The clinical trials and the "experimental use exemption": Are the US and European patent systems getting harmonized?

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Although many changes have been taking place in the last decade, the US and European patent systems are not at all harmonized and many differences still exist as regards both the specific law provisions and the national case law. In particular, one of the areas where no harmonization seems to have been achieved yet is that of the so-called "experimental use exemption"; although, due the EU Directive 2004/27/EC of March 31, 2004, it appears that something is going to change.

Let's see therefore how was the situation before the March 2004 and how it could be affected by the EU Directive. However, before entering the details, it is worth providing some definitions which might be useful for a better understanding of the case.

First of all, the expression "clinical trials" is intended to indicate experimental studies performed with drugs on humans to collect the data required by the regulatory authorities for granting a marketing authorization (MA); they are generally grouped under the following phases:

- phase I: evaluation of safety on a small group of healthy volunteers;
- phase II: evaluation of safety and efficacy on a small group of patient;
- phase III: evaluation of efficacy on an enlarged group of patients, comparison with other drugs and/or placebo;
- phase IV: evaluation of long term side effects, dosage, pharmacovigilance, post-marketing surveillance.

The above 4-phases subdivision applies only to clinical trials carried out with the purpose of placing a drug into the market for the first time; that is, what the US Food and Drug Administration (FDA) refers to as a New Drug Application (NDA). On the contrary, when the aim is that of placing a copy of a patented drug into the market, i.e. a so-called "generic", the related clinical trials are conducted only for demonstrating that the generic drug is "bioequivalent" to the patented one; that is, an Abbreviated New Drug Application (ANDA).

As it can be easily understood, clinical trials performed for the purpose of placing a generic drug into the market are incomparably cheaper and faster than those required for a fully new drug application. The issue is therefore whether performing clinical trials with the final aim of marketing a generic can be considered a patent violation and whether this also applies to manufacturing, importing or selling a patented active principle ingredient (API) in the amounts necessary for performing said clinical trials.

THE ESTABLISHED US SITUATION

In the USA the situation is now well established and it was defined in 1984 by the "Waxman-Hatch Act", which amended the US Patent Code by introducing the so-called "Bolar" or "Bolar-Roche" provision, i.e. 35 USC 271(e)(1), which reads in part as follows: *It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.*

Consequently, since clinical trials are

expressly performed for the development and submission of information with the FDA for the purpose of getting a MA, they are not considered a patent violation, nor is the manufacture, importation or sale of a patented active API in the amounts necessary for performing the trials.

Filing an ANDA may be however considered a patent violation; as a matter of fact, if a genericist files an ANDA and wishes to have it effective before the expiration of the basic patent, he is required to certify that the patent is invalid and/or will not be infringed by the approved drug. The patent holder has then 45 days from the filing of the certification to start an infringement action against the genericist; if, for any reason, the patent holder fails to start such an action within the 45-day period, the genericist is then allowed to request for a declaratory judgment in order to receive assurance about his patent position.

Otherwise stated, clinical trials are permitted by the US law but filing an ANDA isn't.

THE CURRENT EUROPEAN SCENARIO

Such a straightforward and clear-cut approach does not exist in Europe yet; as a matter of fact, and how it will be discussed later on, the previously mentioned EU Directive has not been enacted in most of the EU countries yet (or better to say, it has been enacted only in Italy). Let's see therefore how the experimental use exemption is currently dealt with in Europe on a country-by-country basis.

In **Croatia**, for instance, the experimental use exemption is expressly regulated by the Croatian patent law (No. 78/1999), whose Art. 52(5)2 expressly excludes from a possible patent violation those *acts done for the purposes of the research and which ... are reasonably connected with the experiments and tests necessary for the registration of the human and veterinary medicines..."* Clinical trials are thus allowed by law; the same applies to the manufacture or importation of a "reasonable amount" of an API to be used in the trials.

In **Hungary** the situation is substantially identical: the experimental use exemption is in fact expressly regulated by Article 19(6) of the Hungarian patent law No. XXXIII, 1995, which recites as follows: *The exclusive right of exploitation shall not extend to a) acts done privately or not involved in an economic activity; b) acts done for experimental purposes relating to the subject matter of the invention, including experiments and tests necessary for the registration of medicines...*

Similar explicit provisions also exist in **Poland** (Industrial Property Law, Art. 69) and in Slovenia (Art. 32 of the patent law of March 20, 1992, consolidated on May 29, 1993).

On the contrary, no explicit exemption exists for clinical trials in Ireland. Nevertheless, under the transitional provisions of the '92 Patent Act, which extended the term of all patents in force on August 1, 1992 from 16 to 20 years, preparations during the final two years of an extended patent (to enable the invention to be marketed after the term of the patent) are not considered a patent violation. Accordingly, clinical trials may be carried out from the beginning of the 19th year of an extended patent; the question of whether the exemption would also apply in the final two years of a Supplementary Certificate of Protection (SPC) based on an extended patent is however still open.

