Follow-on innovation or evergreening: what is the difference?

17 JANUARY, 2017
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Key points

- While the terms “evergreening patent” and “follow-on patent” are both used to refer to patents that protect pharmaceutical formulations, new forms of active agent, processes for manufacturing active agents, new uses for pharmaceutical products, new combinations of active agents, new dosing regimes and the like, the pejorative term “evergreening” is reserved by academics and economists for those patents filed by the originator of the active agent.
- Without a full appreciation of the ingenuity involved in the development of pharmaceutical products, and the importance of effective patent term in driving pharmaceutical companies to invest in these developments, it is very easy for academics, economists and others unfamiliar with the technology involved in developing commercial pharmaceutical products to categorise important “follow-on” patents as mere “evergreening” patents, since this categorisation avoids completely the need to assess whether or not inventive ingenuity was involved in creation of the patented invention.
- Incremental innovation is recognised by both innovator companies and generic companies as being of critical importance in the development of improved pharmaceutical products and therapies, and follow-on inventions, and the patents that protect them, are important in achieving these outcomes. All patents should be judged on their merits and an originator company should not be criticised, or accused of “evergreening”, for pursuing patent protection for its inventions any more than generic companies should be criticised for pursuing patents for their inventions.

What is “evergreening” and why has this term gained currency?

The terms “evergreening patent” and “follow-on patent” are both used to refer to patents that protect pharmaceutical formulations, new forms of active agent, processes for manufacturing active agents, new uses for pharmaceutical products, new combinations of active agents, new dosing regimes and the like. However, the term “evergreening” is reserved for a subset of these patents; namely those filed by the originator of the active agent. But does it serve any useful purpose applying the “evergreening” label to these originator owned patents?

An active pharmaceutical agent is not much use if it cannot be produced in a stable form in commercial quantities. It is also not much use if it cannot be
formulated in a manner which allows it to be delivered to a patient in a suitable formulation such that it reaches the site of action in the patient’s body where it can exert its pharmaceutical action to treat the patient’s disease or disorder. The active agent will also not be particularly useful if it is delivered in a manner that hits other targets in the patient’s body causing undesirable side effects, or if the agent is metabolised into other compounds that cause toxicity or side effects. It is therefore not surprising that the process of developing an active agent into a commercially successful pharmaceutical product, which is both safe and efficacious, involves overcoming numerous problems which could potentially give rise to patentable inventions. Despite this, academics, economists and others unfamiliar with the technology involved in developing commercial pharmaceutical products have written papers and articles criticising pharmaceutical companies for seeking protection for these inventions. With the exception of the original patent protecting the active agent, these additional patents are perjoratively referred to as “evergreening” patents in such publications.

It is hard to find a consistent definition of the term “evergreening” as it is used to describe patents relating to pharmaceuticals. However, it is clear that the term is reserved for the patents filed by originator companies who own the original patent on the particular active agent. If other companies, including generic companies, file patents relating to new pharmaceutical forms, formulations, processes for the manufacture of pharmaceuticals, dosing regimes for pharmaceuticals, they are termed “secondary” patents or “follow-on” patents. Apparently it is perfectly acceptable for companies other than the originator to file such patents, and this action is only objectionable when originator pharmaceutical companies carry out additional work on their own active agents.¹

Without a full appreciation of the ingenuity involved in the development of pharmaceutical products, it is very easy for those who use the term “evergreening” to categorise these important patents as mere “evergreening” patents, since this categorisation avoids completely the need to assess whether or not inventive ingenuity was involved in creation of the patented invention. In my view it is unhelpful to draw a distinction between “evergreening” patents and secondary or follow-on patents based on who has filed them. All patents should be judged on their merits and an originator company should not be criticised for pursuing patent protection for its inventions any more than generic companies should be criticised for pursuing patents for their inventions. All patents need to meet the stringent patentability and description requirements imposed by national and regional patent laws. For this reason, if there is any need at all to adopt a term to describe this broad class of patents relating to pharmaceutical products, I prefer to call them all “follow-on” patents. This term takes into account the incremental nature of pharmaceutical development and biomedical innovation, and draws no distinction based on the commercial activities of the patentee.

