Patent Focus

Researched and written by Genericsweb

Genericsweb is a provider of information products and services to the generic pharmaceutical industry. Its flagship product, Pipeline Patent Intelligence is the industry leader in providing comprehensive research and analysis of patents protecting pharmaceutical products worldwide.

For further information please contact:
Leighton Howard
Genericsweb Pty Ltd
PO Box 202
Balmain 2041
Australia
Email: l.howard@genericsweb.com

Genericsweb maintains its headquarters in Sydney, Australia and has a regional office in the UK.

Molecular form: Patentability of known active ingredients

Leighton Howard

is a patent information expert with extensive generics experience. He has worked within the professional patent information industry and major generic pharmaceutical firms and now provides consultancy services to the generics industry and government organisations via his company XIP Pty Ltd. He is also the founder of Genericsweb and remains instrumental in maintaining the high quality and accuracy of data contained in Pipeline Patent Intelligence.

Journal of Generic Medicines (2008) **5,** 247–253. doi:10.1057/jgm.2008.4

TRENDS IN FILING MOLECULAR FORM PATENTS

Over the years, we have seen a shift in focus of patenting by the innovator from formulation patents to process and molecular form patents in an attempt to extend the life of their products in the face of generic competition.[1] Although the impact of process patents should never be disregarded completely, the large number of potential methods of synthesis to arrive at the same compound, combined with a prevalence of technical expertise in this field suggests that they will rarely block a generic from being launched beyond the date of the molecule patent. Conversely, the active ingredient is the foundation of an approval of a pharmaceutical product, thus circumventing patents that protect the molecular form to yield an approvable generic product may not prove to be so simple.

Analysis of a random selection of 20 pharmaceutical products that are established as a brand product demonstrate an average percentage of patent filings relating to molecular form of 11 per cent with the highest percentage being 24 per cent, in respect of Olanzapine (Figure 1). Considering that the average number of filed patents analysed for each molecule is 186, this may come as a surprise to those who still believe that an active ingredient is still only protected by a single patent.

Taking the three products with the highest number of molecular form patent filings from the set analysed, Amlodipine, Atorvastatin and Omeprazole (includes Esomeprazole), and separating the innovator filings out from those of other applicants (Figure 2), we can see that both innovators and their competitors are responsible for a significant amount, although the competitor filings generally outnumber the innovator. It is noteworthy that these three highest ranking drugs in terms of molecular form filings all have a large number of filings by the innovator, resulting in a necessarily large response from competitors to circumvent them.

The patent filings of the same three molecules were mapped in relation to the launch of the innovator (racemic) product launch (Figure 3). This shows that filings by generic competitors begin with three years of launch of the product and generally continue in large amounts throughout the life of the product. This creates problems because patent filings are generally not published for 18 months and generic competitors cannot monitor the R&D activities of each other. For example, three patent applications were filed for the same polymorphic form of Atorvastatin by different generic companies within a few months of each other, suggesting a large waste of R&D effort that simply could not be avoided. It is interesting to note that some innovators choose to file molecular

