Clinical trials and the novelty of the invention

Can clinical trials of a new medicine that are conducted before a patent application is filed result in the loss of novelty by that invention? The caselaw of the EPO shows that it is quite a serious risk that we should take into consideration when preparing the placing of our medicinal product on the European market.

In this Report, we would like to take a closer look at one of the most important decisions handed by the EPO in that area: **the decision of the Technical Board of Appeal of 7 July 2011 in Yasmin case.** The decision resulted in the revocation of a patent held by a German company Bayer Pharma Aktiengesellschaft as it was determined that **the clinical trials conducted before the filing date effectively deprived the tested product of the feature of novelty.**

Our goal is to comment as well on **the Technical Board's of Appeal more recent decision of 2 December 2022** which could contribute in a meaningful way to — and possibly expand on — the existing body of rulings. Namely, the Commission had to assess the validity of a patent EP-B 2 140 867 held by Daiichi Sankyo whose object of protection was the formulation of the antithrombotic agent *Lixiana*. The state of facts in the case quite closely resembled the one in the case of Yasmin and the Commission, in its analysis, drew their comparison. The final conclusions were, however, different and the patent of Daiichi Sankyo was upheld. The reasoning of the decision was published in January 2023.

In this article, we would like to recap, on the basis of the said case-law, the essential aspects of the problem at hand.

The definition of novelty as one of the criteria of patentability

At the very beginning, it should be recalled that novelty is one of the patentability criteria. Pursuant to Art. 52 of the Convention on the Grant of European Patents of 5 October 1973, European patents shall be granted for any inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application. The provision of Art. 54 elaborates on how novelty shall be understood. First, **an invention shall be considered to be new if it does not form part of the state of the art (Section 1); meanwhile, the state of the art comprises everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application (Section 2).**

Of course, a corresponding regulation can be found in Polish legal system, specifically, in the Act of 30 June 2000 — Industrial Property Law. Art. 24 in the same manner establishes the criteria of patentability, while Art. 26, dedicated to novelty, repeats that an invention shall be considered new if it does not form part of the state of the art (Section 1). Likewise, the state of the art is defined as encompassing everything that before the date relevant for determining the priority, was made available to the public knowledge in the form of a written or oral description, by use, exhibition, or disclosure in other manner (Section 2). Pursuant to the established caselaw of Polish courts, the disclosure of an invention takes place when an undetermined number of people could have (but not necessarily actually did) familiarize themselves with it (the judgment of the Supreme Administrative Court of 15 June 2016, case no. II GSK 2854/14).

The proceedings concerning the patent granted for *Yasmin*

EPO is famous for its quite restrictive approach to the criterion of novelty (especially, in comparison with the U.S. courts, more on which below). **The decision of the Technical Board of Appeal in the case T 0007/07 of 7 July 2011** is emblematic of it. As we have mentioned in the introduction to this article, that particular decision requires thoughtful consideration as it can offer us quite a solid idea of the problem that we are dealing with here.

A German company Bayer Pharma Aktiengesellschaft held a European patent EP 1 214 076 for *Yasmin* —an oral hormonal contraceptive (a compound of 2 active ingredients: ethinylestradiol and drospirenone). **The patent application was filed on 31 August 1999. Clinical trials took place in the United States from December 1996 to July 1998.**

Opposition proceedings were initiated by the EPO on the grounds of Art. 100(a) EPC — another German company, Hexal AG, which filed an opposition, argued that the subject matter of the patent does not fulfill the criteria of patentability by lacking novelty and inventive step. Let us focus on the first of those contentious issues.

In the first instance, the Opposition Division in the decision of 23 October 2006 **rejected the opposition.** As for the criterion of novelty, it concluded that the subject matter of patent claims satisfied it since **none of the documents cited as representative of the prior state of the art unambiguously disclosed micronized drospirenone** (one of the active ingredients), contrary to what Hexal claimed.

Hexal lodged **an appeal** against said decision. The intervention of a third party, a company Stragan Pharma, resulted in introducing a new problem regarding novelty into that phase of the proceedings. Namely, Stragan Pharma submitted the judgment by the United State District Court for the District of New Jersey dated 3 March 2008, handed in a case that concerned the U.S. patent no. 6 787 531, the subject matter of which had been identical to that of the patent at issue in the case before the EPO. The litigation addressed the clinical trials that had taken place in the United States before the priority date of the European patent. During it, certain key facts about the trials were ascertained: e.g., that their participants had been informed about the active ingredients of the product, however, they had not signed confidentiality agreements. Furthermore, it was determined that not all pills handed out to patients had been returned.

The importance of confidentiality agreements

In the lack of appropriate agreements obliging participants of trials to maintain confidentiality, it is highly likely that we might be facing a situation qualifying as making an invention available to the public in the meaning of Art. 54(2) of the EPC.