**Encouragement for follow-on innovation provided by the patent system**

Those who criticise follow-on patents in any form fail to appreciate that one of the objectives of the patent system is to encourage follow-on innovation. Although it is often said that the quid pro quo for granting a patent is disclosure of the invention to the public in the patent specification, it is important to note that publication normally occurs well before the grant of the patent. One of the risks of filing a patent application is that details of the invention will be published by the Patent Office may ultimately refuse to grant the patent. The considerable amount of patenting activity in connection with follow-on innovations in the pharmaceutical field is a clear indicator that the patent system is doing its job. This is particularly the case, since most of these follow-on patent applications
are filed by applicants other than the originator company.

In 2013 Professor Andrew Christie (together with Chris Dent, Peter McIntyre, Lachlan Wilson and David Studdert) published the results of a study carried out in relation to Australian patents associated with 15 of the most expensive drugs sold in Australia over the previous 20 years. While the study identified a mean of 49 patents associated with each drug, three quarters of the patents were owned by companies other than the drug's originator. In fact, the majority of the patents identified in the study were owned by companies that do not have a record of developing top selling drugs. In my view, this intensive patent activity around important drugs is an indicator of the amount of ongoing research which is carried out in an effort to improve various aspects and properties of known drugs. In my experience, this work often leads to new pharmaceutical products which have better properties and provide better therapeutic outcomes for patients.

**Distinction between pre- and post-marketing follow-on patents**

Returning now to patents filed by originator companies, I believe it is possible to divide them into two categories, those filed prior to the launch of the original product incorporating the active agent, and those filed after the launch.

In view of the difficulties associated with developing a promising active pharmaceutical agent into a commercially acceptable formulation, it is not surprising that the original commercial formulation of the active pharmaceutical agent may embody a number of inventions. Not only will it incorporate the novel active pharmaceutical agent, which is likely to be the subject of a patent, the active agent may also be in a particular novel crystalline form which provides the required levels of bioavailability, solubility, stability and the like. If ingenuity was involved in developing this particular form of the active agent then there may also be a patent protecting that form. There may also be a patent protecting the particular formulation which was developed to allow the active agent to be administered to the patient in a form which achieves the required pharmaceutical effect. Formulating active pharmaceutical agents, particularly novel pharmaceutical agents, is not as trivial as some academics and economists would have you believe. In some cases there may also be a patent protecting the particular dosing regime associated with administration of the pharmaceutical agent.

In view of the extensive time required to demonstrate that a new pharmaceutical product is safe and efficacious, most of these follow-on patents will have filing dates well before the date the pharmaceutical product receives marketing approval in Australia. In many cases, the patent filed in respect of the active pharmaceutical agent will have been filed from 10 to 15 years prior to the first marketing approval in Australia, leaving 5 to 10 years remaining of the original 20 year patent term. Patents relating to crystalline forms, methods of manufacture, formulations and dosing regimes associated with the product as originally registered will normally have been filed later, and will normally have more of their original 20 year term remaining at the time of first marketing approval. Recognising the substantial reduction in effective patent term caused by the lengthy regulatory approval process, Australian patent law provides for patent term extensions of up to 5 years in an effort to provide the patentee with an effective 15 year patent term. Since no more than 5 years additional term is available, a 15 year effective patent term will only be achieved if the patentee manages to obtain regulatory approval for the pharmaceutical product in less than 10 years from the patent filing date.

Although the final marketed pharmaceutical product may embody several inventions, it is not surprising that generic companies often seek to launch
generic versions of the pharmaceutical product upon expiry of the active agent patent. However, they can only do this if they avoid the other patents protecting various aspects of the approved pharmaceutical product. Other options available to the generic pharmaceutical companies are seek to invalidate these additional patents or to wait until all patents protecting the registered pharmaceutical product have expired before entering the market.

There are very few complaints about patentees of non-pharmaceutical inventions obtaining 20 year patents, even when the patentee is able to start deriving commercial benefit from these inventions soon after patent filing. However, despite the huge investment that pharmaceutical companies must make in order to bring a pharmaceutical product to market, usually well in excess of $1 billion, those who use the term “evergreening”, begrudge pharmaceutical companies the effective 15 year patent term that they may be able to obtain under Australian patent law. Such commentators report upon losses to the government, and therefore the taxpayer, associated with paying for these pharmaceutical products while they are protected by a patent. However, it is abundantly clear that it is the “effective” patent term provided for pharmaceutical products which drives research based pharmaceutical companies to invest in and develop new pharmaceutical products. Indeed, in the absence of new pharmaceutical product development there would not be a generic pharmaceutical industry.

