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Clinical trials in the pharmaceutical industry: The scope of the research exemption under French patent law – clarification is still awaited

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Abstract

This paper discusses a recent French Court decision and its impact on the judicial interpretation of the extent to which pharmaceutical clinical trials may or may not fall within the scope of the exemption provided under French law for infringement of patent rights when conducting unauthorised clinical trials aimed at securing marketing authorisation of a patented drug substance.

Keywords: *plea of research, marketing authorisation, clinical trials, generic, infringement, experimental acts*

On 20th February, 2001, the Paris Court of First Instance handed down an important decision that could have provided greater clarity with regard to the scope of a plea of research – a notion that always causes great doctrinal and jurisprudential uncertainty, both in France and in certain other industrialised countries. The scope of a plea of research in the pharmaceutical industry when trials are undertaken in order to obtain a marketing authorisation (MA) is an issue since such trials could appear to have a commercial aim.

In May 1997, the Wellcome Foundation Ltd (Wellcome) served formal notice on the company Flamel Technologies SA (Flamel) to cease certain Phase III clinical trials (see Table 1 for an explanation of terms used) it was carrying out in France in breach of Wellcome's patent rights. This was on the basis of its supplementary protection certificate (SPC; a title that extends the term of protection for the patentee once a patent has expired for an additional term) for a molecule it had patented (*aciclovir*), which would expire on 15th March, 1999. The

Table 1: Definition of terms

Speciality: medicine authorised and granted Marketing Authorisation by the French Ministry of Health with a specific trademark and registered as a Speciality. **Generic**: medicine (which has the same composition and same form as a specialty product) whose patent or Supplementary Protection Certificate has expired. It is a copycat version of the correspondent specialty medicine, but less expensive. **Generic plus**: medicine which is a generic product (as defined above), but has a different method of administration. In this case, it is the same drug but with a different delivery system as it is encapsulated, which slows down the release of the product in the organism. **Clinical trials Phase III**: the last clinical trials before obtaining Marketing Authorisation (AMM in France or BLA in USA) required before the marketing of a medicine can commence. In these trials usually adverse effects are measured and identified.

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Phase III trials were bio-equivalence trials comparing the properties of the product under experiment with the reference specialty protected by a patent until March 1999.

The involved diffusion process was already patented

The product Flamel wished to develop was not, strictly speaking, a generic of the molecule protected by the SPC until 15th March, 1999, but a 'generic plus'. On the basis of its patent filed on 18th October, 1994, defining the micropump system, Flamel wished to market the application of the patented diffusion process – the Micropump™ – using the molecule belonging to Wellcome.

Wellcome proceeded to carry out seizures of the patent infringement at the head offices of the companies that were carrying out the illegal trials on Flamel's behalf. A writ for infringement of certain claims on its SPC was then served on the companies so that judgment could be passed on the alleged infringement.

No discovery: in France, seizure is the best way to prove the alleged infringement

In its submissions, Flamel maintained in particular that the Phase III trials did not constitute an infringement. It argued that the trials benefited from the provisions of Article L. 613–5b) of the Intellectual Property Code which, by way of exception to the monopoly conferred by law on the patented product, stipulates that 'the rights conferred by the patent do not extend to acts carried out on an experimental basis which relate to the object of the patented invention'.

The Paris Court of First Instance decided on 20th February, 2001, that

> the trials carried out by FLAMEL came under the category of experimental acts, since it was a case of verifying that FLAMEL's product was an alternative to the patented medicine

The patent confers a 20 year monopoly

and that

> to decide otherwise would be tantamount to depriving researchers of the possibility of experimenting with the use of known and protected active agents under new conditions in order to improve both their dosage and the effects of treatment, prior to entering into any agreement with the owners of the initial patents and would thus jeopardise the development of patents relating to improvements, by giving a de facto monopoly to the holders of the first patents.

In so doing, part of the discussion on the bio-equivalence trials taking place in Phase III of the procedure for obtaining an MA, and on the limits of the plea of research compared with an openly commercial aim, was overshadowed. A contrary solution might have appeared more in keeping with the existing laws, without thereby jeopardising the development of patents relating to improvements.

EXPERIMENTAL ACTS AND COMMERCIAL AIM

Phase III, which directly preceded the procurement of the MA and was essential for any marketing of pharmaceutical specialities, provoked major difficulties in terms of the application of the provisions of Article L.613–5 of the Intellectual Property Code.