In the case of the clinical trials of *Yasmin* that were carried out in the United States, such agreements were signed only with the principal investigators, however, not with the participants. The participants, at the same time, were informed about the active ingredients of *Yasmin*; they were not only aware of the fact that drospirenone was applied in a micronized state.

Decision in the *Yasmin* case **references an established case law of the EPO board of appeal, in accordance with which if a single member of the public, who is not under an obligation to maintain secrecy, has the theoretical possibility to access particular information, this information is considered as being available to the public.**

It should be remarked that **confidentiality agreements can be concluded not only explicitly, but also implicitly**. Pursuant to the EPO case law, such an implicit obligation to maintain secrecy, in principle, would be incumbent on the medical staff involved in the trial. Bayer argued that participants of *Yasmin* trials were also implicitly bound by confidentiality. The Technical Board of Appeal, referring to decisions **T 0152/03** of 22 April 2004 and **T 0906/01** of 28 September 2004, held, nevertheless, that the possibility of determining that participants were implicitly bound by confidentiality was limited to a narrow, quite specific group of situations. In the trials that the above mentioned decisions concerned prototype devices were to be implanted in a small number of patients (embolization coils in the former and spinal stabilization system in the former) — **the participants were not in a position to pass prototypes to third parties or to inspect themselves.** Such circumstances were absent in the case of *Yasmin.*

As a side note, it is worth pointing out that participants would not be implicitly bound by confidentiality if they were actively encouraged to discuss the trials with their close ones and family doctors — in such a case, it is presumed that the information was made publicly available (such was the assessment of the Board of Appeal in the case *(***T 0239/16**).

Taking tablets home

The characteristic of particular clinical trials is a crucial factor. The Technical Board of Appeal drew important consequences from the fact that **the conducted clinical trials of *Yasmin* involved a large number of patients who were given tablets to take home with them and use**

for a considerable time. The Board acknowledged findings of the U.S. Courts regarding the participants' failure to return all of the pills. It concluded that "after having handed out the drugs the respondent effectively lost control over them as the participants in the clinical trials were in no way barred from disposing of the drugs as they wanted". Considering those circumstances, **the Board found that handing tablets to patients made them publicly available.**

Would the skilled person be able to determine the composition of the product

What remained for the Board's to assess was **the fact that participants had not been informed that one of the active ingredients was in micronized state.** In that case, the Technical Board of Appeals had to determine whether the skilled person would be able to determine that drospirenon had been subjected to micronization. A positive conclusion would mean that the compound had been the state of the art before the priority date.

The Board referred to the decision in case G 1/92, according to which **"the chemical composition of a product is state of the art when the product as such is available to the public and can be analysed and reproduced by the skilled person, irrespective of whether or not particular reasons can be identified for analysing the composition"**. If the skilled person can discover the composition or internal structure of the given product and subsequently reproduce it without undue burden, then product as well as its composition and internal structure constitute the state of the art. **The Technical Board of Appeal concluded that the size of drospinenon particles could have been ascertained through RAMAN spectroscopy which did not entail any considerable difficulties.**

Let us add that Bayer argued as well that the dosage regimen of the contraceptive in the clinical trials comprised of 21 hormone-containing tablets and 7 placebos. Therefore, it could not have been determined with absolute certainty whether among the unreturned tablets there were those containing drospirenon. The Board did not find this argument convincing: it found that **since the participants of the trials were not bound by confidentiality, the public character of the prior use, rather than being restricted to the unreturned tablets, concerned all the tablets handed out to the participants.** The skilled person would not have any difficulties distinguishing between tablets containing active ingredients and those devoid of them.

A more lenient standard of the assessment in the United States

It is also worth pointing out that the District Court for the District of New Jersey, although confronted with a very similar state of facts with respect to the corresponding U.S. patent, reached **entirely different conclusions regarding novelty.** Notwithstanding that ultimately the patent was invalidates as obvious, **the Court held that the clinical trials had not constituted the public use of the medicine.** It based that position on the following circumstances: (1) the confidentiality obligation binding on investigators; (2) the lack of disclosure of the state of drospirenon to the participants.

In the United States **clinical trials are treated more leniently from the point of view of the assessment of novelty**, comparing to the EPO case law. Trials can be considered as irrelevant for the state of the art due to their confidential or experimental character.

