Process Patent Act & Export of Drugs and Pharmaceuticals

B N Roy and Ms Swati Veera

Lupin Laboratories Ltd, 31-A, 46-47A, 2nd Floor, Raj Industrial Complex, Military Lane, Mumbai 400 098.

This paper deals with process patent infringement issues about which Indian exporter of bulk drugs and formulations should be aware of, to avoid infringement. The infringement issues are discussed with respect to Process Patent Acts of a few industrialized countries. The Process Patent Acts of two leading countries viz. USA and UK are interpreted with reference to case studies.

The Pharmaceutical industry is one of the fastest growing industries in the world and the growth of pharmaceutical industries in India over the past 15 years is spectacular. The production of bulk drugs for 1980-81 was about Rs 240 crores and that of formulations was Rs 1200 crores, which jumped to Rs 1518 crores and Rs 7935 crores respectively in 19951. The pharma production i.e. both bulk drugs and formulations is expected to grow to about Rs 16,000 crores by 20002.

A wide range of bulk drugs are being manufactured and exported to other countries by Indian industries. According to IDMA the exports from India would increase at the rate of 25% per annum. India is now well poised to take the advantage of growing export markets especially in the developed countries for supplying both bulk drugs and formulations.

Out of the ten leading countries USA dominates the generic market. In the year 1994 the value of generics in USA leaped to 5.2 billion dollars and expected to reach 9.5 billion by the year 20003. In the European Union (EU) generic market, the value of generics currently is 6 billion US dollars which accounts for about 15% of the total pharmaceutical market4. Thus, the global generic market is rapidly growing and Indian Pharma Industries should prepare for the competition. The global generic market offers substantial opportunities to Indian Pharmaceuticals since about 120 branded drugs are coming off patents by the end of this century5.
A branded drug becomes generic in a territory when its product patent expires in that territory i.e. inventor no longer enjoys the monopoly of the compound or the composition of the matter. In principle anybody could market the generic product in that territory provided the marketer or the exporter does not infringe any Process Patent Act of that country.

Generally, one would notice that a large number of process patents are taken by the inventor or any interested organization, for the synthesis of a drug and its intermediates. Moreover, processes are upgraded very frequently for improvement in cost, quality and operations, and all these improvements are embodied in new process patents. One would notice a large number of process patents are taken, even for each individual step and their improvements for the synthesis of the final product. This is more so for high value and high volume drugs.

Hence, to be a successful exporter one should not only have a cost-effective process which gives desired quality but also have the processes outside the purview of the Process Patent Act of the targeted territory. This calls for understanding and appreciation of the Process Patent Act of each of the individual country for developing a strategy for the manufacture of the drug in India for export to other countries.

The salient features of the Process Patent Act of a few developed countries vis-a-vis infringement issues are:

**United States of America**

The patent system in the USA is under the control of the US Patent and Trademark Office (USPTO). The US Patent Law recognizes three basic types of inventions for which patents can be obtained products, methods of use, and process (method of manufacture).

Prior to enactment of Process Patent Amendment Act, 1987, anybody could export to US any product after expiry of the product patent by manufacturing the product outside the country by employing the teachings embodied in subsisting US process patents. US manufacturers, particularly of drugs, pesticides, fine chemicals and such like, urged US Congress to enact the Process Patent Amendment Act mainly to prevent export from other countries.

The process patent protection in USA is provided under the Process Patent Amendments Act of 1987 which came into effect on February 1989. This Act protects the process patent owners against unauthorized sale or use of products made by the patented process.

The provisions for infringement of process patents prohibiting the importation, Use or Sale is given under section 35 USC 271(g) which is quoted as:

"Whoever without authority imports into the USA or sells or uses within the USA a product which is made by a process patented in USA shall be liable as an infringer, if the importation, sale or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other sale of that product.

A product which is made by patented process will, for purpose of this title, not be considered to be so made after -
1. it is materially changed by subsequent processes; or

2. it becomes a minor or nonessential component of another product."

The clause of Sec 35 USC 271(g) which states that the product which is made by a patented process will not be considered to infringe the said process patent if the said product is materially changed by subsequent processes; can be further explained as follows:

If a chemical 'A' which is produced by a patented process is imported, used or sold by anyone in the country, then that person is liable for infringement of the said process patent.

However, if the chemical 'A' is subsequently subjected to further processing steps to obtain a clearly different chemical 'B' i.e. the basic characteristics of chemical 'A' is changed during its transformation to chemical 'B' which results in breaking of the connection between the patented process and the chemical 'B' then the importation, sale or use of chemical 'B' does not constitute infringement of the said process patent.

However, trivial or conventional modification of chemical 'A' e.g. formation of simple derivatives, including salts or esters or removal of impurities is not considered as material change and anyone practising this is liable for infringement.