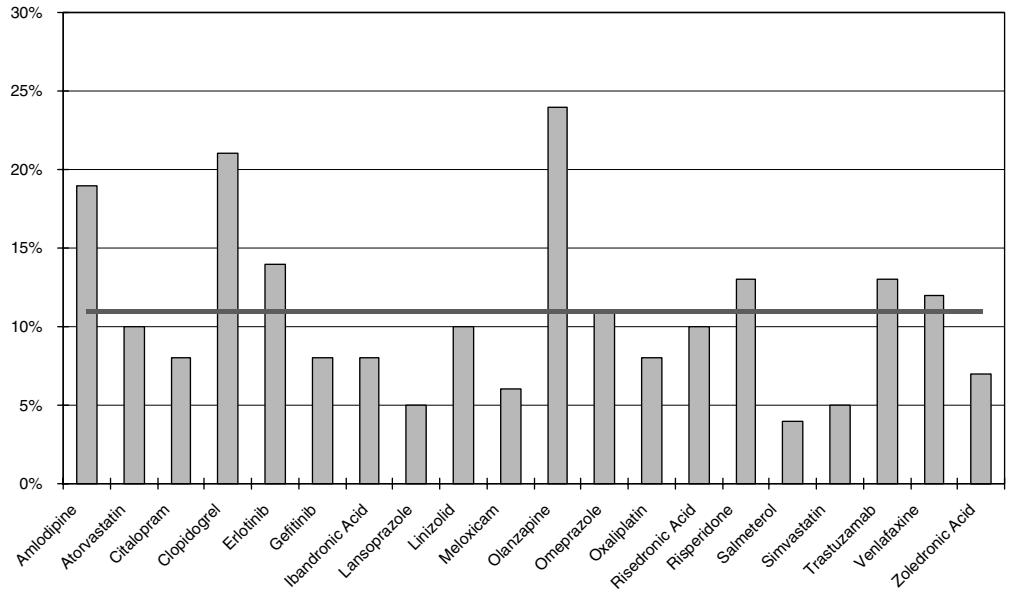

Figure 1: Percentage of molecular form patents protecting a pharmaceutical product

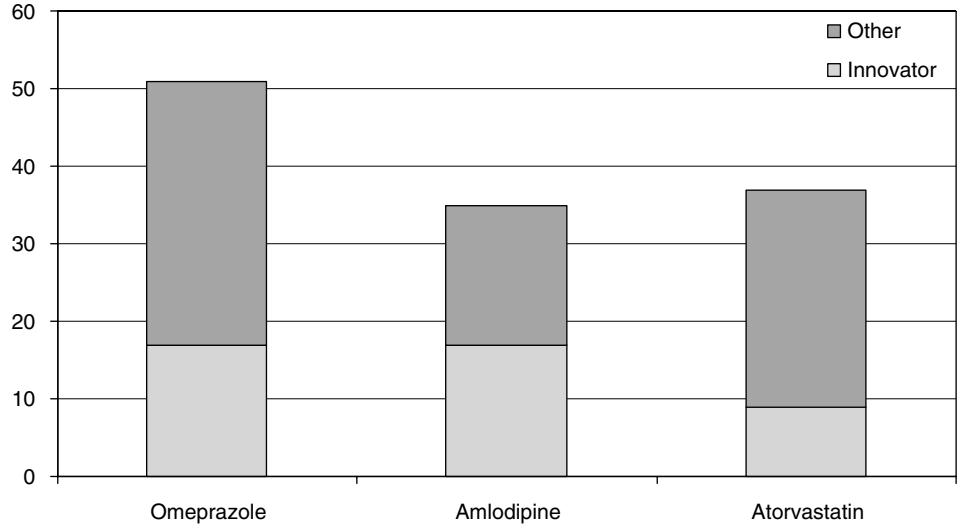

Figure 2: No. of molecular form patent filings by applicant type

form patents very late in the lifecycle of their product, long after generic competitors have done so. This may be a tactic by innovators to yield unexamined applications with broad claims in place to create confusion and uncertainty around the expected time of expiry of the original molecule patent, given that patent applications take a long time to go through substantive examination procedures. It could also represent a 'knee-jerk' response to the imminent threat of loss of monopoly protection of their product in the face of such strong generic activity, with little thought to the pros and cons of such patenting activity.

TYPES OF MOLECULAR FORM PATENT

So, long gone are the days where one can await expiry of 'The Patent' and launch a