In **France** an attempt to officially authorize clinical trials was made in 1999, with Art. 31 of the French Social Security Act No. 99-1140, which recited as follows: *Bioavailability studies conducted to show bioequivalence with an original drug for the purpose of obtaining a MA for a generic drug are regarded as acts of experimental use within the meaning of Art. L613-5 of French Intellectual Property Code.* Such an attempt was however held invalid for procedural reasons by the French Constitutional Court.

Independently on the above, the French case law is very helpful in providing a guidance. According to Promedica and Chiesi vs Allen and Hanburys (March 24, 1998, Cour de Cassation), in fact, *the mere filing of an application for a MA is not* per se *an act of infringement*. In Wellcome Foundation vs Parexel (Court of Appeal, Paris, February 20, 2001), the subject matter of the phase III clinical trials at issue was to compare different methods of administration of the patented molecule and to find out an advantageous posology in terms of daily intake; the Court held that the trials did not constitute an act of infringement and fell within the experimental exemption. Similar conclusions were reached in Science Union vs AJC Pharma (October 12, 2001, Court of First Instance, Paris) and in Science Union vs Biophelia (January 25, 2002, Court of First Instance, Paris).

In view of the above decisions it is now commonly accepted in France that clinical trials performed on new galenic forms or for finding new applications of a patented drug are considered covered by the experimental use exemption. It is a common position that this should reasonably apply also to clinical trials solely performed to demonstrate bioequivalence of a generic drug with respect to the patented one with the only aim of obtaining a MA.

The situation is essentially similar in **Germany**; as a matter of fact, although no explicit law provisions exist, the issue was dealt with by two very famous decisions: in "Clinical trials I" (Federal Supreme Court, 11.07.1995) it was in fact decided that *clinical trials having a regulatory and scientific aim fall within the experimental use exemption*. Subsequently, in "Clinical trials II" (Federal Supreme Court, 17.04.1997)it was held that *clinical trials are admitted even if performed to gather the data required for obtaining the MA; the industrial purpose and the intention to economically exploit the results are not sufficient to render them unlawful; the ultimate aim of an experiment is not relevant as long as it is designated to provide information on the tested product*. Finally, the German Constitutional Court (May 2000) confirmed the Supreme Court's decisions, concluding that *the patentee has to accept such limitations on its rights in view of the development of the state-of-the-art and of public interest*.

In view of the above, it can be reasonably concluded that the experimental use exemption applies in Germany if the patented invention is the subject matter of the research; i.e. also in case of trials demonstrating the bioequivalence of a generic drug with respect to the patented one.

In **Italy** two conflicting decisions were issued by the Courts of Turin and Milan. According to Franco Tosi vs SK&F (Court of Turin, September 24, 1984) *the activity aimed at collecting data for obtaining the MA for a drug is an act of infringement of patent rights*.

But, in Squibb & Sons vs Testaguzza (Court of Milan, June 12, 1995, deciding on a request for preliminary injunction based on a SPC), it was decided that *the experimentation on a patented invention ... is always lawful … even if aimed at obtaining a MA ...even if having commercial purposes ... because it represents an experimental activity which will unavoidably provide new*

knowledge...and that *...if, with the introduction of the SPC the patentee has obtained an extension of the protection which indemnifies him for the delay suffered to obtain the MA, it does not seem reasonable to grant him even the benefit which third parties would suffer in case they were prevented from carrying out the experimentation on the patented invention during the life of the patent in order to get the MA after the term of the patent itself.*

This second decision was strongly criticized in the doctrine mainly because the Judge attributed to the SPC a scope of protection different than that of the basic patent.

Judge Mario Barbuto, president of the Court of Turin, gave his opinion about this situation of legal uncertainty during a conference of the Licensing Executives Society (LES) on December 12, 2002, when he stated that *clinical trials are not infringing independently on when they are carried out and that filing the request for a MA is not an infringement only if done within the year preceding the expiry of the SPC*. All these issues seem however to have been superseded by the EU Directive 2004/27/EC of March 31, 2004, which will be further discussed and which was recently enacted by the Italian government.

The situation appears to be completely different in the **UK**. As a matter of fact, although no explicit law provisions exist, in the milestone decision Monsanto vs Stauffer (Court of Appeal, 11.06.1985) it was stated that:
Trials carried out in order to discover something unknown or to test a hypothesis or even to find out whether something which is known to work in specific conditions, e.g. of soil or weather, will work in different conditions could fairly be regarded as experiments. But trials carried out in order to demonstrate to a third party that a product works or, in order to amass information to satisfy a third party, whether a customer or a body such as the PSPS or ACAS that the product works as its maker claims were not to be regarded as acts done for experimental purpose.

This approach was basically confirmed by Auchincloss vs Agricultural & Veterinary Supplies (Court of Appeal 1999) which stated that *making a composition* – in this case a biocidal composition – *merely for the purpose of obtaining official marketing approval was not excluded from infringement* and by Inhale Therapeutic System vs Quadrant Healthcare (2002, RPC 21).

It can thus be concluded that clinical trials aimed at discovering something unknown or testing a hypothesis fall within the experimental use exemption in the UK; but clinical trials aimed at the verification of existing knowledge (i.e. bioequivalence for fling a MA) are considered a patent infringement.

