books and records to be maintained,
2. prohibition of sale of commodities manufactured or stored under conditions of non-compliance with established standards,
3. an inspection program initiated for all drug plants, and
4. drug sampling prohibited to the general public.

Various amendments followed, including the establishment of standards for drug manufacturing and the prohibition of sale when hazards of use are evident. Then in 1963, major revisions were made to the Act which required submissions to be made prior to clinical testing of a drug (the Preclinical New Drug Submission [PNDS]), and prior to its marketing (the New Drug Submission [NDS]). The latter required evidence of safety and efficacy. In 1971, the QUAD program for review of classes of drugs and plant inspection reports was instituted. From that time until the present a few minor changes (additions) were made, including approval requirements for clinical protocols and new guidelines for procedures.

Some inconsistency continues to exist with respect to the drugs classified as prescription drugs (listed under Schedule F of the Act) and those considered under the Act to be over-the-counter (OTC) drugs. For instance, digoxin is not considered federally to be a prescription drug, although it is classified as such by some provinces.

There is a two-step process with regard to the approval of drugs in Canada. When a manufacturer first wishes to introduce a drug for testing which has never before been sold in the country (a New Chemical Entity), approval must be obtained. The submission must contain detailed information on the chemistry and pharmacy data of the drug, preclinical information on

pharmacology, metabolism and toxicology, any available clinical information from other countries, and details of the proposed study. This information must show the drug is safe. If the submission is found to be satisfactory, the HPB issues an approval to the manufacturer, who can only then proceed with the proposed clinical tests in Canada. Approvals must be obtained for each additional clinical test, and some departments request that separate submissions must be made for each investigator conducting each part of a clinical trial.

When a manufacturer wishes to market a drug, he must make a new drug submission (NDS) prior to this sale. This submission contains information similar to the original PNDS, together with any further information which may have become available. The manufacturer must also include a Product Monograph, which is the document containing the prescribing information which is to be made available to all medical professionals who are to deal with the drug.

Finally, whenever new information is submitted by the manufacturer with regard to new indications, new adverse reactions, or other changes to the Product Monograph, or new suppliers of raw materials, new formulations, or new stabilities, the manufacturer must file a Supplementary New Drug Submission and receive approval for any of the changes before the drug may be marketed in accordance with these amendments.

The Product Monograph is supposed to provide to professionals the approved prescribing information, devoid of advertising and puffery, which represents the uses and all precautions associated with the product. The manufacturer must, when the final Product Monograph is issued, promote his product only in accordance with this monograph information. Unfortunately, the Product Monograph in its present form is extremely long and complicated, containing large amounts of scientific, rather than medical, information (it can range from several to 60 pages in length). Because of the nature of the document, it is often unread by the professionals to which it is intended to be directed. Also, any changes to the Monograph (including warnings or limitations to be added) must be first approved by the HPB. The manufacturer may not make these changes by itself.

After a drug is put onto the market, serious adverse reactions to that drug must be reported by the manufacturer. The normal procedure is that if a serious adverse reaction occurs and a doctor feels a certain drug may be involved, he will report the incident to the manufacturer, who in turn reports to the HPB. But this obligation only goes as far as the manufacturer is made aware of such adverse reactions. Medical practitioners are under no similar legislative requirement to make such reports, and the drug companies and the HPB are faced with relying on their voluntary reporting of such reactions. Some provincial medical associations, and some medical specialty associations, have instituted voluntary reporting schemes. But this means that some difficulties may very well be overlooked, or not drawn to the attention of the regulatory authorities as quickly as possible.

The present legislation does not provide authority for the HPB to require a specific post-marketing surveillance program as part of the approval process. This means that if a drug is important, but there is some concern that it will cause difficulties, the HPB has no other course than to require additional clinical testing before the approval for marketing is granted. There is no ability to approve the drug with the imposition of a requirement for post-marketing surveillance tests on the manufacturer. The effect is that a potentially valuable drug may be held up from marketing because of concerns which would be better dealt with by post-marketing controls.