Also, change in shape, size or form of chemical 'A' which is product of the process patent is not considered to be material change.

Thus, liability for infringement exists if the end product of the process patent is an important or essential component of second product. No liability for infringement would exist if the end product is a minor, non-essential component of the second product.

If the synthesis for a product, P, involves following steps, \( R \rightarrow A \rightarrow B \rightarrow C \rightarrow D \rightarrow P \) one has to identify which is the “Bottleneck” or the “key step”, whether the intermediate has acquired many of the characteristics structurally and otherwise, of the final product i.e. the nexus between the intermediate produced in such a step and the final product exists then such a step would infringe 271(g) of 35 USC. Such assessment except in simple and straightforward cases could be difficult. Two recent judgements on infringement of 271(g) are cited for better appreciation of the spirit of the Process Patent Act.

### Diltiazem Case (Case No: 92-5198 District Court of New Jersey)

M/s MMD is licensee of a US Patent (USP 4 438 035) assigned to it by M/s Tanabe. M/s ABIC is an Israeli Corporation who manufactures diltiazem hydrochloride in Israel which is imported into the USA by M/s Plantex for resale to M/s American Cyanamid.

MMD filed an infringement suit against ABIC alleging that diltiazem hydrochloride manufactured by later falls within the scope of their patent.

The patent under suit (USP 4 438 035) relates to a process for the manufacture of benzothiazepine derivatives i.e. diltiazem precursor wherein the product is obtained by N-alkylation of 3-hydroxy or 3-acetoxy-1, 5-benzothiazepine derivative with the appropriate alkylating agent. Though 3-acetoxy-1, 5-benzothiazepine derivative is neither claimed nor disclosed in the said patent.
The defendant argued that since there is no reference to acetylation in the claimed process of the patent and the product, diltiazem hydrochloride manufactured by them is obtained by subsequent acetylation and hydrochlorination of the said 3-hydroxy benzothiazepine derivative hence, the claim 1 of the said patent is not infringed.

The defendant further argued that product which is imported by them in USA is diltiazem hydrochloride and not the diltiazem precursor. Since the diltiazem precursor is materially changed by subjecting it to subsequent process steps such as acetylation and hydrochlorination to obtain the final product, diltiazem hydrochloride and hence they do not infringe 35 USC 271(g) of Process Patent Act 1988. However, the court rejected ABIC's argument of material change on the basis that the subsequent process steps i.e. acetylation and hydrochlorination are simple conversions and hence, the final product obtained cannot be considered as a material change from the intermediate i.e. the diltiazem precursor. Also both the said precursor and diltiazem hydrochloride possess vasodilating activity and therefore the court affirmed that the importation of diltiazem hydrochloride manufactured by ABIC into USA is infringement of the said US patent under 35 USC 271(g) of the Process Patent Act.

Cefaclor Case (IP 95 536 C-B/S District Court of Indiana)

The plaintiff, M/s Eli Lilly filed an injunction suit against M/s American Cyanamid, and others in the US district court of Indiana for infringing the US patent i.e. US 4 160 085 licensed to them by M/s Shionogi, for synthesis of an intermediate for manufacture of cefaclor. The said patent describes a process for the synthesis of key or bottleneck intermediate i.e. 7-acylamido-3-hydroxy-3-cephem-4-carboxylate.

The plaintiff alleged that M/s Biochimica Opos, an Italian corporation, manufactures cefaclor in Italy by utilizing the process disclosed in the said patent under suit and sells it to each of the defendants i.e. American Cyanamid, Biocraft and Zenith.

Cefaclor is a broad spectrum beta-lactam antibiotic which is one of the largest selling antibiotic in the United States. Manufacture of cefaclor constitutes a number of steps and numerous patents related to cefaclor and its intermediates have been granted to Eli Lilly. The plaintiff argued that 7-acylamido-3-hydroxy-3-cephem-4-carboxylate which is the product of the patent under suit, is a key intermediate for cefaclor. The plaintiff further argued that nobody can manufacture cefaclor without utilizing the said 7-acylamido-3-hydroxy-3-cephem-4-carboxylate and all the three patents for the synthesis of the said intermediate utilizing different chemistry have been granted or licensed to them (Eli Lilly).

The plaintiff alleged that Biochimica Opos manufactures cefaclor utilizing the process disclosed in the said patent under suit wherein cefaclor is prepared starting from Penicillin G [a 4-thia-1-azabicyclo(4.2.0)heptane compound] which is converted to thiazoloazetidinone compound which undergoes ring opening followed by cyclization through a number of steps to yield 3-hydroxy-5-thia-1-azobicyclo(4.2.0)octane compound i.e. the said 3-hydroxy-3-cephem compound having a cephem nucleus. The plaintiff alleges that the 3-hydroxy-3-cephem compound is the key intermediate for cefaclor and formation of the same is the key step and the defendants convert the said intermediate to cefaclor by four steps involving substitution of hydroxy group by chlo-
ride at position 3, two deprotection steps i.e.
deamidification and de-esterification and addi-
tion of the phenylglycyl addendum at posi-
tion 7. It further argues that each of these
steps are conventional, simple chemical re-
actions and hence, the transformation of the
said intermediate to cefaclor is trivial, antici-
patory and not bringing about any material
change since the cephem nucleus of the said
intermediate remains unchanged in the final
product i.e. cefaclor.