The same position is substantially shared by the **Dutch** Courts: in ICI vs Medicopharma (1992, Supreme Court) and in Kirin Amgen vs Boehringer (1994, Court of appeal) it was decided that *research aimed at further improvements of the technique or at finding a novel clinical indication, is not subjectable to patent rights*. But, in Serono vs Organon (1994, Supreme Court) it was held that *conducting large scale clinical trials in order to obtain product registration does not fall within the experimental use exemption*. In line with the above case law, clinical trials with the sole purpose of obtaining the required data for the registration of a generic drug would be considered an infringement.

In **Switzerland** no explicit law provision exist whereas only a decision was issued up to date, holding that *the use of a sample, containing a patented active principle, for the purpose of registering a drug, is not a commercial use of the invention and, consequently, it is not an infringement* (First Instance, Basel-Landschaft, October 1, 1997).

Such a decision, however, never reached the Board of Appeal; and it is quite a commonly accepted position that, if it were, it would have been reversed. Consequently, conducting clinical trials or manufacturing/importing a patented API in the amounts necessary for the clinical trials would probably still be considered a patent violation in this country. Nevertheless, a bill should have been recently presented to the Swiss Parliament for amending the Patent Act so as to introduce an exemption for clinical trials.

As to the remaining European countries, the situation can be summarized as follows.

Testing for academic purpose, i.e. without any marketing objective, is allowable in **Austria**; the decisions of the German Courts might however influence the Austrian courts in a "clinical trials" case.

In the **Czech Republic** the current practice is that clinical trials for the purpose of obtaining regulatory approval are carried out even before the expiration date of the respective patent.

In **Denmark**, clinical trials with the only purpose of testing the invention or discovering new properties are covered by the experimental use exemption. However, conducting clinical trials with the purpose of subsequently placing a generic into the market might be considered a patent violation.

In **Greece**, although no explicit law or case law exist, clinical trials carried out with the purpose of placing a generic into the market would probably not be permitted without the licence of the patentee.

In 1998 the **Portuguese** Ministry of Industry clarified that testing for preparation of generic medicines for registration purposes is deemed compatible with the Portuguese patent law.

In **Spain**, according to the current doctrine, conducting clinical trials with the purpose of obtaining a MA would probably be considered a patent violation; most likely, it would not be considered an infringement conducting clinical trials with the only purpose of discovering new properties of a patented drug.

The same should substantially apply in **Sweden** whereas in **Turkey** it should be lawful to undertake clinical trials provided the data so acquired are neither divulged nor used prior to the expiration of the patent rights.

THE EU DIRECTIVE

The question is how the above-depicted scenario will be affected by the previously mentioned EU Directive 2004/27/EC of March 31, 2004 (published on the Official Gazette of April 30, 2004), whose Art. 10.6 recites as follows: *Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4* (i.e. obtaining the MA for a generic in a EU member state) *and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.*

According to Art. 3 of this Directive, in fact, *member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than October 30, 2005*.

This in theory means that, starting from October 30, 2005, clinical trials having the purpose of placing in the EU market a generic copy of a patented drug would be lawful in the EU. The point is that the Directive is silent about whether the following acts shall be considered as a patent violation:

– carrying out clinical trials in the EU

with the purpose of getting a MA in a non EU member state;
- manufacturing and/or importing into the EU the necessary amounts of API;
- manufacturing in the EU the necessary amounts of API to be exported in a non EU member state for clinical trials aimed at filing the request for a MA outside the EU.

Furthermore, for the time being only Italy has enacted the EU Directive; this was done on February 10, 2005, when the President of the Italian Republic signed the new Industrial Property Code (published on the Official Gazette of March 4, 2005). In this connection it is worth nothing that the new code already answered to the above three questions, at least as far as Italy is concerned.

As a matter of fact, Art. 68 of the code expressly recites that *the exclusive right conferred by the patent shall not extend to: a) acts done privately or not involved in a commercial activity, or b) to acts done for experimental purposes although aimed at the obtainment of a MA, even in foreign countries, including the manufacture and use of the related API*.

Art. 61 further specifies that *the companies which intend to produce pharmaceutical products outside the patent protection are allowed to start the registration procedure of the product containing the active substance one year in advance with respect to the term of the SPC patent coverage of the active substance* (this applies only to SPCs granted under the provisions of the Italian law No. 349 of October 19, 1991, and not for SPCs granted under the provisions of the EU regulation No. 1768 of June 18, 1992).

Thanks to the new code, the situation seems now quite clear in Italy and essentially reflects the US "Bolar" provisions, with the only difference that filing the request for a MA is not considered an infringement provided it is filed within one year from the term of an SPC granted under the provisions of the old Italian law.

CONCLUSIONS

The impression is that Europe, or at least the EU, is moving towards harmonization with the US patent system, insofar the experimental use exemption is concerned. It is not however presently clear whether the EU Directive 2004/27/EC will be enacted by all the EU member states. Furthermore it is also not clear whether a complete harmonization will be reached, as for instance it has just happened in Italy, or whether foggy areas would still exist, in particular as regards the manufacture of API to be exported in a non EU member state for clinical trial purposes.

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