Phase III consists of therapeutic trials, which aim: to confirm and extend results relating to efficacy and safety of use; to assess the efficacy, and medium and possibly long-term safety results; to study the most frequent undesirable effects; and to observe other characteristics specific to the medicine, including factors such as age or medicinal interactions that could affect the results.[1]

These trials, when they form part of a strictly experimental objective, benefit from the plea of research. Such a plea is to be interpreted strictly and was conceived by the legislator to authorise limited interference with the monopoly conferred on the patented product, while allowing scientific research before patented products or processes come into the public domain.

Bio-equivalence trials also occur in Phase III: generic products cannot obtain an MA without them, and an Authorisation is essential if they are to be

marketed. These trials are limited to comparing data that are already known and well established.

Bio-availability studies demonstrate the bio-equivalence with the reference speciality

In fact, Article L. 601–6 of the Public Health Code defines the generic speciality of a reference speciality as 'one which has the same qualitative and quantitative composition in active agents, the same pharmaceutical form and whose bio-equivalence with the reference speciality is proved by appropriate bio-availability studies'.

In the present case, even if Flamel's product constituted a 'generic plus', the trials aimed at comparing the same active ingredient (aciclovir). The trials relied on pre-established data, without any additional research being carried out: it was known that the use of the technology developed by Flamel had already been applied to Wellcome's protected molecule prior to the filing in 1994 of Flamel's patent (cited by way of an example in its 1994 patent). They thus then benefited from the plea of research by being carried out within a strict framework. In 1997, the trials thus constituted a study of the conformity between two identical molecules presenting obviously similar results.

In France, the problem of interpreting the plea of research had not been settled, either in terms of jurisprudence, or in terms of doctrine, when Wellcome decided to uphold the rights granted it by law. In fact, the only jurisprudence concerning the plea of research in matters of clinical trials was limited to two decisions pronounced regarding the same dispute (first instance and appeal) concerning a medicine prescribed for its venotonic properties.[2] The facts and the question placed before the judges in these cases were different, and no principle of a general scope enabling the scope of the plea of research to be defined for clinical trials had been established whatsoever.

Experimental purposes mean researches based on the patented product

Given this lack of jurisprudence, resort was made to doctrine defining criteria that would make it possible to differentiate between what could be considered as experimental and what could not, within the meaning of the text and was thereby of an infringing commercial and industrial nature.

Since 1991, the French group of AIPPI (International Association for the Protection of Intellectual Property) had stipulated that an 'act of an experimental nature' constituted those acts aimed at discovering new properties in a chosen molecule, or a therapeutic use that was not previously known, or an analytical work that would provide increased knowledge about a discovered active agent.[3] A distinction was thus made between 'experimentation' and 'act of exploitation': only the latter would interfere with the monopoly for the patented product.

In his work 'the new Patents law', Maître Mathély recalled that it 'would not be permitted to manufacture or use the patented object for the purposes of other trials which only concern the patented product'. Professors Chavanne and Burst affirmed for their part, in 1998, 'it was obvious that the text of Article L. 613–5 should be interpreted restrictively, like any exception to a general principle'.[4] For them, there was no doubt 'that the acts in question should be carried out for strictly experimental purposes'.[4]

Even more recently, Professor Azéma agreed with them, when he wrote that 'the general spirit of derogation calls for a strict interpretation of what constitutes an exception to the monopoly of the patented product'.[5]

Thus, just like the solution adopted in Germany,[6] a possibility of working 'on' but not 'with' the patented – and hence protected – product was defined, thus complying with the plea of research's limited nature as tolerated by the law.

The commercial and industrial purpose should be kept separate from the strictly experimental purpose, without any distinction between immediate or future commercial purpose being made.

The solution adopted by the Court of First Instance therefore appears to be open to criticism when it states that 'the immediate purpose of the research was to

obtain the Marketing Authorisation'. In fact, in order to engage in any marketing in the pharmaceutical industry, an MA must be obtained. Without one, product circulation would not be allowed: this means that obtaining an MA is strictly for commercial and industrial purposes.

Little should be read into the Allen & Hanbury ruling by the Supreme Court of Appeals,[7] an authorisation to pursue the trials in France with the aim of obtaining an MA, before the expiry of the patent or SPC protecting the product in question. The Supreme Court of Appeals merely considered, wisely and correctly, that if Article L. 613–3 of the Intellectual Property Code prohibited, in particular, 'the use, manufacture or supply' of the protected product, there was nothing to prevent a third party from carrying out 'paper acts', such as filing an application for an MA, a non-listed act, hence not affected by Article L. 613–3 of the Intellectual Property Code.