On the basis of the above argument the
plaintiff requested the court to grant them
injunction against the defendants.

On the other hand the defendants argued
that the said intermediate is materially
changed by subjecting it to subsequent sub-
stantial processing steps to obtain cefaclor
and also affirmed that the said 3-hydroxy-3-
cephem compound and cefaclor are two dif-
ferent compounds in terms of structure,
chemical and biological properties and
hence, their process is out of purview of
271(g) of the

Process Patent

'Eli Lilly appealed against this verdict in the
Federal Circuit court, and it upheld the deci-
sion of District Court of Indiana.

United Kingdom

In UK, the process patent protection is pro-
vided under Section 60(1)(c) of the Patent
Act 1977 which confers right of exclusive
use of the invention to the patent holder
thereby preventing others from using or put-
ting into practice the said invention. The
actual terms of the subsection 60(1)(c) are
quoted as below:

60(1) "subject to the provision of this section
a person infringes a patent for an invention
if, but only if, while the patent is in force, he
does any of the following things in UK in
relation to the invention without the consent

of the proprietor of the patent that is to say....
(c) where the invention is a process, he dis-
poses of, offers to dispose of, uses or imports
any product obtained directly by means of
that process or keeps any such product
whether for disposal or otherwise."

There are not many court cases existing for
clear understanding of the subsection
60(1)(c) of Patent Act 1977 and also the
opinion of attorneys differ on the interpreta-
tion of the word “directly” of the Process
Patent Act. One case which throws some
light on the interpretation of the word “di-
rectly” of 60(1)(c) of the Process Patent Act
1977 is discussed below:

Pioneer Electronics vs M/s
Warner Music (CH 1994 P No.
996 and CH 1994 P No. 4321
The High Court Chancery Division
Patents Court)

In this case, the plaintiff, alleged that the
defendants infringed European Patents viz.
assigned to them by utilizing the process
disclosed in the said patents for the manu-
facture of optical discs and imported the
same in UK.

The defendants admitted that the process
claimed in the said patents under suit have
been utilized by them at a certain penulti-
mate stage of production of the optical discs.
In other words the products of the claimed
inventions were intermediate products of
the process used by them to produce the
optical discs. However, they further argued
that the products of the claimed invention
were subjected to subsequent process steps
to arrive at the final product i.e. optical discs
which were imported in UK.

In this case the court's ruling was in favour
of the defendants on the basis that the sub-
sequent processing steps utilized by the defendants were material steps and therefore, the earlier steps were not relevant. Since the final product was not immediate product of the process disclosed in the European patents under suit, hence, 60(1) (c) of the Process Patent Act 1977 is not infringed.

Thus the word “directly” of 60(1) (c) of The Process Patent Act is interpreted as “without intermediary”.

The Process Patent Act of some of the industrialized countries can be well compared with Process Patent Act of USA and UK and these are briefly discussed below:

**Denmark**

The new Danish Process Patent Act of 1978 provides process patent protection under section 3(1) wherein the exclusive right is conferred to the patent holder and no one can use the invention without the permission of the patent holder and the terms of the Process Patent Act section 3(1) are as given below:

“(1) The exclusive right conferred by a patent shall imply that no one except the proprietor of the patent may without permission exploit the invention: (i) by making, offering, putting on the market or using the product which is the subject-matter of the patent or by importing or stocking the product for these purposes;

(ii) by using a process which is the subject matter of the patent or by offering the process for use in this country if the person offering the process knows, or it is obvious in the circumstances, that the use of the process is prohibited without the consent of the proprietor of the patent."

**France**

In France process patent protection is provided under articles 28 and 29 wherein the patent holder is provided with exclusive rights of using the patent thereby prohibiting others from using the patent without his consent and is quoted as follows:

Article 28

1. The scope of protection conferred by a patent shall be determined by the terms of the claims, the description of the invention and the drawings, however, shall serve to construe the claims.

2. Where a patent relates to a process, the protection conferred by the patent shall extend to the products directly obtained by that process.