Lessons from the case Daiichi Sankyo T 0670/20

Moving back to the EPO: although the Technical Board of Appeals examining the opposition filed against the European Patent EP 2140867 owned by Daiichi Sankyo Company reached a fundamentally different decision regarding the fulfillment of the novelty criterion (confirming the novelty of the claimed invention), **that ruling is undoubtedly consistent with the approach presented by the EPO in the previous decision. In fact, it shall be properly viewed as an elaboration of the established line of reasoning.**

This time, the Board focused primarily on the factual circumstances: despite conducting the second phase of clinical trials with the use of the preparation later submitted for patent protection, the novelty of the invention was preserved on the date of the filing of the patent application. The fact that all the investigators participating in the clinical trials were required to maintain confidentiality was taken into account. In addition, when assessing the risk of disclosure of the preparation used during clinical trials by patients taking it, **it was noted that the patients were required to take all doses of the preparation that they had been provided, and in the event of resignation from further participation in the research, they were obliged to return the remaining doses.** It was in particular that latter circumstance that turned out crucial in the Board's assessment, enabling it to conclude that the patients participating in the trials should not be treated as third parties ("members of the public") who had full freedom to dispose of the tablets provided to them during the tests, in particular when it comes to examining their composition and structure. According to the Board, it was irrelevant that the obligation to return unused tablets had not entailed any sanctions in case of non-compliance. In the Board's opinion, the conditions of the clinical trials and the commitments made by the researchers and patients were sufficient to prevent the

conclusion that during these trials the invention could have been disclosed in an uncontrolled manner to third parties, and as a result, the novelty could have been lost.

In consequence, taking into account said circumstances**, the Board confirmed the novelty of the claimed preparation**. The most important conclusion that can be drawn from the decision T 0670/20 is **the indication of certain minimum standards that should be met so that during clinical trials there is no public use of the invention that would destroy the novelty of the later patent application.** The key issue appears to be to determine whether all study participants and especially patients cannot be considered as third parties who could dispose of the tablets received during the study in any way. In the present case, such a risk was eliminated by obliging the investigators to maintain confidentiality and obliging patients to comply with the recommended dosage and to **return unused tablets.**

The sooner the application is filed, the better?

In the context of the presented case-law a question rises regarding the best moment for filing a patent application. Of course, it is crucial to avoid a scenario where while we are waiting, a given invention becomes the state of the art. However, could filing an application before the start of clinical trials shield us effectively from risk? The case law of the EPO shows that it is not that simple — it might be the case that an application is filed *too early.*

Here, we are touching the problem of **rendering the purported effect of our invention credible — the concept referred to as "plausibility".** While plausibility is not a formal ground for the rejection of a patent application or the invalidation of a patent already issued, it can be noticed how it is successively developed in the EPO case law. It is meant to curb practices of applicants who provide whole comprehensive lists of speculative uses of their inventions.

The key point of reference in that regard is the decision of the Board of Appeal of 1 February 2017 handed in case **T 488/16** concerning the invalidation of the European patent no. 1 169 038 held by Bristol-Myers Squibb Holdings Ireland. The application itself disclosed quite a numerous set of chemical compounds, however the subject matter of the proceedings before the Board was limited to just one of those compounds — dasatinib. Dasatinib, sold under the commercial name *Sprycel*, belongs to the group of inhibitors of tyrosine kinases and finds application as an anticancer drug. Importantly, **the application filed indicated that all the listed chemical compounds act as inhibitors — no concrete data demonstrating that effect was provided.** In the patent description the applicant included barely a general statement: "compounds (…) have been tested in one or more of these assays and have shown activity".

The Board of Appeal held that if "the nature of the invention is such that it relies on a technical effect, which is neither self-evident nor predictable or based on a conclusive theoretical con-

cept**, at least some technical evidence is required to show that a technical problem has indeed been solved"**. Subsequently, the Board stated that it is not permissible to limit an application to disclosing a generic formula, vaguely indicating an effect and "leave it to the imagination of the skilled reader or to future investigations to establish which compound inhibits which kinase and is therefore suitable to treat the respective diseases associated therewith".

Thus, the invalidation of the patent by the Opposition Division was upheld in the *Sprycel* case: the invention lacked the inventive step because it barely indicated a new chemical structure and, in consequence, did not disclose sufficiently its use.

In other words, **the more data obtained during the trials can be included in the application, the greater is the chance that a patent will be issued, and afterwards, in case of an opposition, its defense will be successful.** A tension, therefore, reveals itself between the pressure to file an application as soon as possible and the necessity to collect the experimental data corroborating the effect produced by the invention.

Conclusion: the recommended actions

Filing an application before the start of clinical trials entails a risk — this is quite an appealing option as long as we are able to present results of pre-clinical or *in vitro* trials. It appears that **the most sensible approach is to take proper legal precautions** — in particular, making sure that all the participants are bound by confidentiality. Certainly, it is reasonable to sign an appropriate agreement with each of them but also when it comes to planning the trial, **it must be carefully considered what information are shared with participants and in what manner.** The most secure option involves trials in closed-off settings (e.g., a hospital) where the transfer of information outside is under control.

Trials which involve handing down tablets to patients who later take them at home, cause particular challenges with respect to ensuring that the tested medicinal products do not become the state of the art. The decision in the Daiichi Sankyo case demonstrates, however, that even in the case of such trials it is possible to avoid the loss of novelty: the Technical Board of Appeals concluded that obliging the patients to follow a specified dosage regimen and to return the unused tablets (even without sanctions for non-compliance) constitutes in that regard a sufficient precaution.