"...the efficacy of many drug uses can be evaluated without formal research, i.e., on the basis of clinical experience with the drug. It is also clear that when formal research is needed, non-experimental methods can sometimes be validly applied in post-marketing studies of drug efficacy. ...experimental studies will probably always have an important role in the investigation of drug efficacy after marketing, especially for the important questions of long-term drug effects modified by therapy and questions of relative efficacy. ...the scientific community's reluctance to accept clinical experience and non-experimental studies as the source of drug efficacy information, together with limitations in the applicability of the randomized clinical trial, has resulted in unnecessary gaps in the clinical information currently available. ...potential utility of clinical experience and non-experimental studies would result in the updating of drug labelling based on all the information available at any time after marketing. ...post-marketing research...is...suggested...as a necessary supplement [to pre-marketing research]."⁴⁷

If major problems are found with a drug, the HPB has the power to restrict its use (in effect to change the Product Monograph) or to withdraw its marketing approval.

Because of the major amendments in 1963, a distinction came into being between drugs marketed before and after 1962. These are termed, respectively, "Old Drugs" and "New Drugs." New Drugs require pre-market review whenever they are manufactured for each type of new formulation or by each new manufacturer. The same is not true for Old Drugs. Various anomalies may result; for instance, an Old Drug becomes a new one if it is to be marketed for a new indication.

Old Drugs as a class consist of basically those which were marketed prior to the 1963 amendments to the Act. There are provisions for making a New Drug into an Old Drug under the Act (for reasons of its proven safety), but this is rarely done. An Old Drug can be marketed by a new manufacturer without government authorities being informed of its origin, its quality, its stability, the conditions under which the finished product was manufactured, or the bio-availability of the active ingredient of the drug.

If the manufacturer wants a drug to be sold over the counter, it is submitted to and reviewed by the Bureau of Non-Prescription Drugs. New drugs are only referred to this Bureau for a marketing decision after being

⁴⁷ L. Strom, Alli S. Miettinen and Kenneth L. Melonan, "Post Marketing Studies of Drug Efficacy: How?" *American Journal of Medicine* 77 (October 1984), pp. 705-7.

reviewed initially by the Bureau of Human Prescription Drugs (all part of HPB). All submissions must be reviewed by the latter bureau with respect to the section dealing with pharmaceutical chemistry.

Another bureau, the Bureau of Biologics, deals with products of a biological origin, including vaccines, immunological agents, and hormones. This Bureau is required both to review submissions for clinical testing and marketing, and to inspect the manufacturing plants. All manufacturers of these products must be licensed. Thus one of the main functions of this Bureau is to exercise quality control over the manufacturers. This function is really an anomaly when considered against the duties in this area of the other parts of the HPB. The other branches deal only with quality control of plants as a check; if difficulties are found, approval for manufacturers may be withdrawn.

With respect to the time required for the approval process, toxicology testing of up to 18 months is required. PNDS approvals take approximately five months, and NDS approvals take approximately 24 months. This does not include the time required for clinical testing between the PNDS approval and the NDS application.⁴⁸ HPB deals with all its applications in-house. There is no provision in complex situations for a referral to any type of expert medical panel.

United Kingdom

In 1981, new streamlined regulatory requirements for drug clearance were introduced in the United Kingdom. The change has resulted in the pharmaceutical companies still being required to conduct the same tests and generate the same volume of information, but the requirements for submission of information to the Medicines Division has been reduced. In order to make application for an Exemption for a Clinical Trial Certificate, summaries of the data to support the studies are sufficient, together with an outline of the protocol of the study proposed, and a medical doctor's opinion that the study is reasonable. Approval must then be given for the proposal within 35 days. If it is refused, the company has the right to have the Committee on Safety of Medicines review the application. The company may make representations to this Committee. There is also scrutiny of protocols by ethics committees. If the local Ethics Committee refuses to permit a trial, the licensing authority must be notified.

