NOTICE OF COMPLIANCE (NOC)

PROCEEDINGS IN CANADA

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HISTORY

The position of inventions respecting medicines has historically been different from a patent perspective, from inventions relating to anything else, except for food. A classical patents invention may give an owner a monopoly for up to twenty years on say a bicycle or a chemical dye. When it comes to medicines, particularly those that save lives or alleviate suffering, there is a public reaction against monopolization.

In Canada, and still in some countries, patents for food or medicine were originally prohibited. Later in Canada patents for food or medicine were permitted, but only when they were prepared by a particular process. Still later, the prohibition was lifted and patents were permitted for new foods and medicines.

When patents for foods or medicines prepared by a particular process were permitted the "trade off" given to the public was that any person wishing to sell such medicine in Canada could apply to the Commissioner of Patents and, almost inevitably, receive a compulsory license to sell that medicine in Canada (usually at a rate of 4% for the finished product or 15% for the bulk product).

When patents to the medicine itself, regardless of process, was permitted as of 1993, the compulsory license regime was eliminated and replaced by the Notice of Compliance (NOC) Abbreviated New Drug Submissions (ANDS) procedure. Essentially that procedure was modelled, very imperfectly, on a system adopted in the United States called the Hatch-Waxman Act. This procedure allowed a generic drug company to copy a drug for which approval to sell had already been given by the government health authority provided that if the original company who received approval had one or more patents relating to that drug, an expedited process for dealing with issues as to infringement and validity of these patents was provided. This process does not replace the ordinary patent infringement/validity action and, in fact, is not binding on the parties in a res judicada sense. It was intended as a summary process to determine initially if any valid claim of any patent would be infringed if the generic sold the drug in Canada. If yes, the Minister of Health was prohibited from granting approval (NOC) to the generic to sell the drug. If no, then the generic would get approval, put the drug on the market, and ordinary patent actions could be taken if anyone was so advised.

APPROVAL TO SELL A DRUG

The Minister of Health is responsible for administering a system, through the Health Protection Branch, Therapeutic Products Division (TPD), for approving drugs for sale in Canada. The approval takes the form of a Notice of Compliance (NOC) and the drug will receive a Drug Identification Number (DIN).

A party seeking such approval will make a New Drug Submission (NDS) in which it must demonstrate to TPD the safety and efficacy of the drug. Usually years of clinical trials, in laboratory vessels, on animals, on humans, are conducted. All very expensive.

The drug may be deemed to be effective but only for certain defined uses, and subject to certain precautions. The uses and conditions together with other information, is compiled in a product monograph, the form and content of which is the subject of much negotiation with TPD. The product monograph is a public document but usually is provided only to physicians and pharmacists. The labelling of a drug and packaging which the consumer will see are abbreviated versions of the product monograph and contains essential information as to usage, dosage and conditions under which the drug is to be taken. Again all of this is the subject of much negotiation between the applicant and TPD.

The NOC procedure instituted in 1993 permits a "generic" drug company to submit an Abbreviated New Drug Submission (ANDS) in which it is permitted to refer to the studies of the original drug company (often called the "brand" or "innovator" or, in the Regulations, the "first party") and to copy the brand's product monograph and labelling. The generic is allowed to make small differences in its drug provided it can show that its drug is "bioequivalent" to the brand's drug, that is, it is biologically the same when taken by a patient

If the generic can demonstrate by laboratory and perhaps clinical testing, which is much less rigorous that the initial company's testing, that its drug is bioequivalent then the generic will receive an NOC and DIN, unless there is an order of the Court prohibiting that issuance. A brand company that owns one or more patents related to the medicine or its use and it has listed those patents with the Minister must be served with Notice of Allegation by the generic stating that:

- it will wait until the patent expires before selling the drug
- the party listing the patent is not the owner or does not have permission from the owner
- the patent is invalid
- the patent will not be infringed

The brand may then institute summary proceedings a court (usually Federal) to prevent an NOC issuing to the generic on the basis that the allegation(s) is (are) not justified. The win/lose consequences have been previously discussed.

CHEMISTRY

Medicines are the essential ingredient which are mixed with other materials (excipients) to create a drug which is administered to a patient.

Essentially medicines are of two types:

- Chemical
- Biological

Chemical medicines are made from inanimate ingredients, elements and molecules. Biological medicines are made from cells and organisms. While it is possible that biological medicines could be the subject of NOC proceedings, since the production of

these medicines is complex and dependent upon acquiring the correct strain of molecule for production, so far there have been no proceedings respecting such medicines.
Chemical medicines can be composed of relatively simple molecules, such as aspirin, a derivative of vinegar, or much more complex molecules involving chains of molecules, ring structures, three-dimensional manifestations and so forth. When complex molecules are studied, it is usual that a "family" of such molecules, involving the substitution of different parts or changes in the three-dimensional configurations are studied. Often only a few members of the family offer significant medicinal properties. The sorting out can be tedious or subject to a "lucky break". Sometimes when one company discovers an effective molecular structure, a competitor will work "around" that structure and find an unpatented structure having similar medicinal properties.

PHARMACY

For these purposes, pharmacy can be considered to be the art and science of preparing a medicine in the form of a drug and its administration for appropriate uses subject to appropriate safeguards.