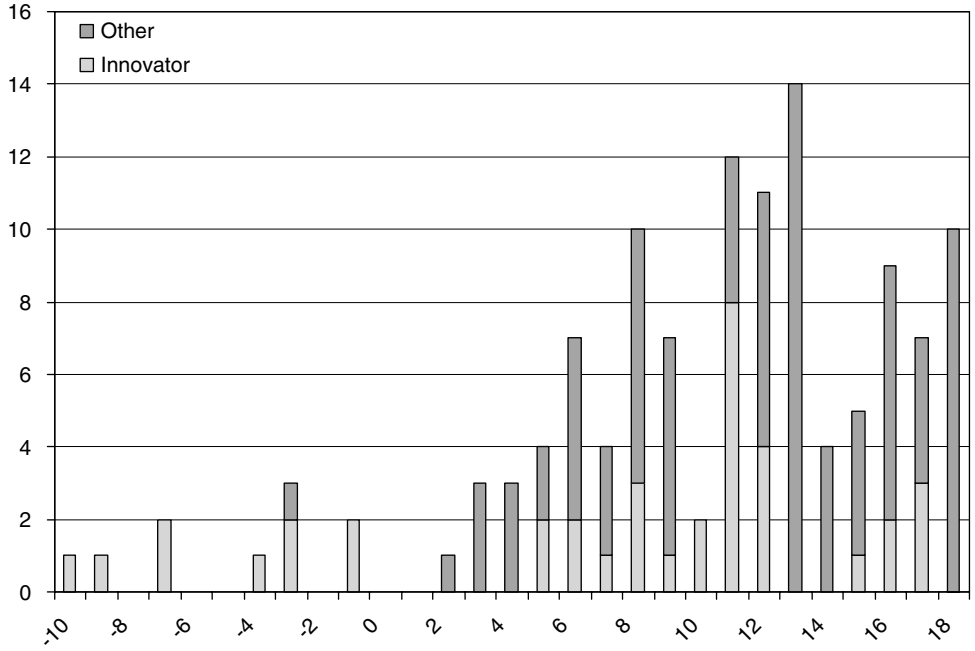

Figure 3: Timing of molecular form patent filings by applicant type

generic product. It is now necessary to evaluate all of the patents filed in relation to a particular active ingredient to work out which one is constraining in terms of all generic competition, then to work out if a product can be developed that circumvents all of the other patents filed around that technology. I will provide a few examples of how this may work in relation to the molecule *per se*.

Molecule selection: This occurs where the molecule is initially protected by a claim to many compounds sharing a common formulaic core structure. One or more specific compounds may later be selected from the group and patented again, where those compounds that are selected possess properties that substantially differentiate them from the remainder covered by the original formula.

Enantiomers: Where the original molecule was patented as a racemic mixture or did not specifically disclose enantiomeric forms, one of those enantiomeric forms may be patented later. This is often based on the premise that it offers higher activity or lower side effects than the racemic mixture. An example of this is the enantiomer patent protecting Atorvastatin *per se* (in some countries), and those patents protecting the S-enantiomers of Omeprazole and Citalopram.

Salts: Given a basic chemical compound as defined by its atomic structure, many may form salts with other compounds, usually acids. This may beneficially change the physicochemical properties of an active ingredient without changing its pharmacological action thus giving rise to an argument for patentability. The benzenesulfonate salt of Amlodipine was patented and generally offered protection much later than the original patent disclosing the molecule *per se*.

Hydrates and other solvates: This term generally relates to a molecule, its enantiomer or salt which is bound to water or other solvent atoms by complexation and/or trapped in a crystal lattice. Again, the level of solvation may beneficially change the physicochemical properties of an active

ingredient without changing its pharmacological action and therefore becomes patentable. Aripiprazole is an example of a compound that exists in many hydrated states, many of which are subject to patent protection beyond that of the original patent disclosing the molecule *per se*. Problems arise where hydrates spontaneously convert to protected hydrates under certain atmospheric conditions.

Crystalline forms: Different crystallisation solvents, temperatures and methods may result in different crystalline forms, each of which may have different stability, bioavailability and other characteristics. Often referred to as polymorphs (the compound is said to be polymorphic) defined by X-ray diffraction, infra-red spectroscopy and other analytical parameters, patents are increasingly found protecting numerous polymorphic forms of a single molecule, its salt or a solvate thereof. The Perindopril alpha polymorph is a classic example of a crystalline form patent that extended the monopoly of the products containing this active ingredient, and where most other suitable alternatives were also protected by the innovator.

Purity (chemical and crystalline): Given a particular molecular form falling into any of the above categories, the chemical or crystalline purity or the corresponding ratio of one to another in the active ingredient may be patented, regardless of how the impurity or ratio occurred. For example, Simvastatin benefited from protection of a certain level of dimeric impurity (formed by the active ingredient bonding to itself) required for regulatory approval, and Tibolone benefited from patent protection of crystalline purity above 90 per cent.

Particle size and other physical characteristics: Finally, once all of the above categories have been considered for patentability, many innovators turn to optimal particle size, colour, stability or even density of the bulk active ingredient to seek protection, based on the optimal characteristics one may demonstrate over the other.

THE FUTURE FOR MOLECULAR FORM PATENTS

However unfair this may all seem, there are conflicting arguments for the patentability of these seemingly unimaginative improvements to something that is already known. From the side of the innovators the argument is that one cannot simply identify a molecule and it immediately becomes available in an approvable form. Much work is required in identifying the appropriate molecular form to gain approval by selection from a myriad of alternatives and is considered to be worthy or patent protection by many patent offices, provided the selected form has an unexpected technical effect over the others. From the side of the generic manufacturers a great deal of abuse of the patent system is claimed, where patents are filed with the sole intent of blocking generic competition, rather than to raise the level of the state of the art, as is the intent of the system.