The exemptions scheme for clinical trials applies to all proposed trials which would have previously required a certificate. Any company is at liberty to apply for a certificate in the usual way, and a company that has had an exemption refused may apply for a certificate. That application will then be referred to the Committee on Safety of Medicines.

⁴⁸ Ibid.

Previous to the amendment, the manufacturer had to get a Clinical Trial Certificate prior to commencing the tests. Now, with the application for the Exemption, if the Exemption is granted, the manufacturer may proceed with his trial providing he notifies the licensing authority of any of the following:

1. any change made to the protocol,
2. adverse reactions arising out of the trial,
3. any information casting doubt on the safety of the substance, and
4. any objections made by an Ethics Committee to the proposed study.

The experience with the new program seems to have been very positive. Both the time for granting of Exemptions has been much faster than the previous experience with the granting of Certificates, enabling drug testing to be initiated sooner than before (thus speeding the entry of important new substances to the market), and the number of Exemptions applied for and granted have indicated that the manufacturers and the medical community are finding the procedure useful (encouraging manufacturers to use the United Kingdom as a location to conduct clinical trials). Few Exemption applications were refused. In few cases was a full assessment of the raw data required.⁴⁹

With respect to the time required for approvals in the United Kingdom, toxicology testing is required for six months. PNDS submissions take about one month, as do trial protocols. Average time for approval of an NDS is about 5.8 months.

For complex Clinical Trial Certificate applications, the Department of Health and Social Security will refer the application for review to an advisory committee made up of experts from all fields of medicine, including pathologists, clinical pharmacologists, toxicologists, biochemists, biostatisticians, etc.

United States

Before the new rules for approval of generic drugs were passed recently, drugs first approved after 1962 were dealt with on a different basis than those approved previously. If the original had been approved earlier (that standard had been one of safety only), the Federal Drug Administration (FDA) permitted generic manufacturing without a requirement that the company duplicate previously approved tests. Drugs approved later could not be generically copied without the company basically duplicating the original safety and efficacy studies.

“The FDA rules on generic drug approval for drugs approved after 1962 have had serious anti-competitive effects. The net result of these rules has

⁴⁹ C.J. Spiers and J.P. Griffin, “A Survey of the First Year of Operation of the New Procedure Affecting the Conduct of Clinical Trials in the U.K.,” *British Journal of Clinical Pharmacy* 15 (1983).

been the practical extension of the monopoly position of the patent holder beyond the expiration of the patent. This is so because of the inability of generics to obtain approval for these post-1962 drugs without enormous expenditures of money for duplicative tests.”⁵⁰

Now the only tests which must be submitted are those which prove the generic is the same or therapeutically equivalent to the original drug.

The new Act also

“...permits generic applications to be effective after a patent expires. In addition [it] provides that a generic manufacturer may request FDA approval to begin marketing before the patent on the drug has expired....If the generic manufacturer seeks such an approval, it must allege that the existing patent is invalid or will not be infringed. In this instance notification must be given by the generic to the patent holder concerning the application for FDA approval. In these cases the FDA may not approve the generic application until either: (1) 18 months have expired or (2) a court has determined that no infringement will take place. After the expiration of 18 months, if there has been no intervening judicial determination, the FDA will approve the generic application, even if the drug is still on patent.”⁵¹

Finally, the Act “...provides for a four year grant of market exclusivity to be granted by the Commissioner of the FDA for unpatentable substances which have been approved for use as drugs by the FDA.”⁵²

It is not necessary to have protocols approved. As in France, they only must be filed. With respect to time for approvals, toxicology tests of 12 months duration are required. Innovative New Drug submissions (IND) take about one month, and approvals for marketing of new chemical entities vary between an average of 12.3 months for those with modest to major chemical advances, 19.5 months for those with minor therapeutic advances, and 11.3 months for all others (new indications, new formulations, etc.). (Data are for 1983.)

Negative responses from intramural staff are dealt with by the numerous expert non-governmental advisory committees.