In fact, there can be no confusion between paper acts and other pre-marketing acts, since the latter are prohibited and should remain so, whatever form they may take (manufacture, supply, usage, importation or possession) 'in the absence of consent by the owner of the patent'.

TRIPS have come into force on January 1, 1995 and concerns IP rights in their trading aspects

THE SOLUTION ADOPTED BY THE COURT OF FIRST INSTANCE APPEARS CONTRARY TO THE PRESENT LAW AND THE EUROPEAN POSITION

As the legislation now stands, there is no provision authorising the conduct of bio-equivalence trials before the expiry of the protection conferred by law on the patented product. The situation is clear as regards generic medicines, and should therefore apply to all other molecules, including any 'generic plus', when checks specific to the comparisons required for obtaining MAs for generic products, such as bio-equivalence trials, are carried out.

Article 31 of the law on Social Security funding for 2000 proposed an in-depth modification of the system of experimental use, as an exception to the law on patented products, in these terms:

> for a generic speciality referred to in No. 5 of Article L. 5121–1, the marketing authorisation may be issued before the expiry of the intellectual property rights attached to the reference speciality concerned. However, this reference speciality may only be marketed after the expiry of those rights.

However, the Constitutional Council judged that equating of bio-equivalence trials to acts that could benefit from the plea of research and hence be qualified as experimental acts was contrary to the Constitution.

This position is similar to that taken by the European Union, which is in favour of protecting intellectual property rights, as seen in the recent claim filed by the European Commission, in the name of the States of the Community, at the World Trade Organization (WTO), against Canada, which had adopted a reference in its legislation indicating that a manufacturer of generic medicines could test and store the unauthorised product for six months prior to the expiry of the patent.

According to the European Commission, these provisions of Article 55–2–1 of the Canadian law were contrary to Article 30 of the TRIPS (Trade-Related aspects of Intellectual Property rights) agreement which stipulates that

> the Members may provide for exceptions limited to the exclusive rights granted by a patent, provided that the latter do not unfairly jeopardise the normal exploitation of the patent or cause unfair prejudice to the legitimate interests of the patent, taking account of the legitimate interests of third parties.

The WTO rejected the European Commission's claim in relation to the

clinical trials aspect of the provision, indicating that 'the TRIPS Agreement is not opposed to the existence of national provisions which facilitate the marketing of generic medicines'. The decision did not, however, settle the problem of defining the scope of the plea of research with regard to clinical trials.

This being the case, uncertainty persists and the best proof of this is that countries favourable to the development – controlled or otherwise – of generic medicines, ie the USA, Australia, Canada and Israel, have been forced to adopt new, appropriate provisions to settle specific problems that existed concerning generic medicines. Consequently, in the absence of a new enactment, bio-equivalence trials should be seen as constituting an infringement, if the reference speciality is still protected by a valid intellectual property right.

Authorisation is required from the patent holder for improvements

Lastly, it should be noted that a decision to the contrary supporting a monopoly defined by law and protected by practice would not put a brake on the development of patents relating to improvements. In fact, while Article L. 613–15 of the Intellectual Property Code recalls that

> the owner of a patent relating to the improvement of an already patented invention on behalf of a third party may not exploit its invention without the authorisation of the holder of the previous patent; the said holder may not exploit the patented improvement without the authorisation of the holder of the patent relating to the improvement'

the fact remains that the law offers the owner of the improvement the possibility of obtaining a licence

> insofar as is necessary for the exploitation of the invention which is the subject of that patent, and provided that the invention which is the subject of the patent relating to improvement offers major technical progress and economic interest compared to the previous patent.

Consequently, Flamel could have asked the Wellcome Foundation for an operating licence in order to be able to exploit its improvement before undertaking the Phase III trials.

In the absence of legislative provisions, we are obliged to abide by the law and its principles of interpretation as applied to exceptions.

In conclusion, it should be noted that the Micropump^{TM}, protected by Flamel, enabled the medicinal dosage of the then protected product to be reduced from five daily doses to two, as developed independently by Wellcome, without recourse to a release system. Patients would therefore not have been in the least inconvenienced by a decision by Paris's Court of First Instance to uphold the rights conferred on the Wellcome patent by law, enabling Flamel's micropump system to be used for other molecules, free from any right, like aspirin.

Thus, law and health would have cooperated in maintaining a balance between the law and economic requirements, without sacrificing one to please the other, at a long-term cost of dangerous risk to the cohesion of the entire system.

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