

The peculiar patent and generic situation in Spain

When Spain modified its laws on generics it introduced an unusual and controversial set of regulations. The following pages look at these changes, and provide the opportunity for industry figures to air their views.

Professor Pascual Segura

On December 30, 1996 the Spanish Medicines Law was modified to include new generic medicines called especialidades farmacéuticas genéricas (generic pharmaceutical specialties). These generics are governed by a peculiar set of conditions not shared by their counterparts in other countries of the European Community.

Under the modified law, all packs of generics will be required to carry the acronym EFG (especialidades farmacéuticas genéricas). The products will be sold under international non-proprietary names (INNs) plus the manufacturer's name or trademark. The new law states that if a doctor prescribes an EFG, the pharmacist may substitute but only with another EFG. It also states that an EFG must be proven bioequivalent to a 'reference product' which has an 'efficacy and safety profile well established by its continued clinical use'. The introduction of a form of reference pricing is also contemplated.

Exclusivity

An interpretation of these changes to the law followed on February 6, in Circular 3/97 of the Spanish Health Ministry's directorate general of pharmacy (DGFPS). It ruled that, for the purposes of EFG registration, the reference product must have been registered for ten

years in Spain, or a corresponding generic has to be approved in a country of the European Community in which product patent protection for the active principle was available.

These rules have been presented by the DGFPS as a compromise, which, it argues, takes into account the opposing interests of the different industrial sectors as well as the government's interest in generic medicines as a way to reduce the growth of expenditure on reimbursable medicines. But it is evident that the interpretation of the law in the Circular – and not the law itself – has created a peculiar registration-derived exclusivity.

Under Directive EEC 87/21, which was implemented in Spain by Royal Decree in 1993, original pharmaceuticals in Spain, Ireland, Luxembourg, Greece, Portugal and Denmark were afforded six years' protection. In all other countries of the European Community the period of protection is ten years. However, Circular 3/97 rules that this period of exclusivity can extend beyond the six years provided by the directive. The extra time involved will depend on the case,

because the ten-year exclusivity period of the Circular relates to the granting of marketing authorisation, and takes effect from the first authorisation of the original product in Spain, whereas the six-year protection period of the Directive relates to filing of an abridged application, and takes effect from the first authorisation in the European Community.

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instead of the six legally approved. However, the European Generic medicines Association has said it will refer these rules to the EC Commission to investigate their legality¹. It is important to note that these rules, which have been established in an administrative circular rather than in law, are relatively easy to modify.

A peculiar market

Spain is the seventh largest pharmaceutical market worldwide but it has a very different market structure from most other countries of the European Community. In fact it is a co-marketing paradise. Multinational R&D-based companies are well established in Spain and market their own branded original products. But most blockbuster drugs are also marketed by two or three national companies as branded licensed products. Co-marketing currently serves both sides, but this may change in the near future when innovative products enjoy product patent exclusivity.

Besides this reliance on licences, the largest Spanish-owned companies (the merged Almirall-Prodesfarma, Esteve, Ferrer, Uriach, etc), and a few smaller ones, carry out important R&D and market their own original branded products. Original and licensed products together account for about 70% of the market. The rest is made up of a myriad of branded copy products, many of them priced similarly to original or licensed ones. This practice has thrived because of Spain's unusual patent system (see following page) and because health authorities have accepted abridged applications, without bioequivalence.

Ciprofloxacin, enalapril and omeprazole, for instance, each have more than 15 branded copies, despite considerable patent litigation. Famotidine has more than 20 copies, two of which were even marketed prior to the launch of the first licensed brand. However, for the new chemical entities (NCEs) launched in the last five or six years, only the original product

and two licensed products have been authorised. Contrary to what has been said, this current policy of the Health Authority is not the result of a change in the patent system, because the first patents of all commercial NCEs are still old-law process patents. This policy affects, for instance, fluoxetine, lovastatin, simvastatin and sumatriptan.

In Spain there are already about 100 INN-named products, which represent about 1% of the market. The most important ones commercially, such as Calcitonina-Almirall, Elcatonina-Cepa, Aciclovir-Alonga, Diazepam--Prodes, etc, have never been promoted as 'generics'. But in 1992 ratiopharm started to market a whole range of INN-named products, explicitly promoted as 'generics' and sold at reduced prices, the two most important being Enalapril-ratiopharm (20% below the price of the original) and Famotidina-ratiopharm (25% below). Ratiopharm products derive from previously existing branded copies which, without being proved bioequivalent, were allowed to switch their brands to INN names, a practice that was stopped after 1992. In 1996, before the new EFG law was enacted, Zidovudina Combino Pharm was authorised at a reduced price (-25%), after being proved to be bioequivalent to Glaxo Wellcome's Retrovir².

Peculiar patents

The Spanish pharmaceutical market cannot be understood without reference to its patent system. But, contrary to some oversimplified complaints, patent rights are being respected in the pharmaceutical field.

Today's situation is a consequence of the fact that, in the pharmaceutical field, about ten years pass from patenting to marketing. Spain joined the European Patent Convention in 1986 but, as in Greece and Portugal, pharmaceutical products are patentable from October 8, 1992, the day following the expiry of a transitional period according to Article 167 EPC. Consequently, pharmaceuticals

patented as products in 1992 will be marketed around 2002, and their product patents will expire in 2012, with a maximum supplementary protection certificate (SPC) up to 2017. Only then will 'true generics' based on patent-derived exclusivity appear in Spain.