Japan

Applications for registration of drugs may be refused on the general grounds of safety and efficacy, but if a therapeutic advantage over existing drugs is not statistically significant, if proof of safety and efficacy is considered insufficient, or if not enough local data is available (toxicology, teratology, pharmacology, etc.), the submission may also be refused. In practical terms, the time required for registration is one year, but can be up to three years for newly developed drugs.

⁵⁰ U.S. House of Representatives, *Drug Price Competition and Patent Term Restoration Act of 1984* Rept. 98-857, Part 2, p. 4.

⁵¹ Ibid., p. 5.

⁵² Ibid.

Reduced documentation may be submitted for drugs which do not represent a new chemical entity, those listed in the Japanese Pharmacopoeia, and non-prescription drugs. Generally these require only specifications and method of analysis with actual experimental data, stability data, and locally conducted bio-availability studies.

There is currently no requirement concerning prior authorization of clinical trials, but prior notification is required for some types of drugs. Trials must be performed by experienced doctors with adequate facilities. All studies must be carried out locally, the only use to which foreign data is put is as reference material. Japan requires toxicology studies of 12 months duration (the same as in the U.S.).

There is also no specific requirement to report scientific data generated after registration. However, serious adverse reactions must be reported immediately by the manufacturer. There are no legal reporting requirements on physicians.

Packaging leaflet information is required for almost all drugs; it must contain the method of administration, dosage, handling precautions, contraindications, warnings, indications, and side effects, etc.⁵³

France

There are no grounds for refusal of proper applications for drug registrations other than the commonly accepted criteria of quality, safety, and efficacy. Registrations are granted for a period of five years with provisions for five-year renewals at the request of the manufacturer. Any renewal is subject to a requirement that the manufacturer declare that no modification has occurred in the data submitted in support of the original application. In practical terms, the average approval time is six months. In terms of regulatory requirements, the Minister of Public Health must announce a decision within 120 days from receipt of the completed submission; exceptional extensions for 90 days are possible.

Reduced documentation may be submitted for drugs with well-known active ingredients, additional presentations of already marketed drugs, or specialties corresponding to formulations in the French Pharmacopoeia or in the French National Formulary. Analytical data (control of raw materials and of finished product) must nonetheless be submitted in all cases.

Before commencement, notice of clinical trials must be given to the Ministry of Health. All required trials must be carried out by experts selected from a list approved by the Minister, and procedures to be followed have been established by the Ministry. If the protocols set forth in regulations cannot be followed, the trial program must be submitted.

⁵³ Unless indicated otherwise, the source for this Appendix information on Japan, France, and West Germany is IFPMA, *Legal and Practical Requirements for the Registration of Drugs (Medicinal Products) For Human Use* (Switzerland, 1975).

Data from studies carried out in foreign countries will only be accepted if the scientists who conducted them are on the list of approved experts. France requires toxicology studies of six months duration (the same as in the United Kingdom). PNDS submissions take about one month for approval (see Table A1.2).

The Minister may also consult on applications with approved or designated experts.

With regard to adverse reactions, if the data in the original file change, the manufacturer must inform the Ministry. Physicians report serious adverse reactions to health authorities and to the manufacturer. The National Drug Monitoring Centre receives reports on these adverse reactions from health care specialists and government and analyses the data.⁵⁴

West Germany

In order to obtain approval to market a drug, only the normal criteria on quality, safety, and efficacy are required. Registration is valid for a period of five years with renewals. Generally the time period for approval is from one to three years.

Reduced documentation is possible for drugs which do not represent a new chemical entity and drugs with an existing pharmacopoeia monograph. Nonetheless, data must be included on control methods for active ingredients, analytical tests during development of the finished dosage form, and information on efficacy and tolerance.

Notification is required prior to commencement of clinical trials, but data on pharmacology and toxicology must be included. Trials must be conducted by physicians with experience in clinical investigation.

With respect to studies conducted in foreign countries, all investigations that are carried out correctly and are suitably presented are taken into account if they are conducted under conditions comparable to those in West Germany. Otherwise, additional clinical trials must be carried out in West Germany.