In one particular case currently under opposition at the EPO, the molecular form was seemingly patented after first marketing of the product, but the fact that the molecular form was not capable of being characterised at that time is being used as argument for novelty. The problem for patent offices in examining such patent applications is not only in establishing novelty but also that the argument for unexpected technical effect is often not tested thoroughly at the examination stage due to constraints placed on the examiners, and the patents are thus granted. This leaves the onus on the generic competitor to prove that the monopoly is unjustified by opposition, re-examination or litigation at great cost, leaving other generic 'observers' with a great deal of uncertainty as to when they can launch their generic.

The opposition boards and national courts appear to be successfully establishing and clarifying the ground rules for patentability in each individual country or territory on a case-by-case basis. For example, enantiomer protection of molecules such as Citalopram

and Omeprazole have been successfully challenged, the EPO has stated its position on patentability of the purity of known compounds. Furthermore, regulatory authorities have made adjustments or clarifications to their requirements for a generic active ingredient, allowing alternative molecular forms to the reference product providing other, strict criteria are met.

However, if granted, patents will remain in force until successfully challenged regardless of any legal precedent. There remains in force a multitude of patents that protect various 'improved' molecular forms of known active ingredients, and examination resources still mean that outrageous patents still slip through the net and proceed to grant. For example, a US patent to a generic company has recently been approved for grant in a form that protects all crystalline forms of Tolterodine Tartrate — including the currently marketed innovator form. In contrast, India has taken a stance against this type of patenting activity seeing it as a potential problem in implementing its new IP laws and has tried to prohibit patenting that may be considered abuse of the system by generic competitors. Indian legislation states that 'the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance' is not patentable. It then goes on to state that 'salts, esters, ethers, polymorphs, metabolites etc shall be considered as the "same substance", unless they "differ significantly in properties with regard to efficacy".

It is worth considering that each molecular form patent application has its own prior art base and arguments for novelty and inventive step because no two compounds are the same, hence there is a large element of uncertainty in regards to patentability and enforceability, even in countries where an attempt has been made to give certainty to both patent applicants and observers.

Also, purity patents represent a significant problem whenever the publication of monographs used by regulatory authorities remains controlled by an independent entity that relies on submissions by the innovator, that is if an innovator successfully patents a pure molecular form, it may submit a new monograph detailing the purer form that would effectively prevent a generic competitor from using it as a reference.

Thus, from the viewpoint of the innovator and the generic competitor alike, there remains a lot of merit in filing, prosecuting and enforcing patents in relation to molecular forms. A molecular form patent may just buy an extra few months of monopoly for an innovator, or it might enable a generic to attain a larger market share by preventing other generics. It may create confusion in regards to patent term extensions such as Supplementary Protection Certificates in Europe or it may keep generic companies so busy trying to circumvent it, that they must limit the products they develop and keep prices higher.

It should be noted, however that 'blizzarding', that is, patenting all possible molecular forms at the same time, is not likely to be successful. This tactic often negates the argument for an unexpected technical effect as there remains no advantage in selection of the particular form, unless of course it is done over a period of time allowing one patent to grant before applying for another. Also, the more often a particular style of molecular form has been patented, the less inventive it becomes to try it on a new molecule. Furthermore, software is now available that purports to predict the number and structure of crystalline forms given a particular molecule. This type of technological advancement could put an end to successful patenting of polymorphic forms in the future.

Although patenting of molecular forms appears to have a limited life for small molecules, the prevalence of Biosimilars opens up a realm of new opportunities for this particular tactic in lifecycle management of future products. Molecular form patenting is a

  1741-1343 $30.00 **JOURNAL OF GENERIC MEDICINES.** VOL. 5, NO. 3. 247–253. APRIL 2008

significant problem in generic drug development, and it will remain that way for a long time to come. The best strategy is therefore to understand the molecular form protection surrounding a particular active ingredient by reviewing the results of a good patent search, and monitoring the patent landscape for changes to enable fast responses to any opportunities or threats that occur.

Reference

1. Howard, L. (2007). The changing face of patents in generic pharmaceutical development: Facts and figures. *Journal of Generic Medicines* **4**, 153–157.