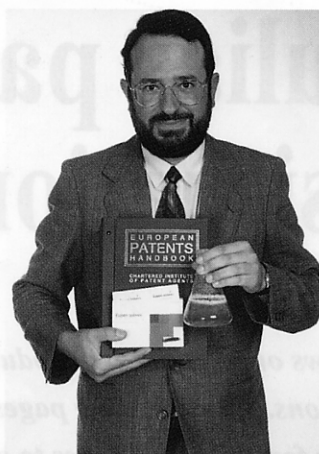
This scenario would be somewhat different if, as this author believes, pharmaceutical uses are not affected by the transitional period. If so, claims that read 'use of product X for the preparation of a medicament against indication Y', would be patentable from 1986 onwards. This would prevent registration of copies, and EFGs for the claimed use, of any NCEs invented between 1986 and 1992.

Under the old patent system – prior to the enactment in 1986 of the EPC and the new Patent Act – only processes for the preparation of NCEs were patentable. Under the new patent system, processes, and probably uses, have been patentable since 1986, but products only since 1992. As most of the blockbuster NCEs were invented before 1986, their first Spanish patents are old-law process patents, weaker than in other European Community countries, but two to three years longer (they last 20 years from granting).

Preventing copies

The multi-source availability in Spain of many NCEs still under patent in other European Community countries is a clear indication that their patent protection in Spain is ineffective. Depending on the case, either the product can be prepared using a non-infringing process, or the infringement cannot be demonstrated in court. In cases of infringement, however, the situation has improved for the patentee.

Prior to 1986 no patentee had ever enforced a patent in the pharmaceutical field. Proceedings were very long and defendants' patents, granted subsequent to the original for the preparation of the same product, had first to be invali-



Professor Pascual Segura maintains that contrary to some, oversimplified, complaints, pharmaceutical patent rights are being respected in Spain.

dated. These spurious patents, filed only for protective reasons and granted without novelty examination, often disclosed 'paper chemistry'.

Since 1992 the same old-law process patents, without changing their claims, have become much stronger as a consequence of the coming into force of: (a) reversal of the burden of proof, restricted to the first process patent; (b) proceedings to substantiate facts (the French 'saisie description'), which are used without warning for getting proof of infringement (c) provisional measures (preliminary injunction) when the product is actually made in Spain. Thus, it is not surprising that in the past six years several patent infringement lawsuits on blockbuster NCEs have started. In some of these cases the plaintiff's patent has been considered to be invalid or not to have been infringed. But in others the defendant has been forced into an agreement with the plaintiff, or even found guilty of infringement (something previously unknown). This 'renewed' strength of old patents will deter imitators from introducing infringing copies/EFGs. But legal copies/EFGs will still be possible.

Ten-year paradoxes

The ten-year rule of registration exclusivity for EFGs will create certain paradoxes. In 1997, for instance, NCEs such as

ciprofloxacin, enalapril or omeprazole cannot be registered as EFGs because they are not ten years old, but they already have many copies on the market. On the other hand, NCEs such as aciclovir, famotidine or zidovudine can – in principle – be registered as EFGs, but still have their first Spanish process patents in force (one until 2008). In fact, for most NCEs the ten-year registration exclusivities will expire before their first patents.

If their sales are at stake, innovator companies would probably take systematic legal actions for patent infringement against competing EFG applicants, infringers or not (lawsuits are sometimes started to intimidate or denigrate). In these attacks, they would use not only their first process patents, but also all their subsequent patents on intermediates, galenic forms, compositions, uses, etc. Therefore, in order to make good decisions, EFG applicants – not health authorities – should scrutinise in advance the validity and efficacy of all relevant patents.

Future for generics?

A generic market share in Spain, where prices are low, would probably reach only 4-5% by the year 2000 unless the government introduces drastic measures³. As the goal of the Spanish government is 10%, it seems that the reference pricing system contemplated in the EFG law will be introduced sooner or later.

Generics in Spain might represent good business opportunities if the project on 'euro-generics' (mutual recognition, with only one bioequivalence study, for the whole European Community) is established. Besides low prices, Spanish generic companies would get a competitive edge from the absence of product patents, the absence of SPCs for products marketed before 1998, and the absence of case-law preventing generic companies from preparing to market a product during the lifetime of its patent.

Cinfa (with the Navarra regional government), Bayvit

(Bayer and Vita), Knoll, Alter, Astamedica SmithKline Beecham and Unysatel (wholesalers Hefame and Cofares) are among the companies that have already expressed their interest in marketing EFGs. Mundogen, a generics marketing company set up by Glaxo Wellcome, Hefame and Cofares, will market SmithKline Beecham's generic amoxicillin. EFGs of amoxicillin, diclofenac, allopurinol, atenolol and tramadol have already been approved, with prices 20-25% below their branded originals. It has been reported that between 80 and 90 EFG authorisations are expected before the end of 1997, a fact that is no doubt causing considerable interest among the Spanish industry, both national and multinational. **SM**

References

1. 'Spanish split on generic effects', *Scrip*, 2208, 2, February 21, 1997.
2. 'GW sues over Spanish zidovudine', *Scrip*, 2178, 17, November 5, 1996.
3. J.M.Peny and R.Young, 'Are generic strategies worth the effort?' *Scrip Magazine*, 47, 28-32, June 1996.

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