West Germany requires toxicology studies of six months duration (the same as France and the United Kingdom). Nothing more than notification is required for PNDS submissions and protocols.

Physicians report adverse reactions to the manufacturer and to the Drug Commission. A report on side effects gained during an initial marketing period is required to be submitted.⁵⁵

⁵⁴ Idem.

⁵⁵ Idem.

Table A1.2

**European Clinical Trial Requirements—Regulatory Documentation
(Either Supplied to a Regulatory Agency or to an Investigator)**

Country	Type of Study Volunteer (Phase I)		Early Clinical Trials Establishing Initial Safety and Efficacy (Phase II)		Longer Term Clinical Trials (Phase III)	Required by Investigator
	Single Dose	Multiple Dose	Single Dose	Multiple Dose		<div>A B C D</div>
Belgium					Additional data as it becomes available (Full reports may be required by some countries)	B (6 weeks) local Q/C testing may be required.
Holland						A/B (4-8 weeks) to arrange investigator and agency approval plus import certificate
Austria						B (approx. 3 months) study under the aegis of "authorized investigator"
Denmark	1,2,4(S), 5(S),6,7(S)	1,2,4(S),5(S), 6,8(S),13(S)	As volunteer studies 1 13(S)	1,2,3,4(S),5(S), 6,8(S) or 9(S), [11(S)] + 13(S)		C (2 weeks)
Finland						B (8 weeks)
Greece						D/A (2 months) plus import certificate from KEEF (2 weeks)
Norway						B (2-6 weeks)
Spain						B (3-6 months) government approved centre

Sweden				
Switzerland				
France	-----Illegal -----		1,2,3,4,5,6, 7 + 13(S)	1,2,3,4,5,6,8 or 9,11 + 13(S)
W. Germany	1,2,3,4,5,6,7	1,2,3,4,5,6, 8 + 13(S)	As phase I	1,2,3,4,5,6,8 or 9,11,12, + 13(S)
Italy	1,2,3,4,5,6, 7,12	1,2,3,4,5,6, 8,12	As phase I	1,2,3,4,5,6, 8 or 9,11,12
U.K.	None 1,2,4(S), 5(S),6,7(S)	None 1,2,4(S),5(S) 6,8(S),13(S)	1,2,3,4,5,6,7, 12 + 13(S) 1,2/3(S),4(S), 5(S),6,7(S), 12(S) + 13(S)	1,2,3,4,5,6,8 or 9,[11],12,13(S), 14 1,2/3(S),4(S), 5(S),6,8(S) or 9(S),[11(S)], 12(S) + 13(S)
Eire	1,2/3(S), 4(S),5(S),6, 7(S),12(S)			

B (6 weeks)
A—signed, agreed protocol
C (2 weeks) assumes “expert” approval (can take up to 3 months)
D
B (6-12 months) assumes local Q/C testing completed. Local, repeat pharmacology/toxicology testing may not be required.
B (4-6 months)
B (5 or 9 weeks)
B/C (4-8 weeks)

Notes to Table A1.2

European Clinical Trial Requirements—Regulatory Documentation

Table A1.2 summarizes the experience of a number of companies in the countries concerned. It is believed to be accurate but no responsibility can be accepted either by its compilers or by the ABPI in respect of any errors or omissions which it may contain. It should be borne in mind that requirements are subject to frequent changes.

Key

1. Structural formula and Quantitative/Qualitative formula
2. Protocol of Analysis of Clinical Supplies
3. Specs. and test methods for formulated product
4. Pharmacology
5. Pharmacokinetics
6. Acute Toxicity
7. 14 day 2 species
8. 30 day 2 species
9. 90/180 day 2 species
10. Seg. I Fertility
11. Seg. II Teratology
- [11.] Seg. II Teratology only required if women of child bearing potential are to be included in the trial
12. Mutagenicity
13. Phase I results (if available)
14. Overall summary
15. Summary of data

Ethical Committee Approval

In addition to regulatory agency approval, Ethical Committee approval is also required in some countries.