Article 29

A patent confers the right to prohibit any other person, without the consent of the proprietor of the patent:

(a) from making, offering, putting on the market, using, or importing or storing for such purposes the product to which the patent relates;

(b) from using the process to which the patent relates, or where such other person knows, or where it is obvious in the circumstances, that the use of the process is prohibited without the consent of the proprietor of the patent, from offering the process for use within French territory;

(c) from offering, putting on the market, using, or importing, or storing for such purposes the product obtained directly by the process to which the patent relates.
Germany

The old Germany Patent Act of 1877 did not have any provision for the protection of products of patented processes. Later an amendment in the Patent Act made a necessary provision for the protection of the products of the patented processes. However, the law was framed in such a manner that the protection was restricted only to the products obtained directly from the patented process and is not extended to the products obtained by subsequent process steps.

Thus, the provision for the protection of process patents is provided under Article 74 of the German Patent Act the terms of which are quoted below:

Article 74

"(2) A person making such use intentionally or negligently shall be liable for compensation to the injured party for the damage suffered therefrom. If the infringer has acted with only slight negligence, the court may fix, in lieu of compensation, an indemnity being between the damage of the injured party and the profit which has accrued to the infringer. (3) In the case of an invention whose subject matter is a process for the production of a new substance, any substance of the same nature shall, in the absence of proof to the contrary, be deemed to have been produced by the patented process."

Italy

In Italy, the exclusive use of the patent related to a new industrial method or process is conferred upon the patentee and it is quoted as follows:

"The patent concerning a new industrial method or process confers upon the patentee the exclusive use thereof. The exclusive use includes commercializing the product directly obtained by the new industrial method or process. If the product is a new one, then every identical product is presumed to have been obtained, unless there is evidence to the contrary, but the method by using the process of the patent, unless there is evidence against the same."

Japan

In Japan, the process patent holders are provided protection under the process patent act which is quoted as below:

"Working" in respect of an invention in this law shall mean the following acts:

(1) In an invention of a thing, acts of manufacturing, using, transferring, leasing, exhibiting for the purpose of transfer or lease, or importing the thing;

(2) In an invention of a process, acts of using the process.

(3) In an invention of a process of manufacturing a thing, acts of using, transferring, leasing, exhibiting for the purpose of transfer or lease, or importing the thing produced by the process in addition to those as mentioned in the preceding items."

Sweden

The process patent protection in Sweden provides exclusive use of the patent to the patent holder under Sec.3 of the Process Patent Act which is as quoted below:

"The exclusive right conferred by a patent implies, with the exceptions stated below, that no one except the proprietor of the patent may, without the proprietor's consent, use the invention by:

(1) making, offering, putting on the market or using a product protected by the
patent or importing or possessing such product for these purposes;

(2) using a process which is protected by the patent or, while knowing, or it being obvious from the circumstances, that the use of the process is prohibited without the consent of the proprietor of the patent, offering the process for use in this country;

(3) offering, putting on the market, or using products made by a process protected by the patent or importing or possessing the product for these purposes."

Switzerland

In Switzerland a Process Patent is protected under Sec. 67 of the Process Patent Act which is quoted below:

“If the invention concerns a process for the manufacture of a new product, every product of the same composition shall be presumed to have been made by the patented process until proof to the contrary has been adduced.”


<table>
<thead>
<tr>
<th>Country</th>
<th>Process Patent protects its direct product</th>
<th>Importation constitutes infringement</th>
<th>Presumption in favour of process patentee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>France</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>-</td>
<td>Yes*</td>
</tr>
<tr>
<td>Japan</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>UK</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
</tr>
</tbody>
</table>

* Applies to new substances only.

Conclusion

The Process Patent Acts of each of the country are different and need thorough appreciation. Any manufacturer desiring to export any bulk drug or pharmaceutical must carry out a thorough patent search on process patents and identify patents which relate to their process. This is best done by carrying out searches through various databases or various patent offices or outside organizations.

Once the synthetic scheme for a particular molecule has been selected, infringement searches must be carried out in the respective country by a specialist and/or by the patent attorneys of the respective territory. Such type of activity is imperative for a drug or pharmaceutical whose product patent has just expired or expiring soon and a number of process patents exist. Incidentally, this is the most opportune moment for entering the generic market for obvious reasons.

It must be noted that infringement searches are complex and must be done keeping a number of things in mind such as literal infringement, anticipatory infringement and infringement due to doctrine of equivalents which is best done by experienced patent attorneys. The problem is complex in the
area of biotechnology since even the attorneys are not sure of the interpretation of patent laws in this field and also changes being brought about in the laws e.g. modification in 35 USC 103(b) in 1995.

If a novel process is developed it is important to carry out novelty search for each step and the export should be attempted only when whole sequence is found satisfactory, because the cost to be incurred in infringement/injunction suit is prohibited and more often than not would be beyond the means of Indian companies.

It is strongly recommended that to achieve the above, the exporter must develop necessary expertise in patent system within the organization and importantly R&D be focused for innovation rather than Indianization of existing knowledge or colourful imitation.

References