In many ways, those patents filed prior to product launch are not “follow-on” patents at all, since they all contributed to the success of the original product as launched. However, they can be considered follow-on patents to the extent that they build on the original work done by the originator company to identify the active agent.

The second class of follow-on patents filed by drug originators are those filed after regulatory approval and launch of the original product. The inventions claimed in these patents will not be embodied in the originally approved product, and cannot be used to prevent generic companies from marketing the original product for the original indications when the patents covering the original product expire. Despite what might be suggested by those who use the term “evergreening”, it is not possible to obtain more than 20 years effective patent term for a pharmaceutical product. If originator companies produce new and improved products and make them available to the public at a later date, following additional clinical trials and regulatory studies, then the success or otherwise of the new and improved product will necessarily depend on the benefits associated with the new product. The success or otherwise of a pharmaceutical company in marketing a new and improved product is completely unrelated to the existence or otherwise of a patent on the product, except to the extent that the patent will prevent generic companies from marketing the new product while the patent is in force. However, the new patents will not interfere with the ability of the generic company to sell the original product upon patent expiry.

Upon expiry of the original patents covering the original pharmaceutical product, it is not uncommon for generic companies to rely upon patents to protect their own formulations, crystalline forms or methods of administration in connection with the marketed versions of their products. This is not objectionable and is important for many generic companies in their quest to compete with the originator company, and other generic companies.

**Examples of follow-on innovation in relation to successful pharmaceutical products**

It is useful to consider a number of patents for pharmaceutical products which have drawn the attention of those who use the term “evergreening” to
Astrazeneca's patent on Losec™

Commentators who have discussed the so-called “evergreening” problem in Australia have often made reference to Astrazeneca’s patent on Losec™, a pharmaceutical product used to reduce stomach acid containing the active ingredient omeprazole. The validity of the Losec patent was upheld by the High Court of Australia, although the equivalent patent in the United Kingdom was found to be invalid. However, when the background to the development of the Losec formulation is analysed, it is clear that the Australian High Court was justified in upholding the patent’s validity.

Although the first patent application in respect of omeprazole was filed in 1978, it was not until 1985 that Astrazeneca identified a suitable commercial formulation that would allow delivery of the active agent to the patient. Various problems had to be overcome in order to arrive at this formulation. The first problem was that omeprazole is acid sensitive, meaning that it would break down on contact with stomach acid. Another problem which impacts on the bioavailability of omeprazole is that it is sparingly soluble in water. After several years of work, the inventors eventually arrived at a formulation in which the active agent was combined in a central core with an alkaline material, this being coated in a water soluble sub-coat over which there is applied an enteric coat. The enteric coat allows the formulation to pass through the stomach without bringing omeprazole into contact with the stomach acid. After passage through the stomach the enteric coat and the water soluble sub-coat dissolve allowing uptake of the omeprazole in the upper part of the small intestine.

There was no evidence presented at the trial to the effect that omeprazole, or its properties, formed part of the common general knowledge in the art in Australia. There was no evidence that any researchers other than the inventors considered omeprazole was worth developing into a commercial formulation. Despite these factors, for the purpose of assessing whether the Losec formulation possessed an inventive step, the Court assumed that the person skilled in the art would have commenced with knowledge of omeprazole and its properties. One of Alphapharm’s witnesses was provided with information regarding omeprazole and its properties and was asked, with prompting from Alphapharm’s lawyers, to outline the steps he would take to develop a suitable formulation. Despite being given information about omeprazole and its properties, and being prompted by Alphapharm’s lawyers, he was not able to arrive at the allegedly obvious formulation claimed in the patent.

It is also important to note that the Losec patent had a filing date well prior to the date Losec received marketing approval in Australia. Accordingly, when combined with the patent previously filed in respect of omeprazole, the effective patent term obtained by Astrazeneca for their Losec product was less than the statutory 20 years. The term “evergreening” should therefore never have been applied to Astrazeneca’s Losec patent.

Abbott’s patents on Norvir™

Another pharmaceutical product often mentioned in “evergreening” papers is Norvir™, an anti-HIV/AIDS drug marketed by AbbVie which contains the active agent, ritonavir. The complaint against AbbVie, or at least Abbott who originally marketed the drug, appears to be in relation to the number of patents filed to protect the active agent and combinations with other agents. However, sufferers of Hepatitis C are particularly happy that AbbVie did not stop its research on ritonavir and combinations with other agents because AbbVie have now developed a new combination of antiviral agents with ritonavir which has recently been approved for the treatment of Hepatitis C. According to some
reports, this combination of antiviral agents has achieved a 97% cure rate for sufferers of Hepatitis C. This cure rate compares well with that achieved by Gilead’s antiviral combination products containing the active agent, sofosbuvir. Again, combinations of the active agent with other antiviral agents have been shown to achieve a better cure rate than the active agent itself.