A medicine, the essential ingredient, is almost never taken as such, it is "formulated" with other ingredients, usually called "excipients" to make it suitable for administration. Common excipients include:

- fillers (to "bulk-up" the drug)
- stabilizers (so the drug will have suitable shelf life)
- lubricants (so that the tablets will be made well)
- diluents (to disperse the medicine)
- flavourings

The precise formulation of a medicine into a drug is a skill unto its own and can make or break the success of the drug. TPD will permit a generic to vary its formulation from that of the brand, provided bioequivalence can be demonstrated.

The form in which the medicine is administered can vary, to name a few:

- oral (tablets, capsules, liquid)
- injection
- transdermal patch
- Topical (creams, etc)

Stability of a drug is critical. How long can it be kept for instance in a medicine cabinet near a hot steaming shower. Often two years is a criteria. Medicines sensitive to acid may need to be mixed with an alkali (base) medicines sensitive to moisture may need to be kept dry. Medicines that break down in the stomach may need to be coated so they release only in the intestines.

The uses to which a medicine may be put are limited by TPD essentially a use must be shown to be safe and effective, supported by clinical studies. A medicine may be approved for use only in respect of a certain condition and subject to certain constraints as set out on the label in the product monograph. New uses may be discovered and subsequently approved by TPD.

Some medicines may enhance the effect of other medicines for certain uses, thus a combination of medicines for certain uses may be approved by TPD.

THE NOC REGULATIONS

The NOC Regulations provide in brief, a summary process instituted by a first party who owns or controls one or more patents relating to a drug, to prohibit the Minister of Health from issuing a Notice of Compliance to a generic drug company which would otherwise permit the generic to sell that drug in Canada. The whole process, from the date an Application is filed with the Court Registry, until final judgment is issued by the Federal Court, must be done within twenty-four months (subject to extensions on consent or ordered by the court). Once the Application is filed there is, in effect, an injunction preventing the Minister from the issuing a Notice of Compliance until the proceeding is determined or withdrawn. The pressure on the court system to do its part within twenty-four months, is onerous.

a) Listing a Patent

The Regulations contemplate a "first party" who is usually a "brand" or "innovator" drug company, who has or has applied for approval to market a drug in Canada. That company may own, or be licensed under a patent or simply have "approval" of the owner to list a patent relating to the drug.

The timing as to what patents can be listed is tricky. The patent must have been applied for in Canada prior to the first party applying for approval from the Minister to market the drug in Canada. Where the patent has not issued before the application to market is filed, it must be listed within 30 days from the date of issuance.

Patents that "relate to" the drug are also tricky. Where the drug is approved only for certain uses, patents relating to other uses may not be listed (subject to new Regulations).

Patents can be "reissued" to correct errors, they should be re-listed within 30 days of reissue.

Only patents relating to medicines or their use can be listed. No patent relating to a process, or to how a medicine is administered (e.g. transdermal patch patents) can be listed).

b) Generic Notice of Allegation

A generic "second party" who files an Abbreviated New Drug Submission (ANDS) for a drug in respect of which one or more patents are listed must serve on the first party a Notice of Allegation (NOA) stating one or more of:

- it will wait for approval until after the patent has expired
- the listing party is not the owner or licensee of the patent, or has no consent of the owner, to list the patent
- the patent is invalid
- the patent will not be infringed
- the patent has expired

The NOA has been held by the court to be a critical unamendable document. It must deal with every issue, it must set out its "factual and legal grounds" asserted by the generic as to every issue. Subsequent NOA's can be filed provided they raise new and different issues, however since each NOA starts a new process, the generic may face a series of twenty-four month injunctions.

Unlike in the United States, a first party can add patents to the list even after an NOA has been issued, requiring the generic to serve a new NOA as to the new patent.

The first party has forty-five days from service of the NOA to institute summary proceedings to prohibit the Minister from issuing an NOC to the generic. Once these proceedings are instituted the Minister is prohibited from issuing an NOA for up to twenty-four months, or earlier until the proceedings are over.

c) Proceedings

The proceedings are instituted by the first party by the filing of a Notice of Application to prohibit the Minister from issuing an NOC. The first party is not obliged to assert every claim of every patent listed. The first party is not obliged to challenge everything which is raised in the generic's Notice of Allegation.

The Notice of Application usually contains a very detailed recital as to the patents which the first party wished to put in issue and the basis for its position. The generic usually files only a simple Appearance and no substantive response.

The "pleadings" are, in effect, its Notice of Allegation made by the generic (second party) and the Notice of Application filed in court by the brand (first party).

It is generally conceded that, once an issue is raised, the brand bears the onus to prove infringement and the generic the onus to provide some evidence of invalidity.

A schedule is often worked out by the parties as to when affidavits are filed and cross-examination conducted. Sometimes a party wants to strike out all or parts of an affidavit of its opponent. The usual result is, leave it to the trial judge.

The trial (hearing) is conducted only on the basis of written material, the "pleadings" including the NOA and Notice of Application the affidavits and cross-examination transcripts.

A decision is required from the Court within twenty-four months from the filing of the application with the court by the first party.

d) <u>The Disincentive – Section 8</u>

There is a disincentive provided by section 8 of the Regulations to make a first person (brand) cautious in instituting NOC proceedings. If the brand loses, the generic can sue for "damages" for any delay in obtaining its NOC caused by the proceedings. Usually it takes up to two years anyway for a generic to get approval thus the "delay" may be somewhat problematic.

Some proceedings have been instituted under section 8 but none yet fully decided thus much more is expected.