The development of these combination products for the treatment of Hepatitis C is a demonstration of the importance of drug combinations and incremental innovation in the fight against chronic disease. These new products are far superior to the interferon therapies first trialled in Australia in 1989.

The difficulties associated with finding a stable form of ritonavir for use in pharmaceutical products represents a good example of the importance of identifying an appropriate form of an active agent for incorporation into a commercial pharmaceutical product. Commentators on the topic of “evergreening” often dismiss this important work by referring to these forms of active agent as “minor variations” or “a mere new form”, or similar.

The original form of ritonavir, known as Form I, seemed appropriate at the time for incorporation into Abbott’s Norvir product. At that time this form of ritonavir showed appropriate levels of solubility and stability, and there was no indication that the form was not stable. The drug, which was initially formulated in the form of soft gelatin capsules and as an oral solution, received marketing approval in Australia in 1996.

However, something happened in 1998 in the US manufacturing facility which caused the production of a new crystal form of ritonavir, referred to as Form II. Since Form II was more thermodynamically stable than the original Form I, it was not long before Abbott was unable to produce ritonavir in its original form. It also appears that scientists from the US travelled to the other manufacturing facility in Italy and contaminated the atmosphere in the facility with crystals of new Form II. From that point onwards it was also not possible for Abbott to manufacture ritonavir in its original form in the Italian manufacturing facility. It also turned out that the solubility characteristics of Form II were unsuitable, and as a result, Abbott had to withdraw its product from the market. This obviously caused difficulties and concern for the patients who were on this HIV medication at the time.

Eventually, Abbott was able to find a solution to the stability problem and launch a new formulation of ritonavir which required refrigeration. In more recent times Abbott (now AbbVie) has developed a new form of ritonavir which does not require refrigeration.

**New therapeutic indication for Prolia™**

As a final example of “follow on” innovation I refer to the recent announcement by researchers at the Walter and Eliza Hall Institute (WEHI) that they have identified a new pharmaceutical use for the biologic drug, Prolia™ (denosumab), which has been used previously in the treatment of osteoporosis in postmenopausal women and for increasing bone mass in men with osteoporosis or osteopaenia. The WEHI researchers have now found that this drug might be useful in targeting and preventing the development of breast cancer in women carrying the faulty BRCA gene. Again, this finding demonstrates the importance of follow on innovation based on known drugs.

**Follow-on innovation critical for public health**

It is clear from the examples presented above that incremental innovation is of critical importance in the development of improved pharmaceutical products, and that follow-on inventions, and the patents that protect them, are important
in achieving these outcomes. It is very easy for those not involved in the biomedical research sector to bundle all of these patents into the “evergreening” bucket without giving any consideration to the ingenuity and inventiveness involved in solving the significant problems encountered in drug development.

In a presentation given in Cape Town on 14 April 2015 at the FICPI Congress, Dr Fiona Bor, who at that time was the Vice President and Director of IP of the generic pharmaceutical company Mylan, made the following comments about incremental innovation:

During the life cycle of a small molecule product, improvements are likely to be discovered. It is unrealistic to expect innovator companies to keep on producing exactly the same product according to its original formulation, when experiences both in the laboratory and in the clinic may demonstrate that a particular finished dose product (and perhaps the efficiency of its manufacture) can be improved.

Incremental innovation in the pharmaceutical industry is therefore inherent and overall it is probably a public good that is to be encouraged!

It therefore appears that all of those actually involved in the manufacture and development of pharmaceutical products realise and appreciate the importance of incremental innovation. One can only hope that academics and economists will come to recognise this as well, and remove the inappropriate and pejorative term “evergreening” from their lexicon.

End notes

2. Christie, A et al; Patents Associated with High-Cost Drugs in Australia” [2013] UMelbLRS 10
4. ABC news; 21 June 2016
5. Fiona Bor, Incremental Innovation - a generic industry perspective, presentation given at FICPI Congress, Cape Town, 14 April 2015