Clinical trial disclosures and patentability at the EPO – Part 1

Clinical trial disclosures can play a pivotal role in shaping the patent landscape. Whilst such public disclosures can showcase a company's innovative developments, they can also place new information, including new data, into the public domain that may present challenges to overcome for demonstrating novelty and inventive step for later patent claims. The timing and content of these disclosures are crucial considerations for pharmaceutical and biotech companies seeking to protect their intellectual property.

Companies are faced with important strategic decisions around filing patents early in the development process, possibly before clinical trial results are available, versus filing later with clinical trial results and delaying publication of trial outcomes to prevent prior art from interfering with patent claims. Such decisions have been brought to the fore in view of an increased focus from regulatory authorities on transparency and therefore public disclosures. Understanding the legal issues and, in particular, the rapidly developing case law at the EPO, are key for decision making.

In the first part of this two-part article, we discuss the changes regarding the publication of information relating to clinical trials at the European Medicines Agency ('EMA') and patent filing strategy considerations as a result. We then review decisions of the EPO Boards of Appeal where the novelty of therapeutic use claims or product claims was assessed in view of clinical trial related disclosures.

In the second part to be published in the April issue of the CIPA Journal, we will discuss decisions of the EPO Boards of Appeal where inventive step of therapeutic use claims or product claims was assessed in view of clinical trial prior art. We will also consider whether product codes in clinical trial prior art documents affect the status of such documents as relevant prior art against patent claims, particularly in the context of inventive step.

Nadège Beynon and Sophie Skidmore.
See author details on page 34.

Balancing transparency and innovation: Regulatory clinical trial disclosures and strategic approaches to patent filings at the EPO

In the context of drug development, information relating to a drug, as well as details about its use in therapy, will be of high commercial importance and therefore at the centre of patent protection strategies. As a result, information disclosed in clinical trial documents submitted to regulatory agencies may be directly relevant to a patentable invention. Such information includes disclosures relating to the drug being investigated, such as its structure and methods of making it, but also how it is formulated (e.g. the excipients used in the formulation) and whether it is combined with one or more other drugs. Other relevant disclosures relate to the clinical trial design and include the dosage of the drug, the administration schedule, the route of administration, as well as the patient group being treated. By Gabriela Staber and Nadège Beynon.

Regulatory clinical trial disclosures at the European Medicines Agency

European Union pharmaceutical legislation known as the Clinical Trials Regulation entered into force on 31 January 2022.[1] It aims to ensure the EU offers an attractive and favourable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants. Before the Regulation, clinical trial sponsors were required to submit separate applications to the national competent authorities and ethics committees in each country to obtain regulatory approval for conducting a clinical trial. The Regulation streamlines this process by allowing sponsors to submit a single online application through the Clinical Trials Information System ('CTIS'), thereby enabling approval for running clinical trials across multiple European countries more efficiently.

The transparency rules, revised in June 2024, govern the publication of clinical trial information submitted via CTIS. These rules aim to balance transparency and the protection of personal data and commercially confidential information ('CCI'). In this respect, the European Medicines Agency ('EMA') considers that a piece of information can be considered CCI if it meets simultaneously the following two criteria: (1) not being in the public domain or publicly available and (2) its disclosure would undermine the legitimate economic interests or competitive position of the concerned entities, e.g. sponsor, marketing authorisation applicants/holders or service providers, unless there is an overriding public interest in the disclosure.[2,3] The mere fact that certain pieces of information are not publicly available does not automatically imply that the information can be classified as CCI. For example, information describing the compliance with regulatory and scientific guidelines and application of scientific knowledge available at the time of the trial lacks any innovative elements since it is 'built upon logic and common sense in line with the content of publicly available documents' and can therefore not be considered CCI.[4]

The EMA Guidance indicates that the following are examples of elements that may be considered CCI[5]:

- The excipients' quantitative composition of the investigational product.
- Detailed information on the synthesis or manufacture of the active substance.
- Information related to future development plans for indications other than the one under investigation and not yet disclosed in the public domain.
- New biomarkers or novel methodologies not yet qualified.
- Detailed information concerning innovative analytical methods.
- Details of the daily dose allowed and maximum dose allowed for the medicinal product under investigation.

1. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
2. EMA's definition of CCI in EMA/212507/2021 Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System ('CTIS') Version 2 (18 June 2024) in accordance with POLICY/0043 (EMA/729522/2016; 4 October 2018).
3. Overriding public interest applies in exceptional circumstances only, e.g. in case of declared pandemic, public health emergency.
4. EMA/212507/2021 Guidance document on how to approach the protection of personal data and commercially confidential information while using CTIS Version 2 (18 June 2024).
5. EMA/212507/2021 Guidance document on how to approach the protection of personal data and commercially confidential information while using CTIS Version 2 (18 June 2024).

<table>
<tr><th rowspan="3">Exemplary documents and data subject to publication[1]</th><th colspan="3">Publication timelines</th></tr>
<tr><th colspan="2">Category 1
Pharmaceutical development clinical trials
Phase 0 trials
Phase I trials</th><th rowspan="2">Category 2
Therapeutic exploratory and confirmatory clinical trials
Phase I and phase II integrated trials
Phase II trials
Phase III trials
& Category 3
Therapeutic use clinical trials
Phase III and phase IV integrated trials
Phase IV trials</th></tr>
<tr><th>Paediatrics and/or PIP [2]</th><th>Adults</th></tr>
<tr><td>CTIS Application fields regarding information relating to the phase, the therapeutic area, the patient group being treated</td><td colspan="2">Upon first MSC decision [3]</td><td rowspan="4">Upon first MSC decision[4]</td></tr>
<tr><td>CTIS Application fields regarding information on the dosage and administration schedule</td><td colspan="2">30 months after the end of trial date in EU/EEA</td></tr>
<tr><td>Protocol</td><td>Upon results' submission</td><td>30 months after the end of trial date in EU/EEA</td></tr>
<tr><td>Summary of Product Characteristics (SmPC)</td><td colspan="2" rowspan="3">Never</td></tr>
<tr><td>Recruitment arrangements, including procedures for inclusion and copy of advertising material</td><td rowspan="2">Upon relevant MSC decision[5]</td></tr>
<tr><td>Subject information and informed consent form</td></tr>
<tr><td>Final summary of results, including lay person summary [6]</td><td>Upon submission</td><td>30 months after the end of trial date in EU/EEA</td><td rowspan="2">Upon submission</td></tr>
<tr><td>Clinical study report</td><td colspan="2">Upon submission</td></tr>
</table>

1. Documents that often contain CCI such as, but not limited to, the Investigator's Brochure (IB), Investigational Medicinal Product Dossier (IMPD) documents, and assessment reports are not made public.
2. Paediatric Investigation Plan (PIP).
3. Upon the first decision by a Member State Concerned (MSC) on the authorisation of the clinical trial application.
4. Upon the first decision by a Member State Concerned (MSC) on the authorisation of the clinical trial application.
5. Upon decision by the relevant Member State Concerned (MSC).
6. Interim results are not made publicly available.

Examples of data and documents submitted to CTIS that are subject to publication are set out in the table on page 33.[6] Disclosure timelines in accordance with the rules mainly depend on the trial category, the trial phase, and the trial population age. CTIS allows users to submit both a 'for publication' version and a 'not for publication' version of documents. This feature enables the redaction of personal data and CCI from the versions that are publicly published. It lies within the responsibility of the user to ensure that the version for publication does not contain such information.[7]

The structured data fields filled out on the CTIS application form, which include information on the trial title, study design, inclusion and exclusion criteria, primary and secondary endpoints, details on the investigational medicinal product, clinical investigator sites in the Member States where the trial is to be conducted, and the sponsor's contact details, cannot be redacted. Therefore, for these fields consideration should be given to using 'blank' entries (e.g. 00 digits) for information that should be exempted from publication, since otherwise that data may be published. The full information should, however, be provided to the Member States for assessment in the document version 'not for publication'.[8]

6. EMA/194159/2023 Annex I: Guidance document on how to approach the protection of personal data and commercially confidential information while using CTIS (13 December 2024). Of note, 'historical trials' submitted to CTIS before the 18 June 2024 are subject to specific publication rules designed to avoid unintended disclosure of confidential information contained in documents which could have been subject to deferrals under the previous transparency rules.
7. EMA/194159/2023 Annex I: Guidance document on how to approach the protection of personal data and commercially confidential information while using CTIS (13 December 2024).
8. EMA/898965/2022 Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS, Section 3.3.

Other regulatory clinical trial disclosures

Of course, whilst we focus here on the recent changes on the publication of clinical trial information at the EMA, clinical trial publication in any jurisdiction will be relevant to a patent filing strategy. This is because there 'are no restrictions whatever as to the geographical location where or the language or manner in which the relevant information was made available to the public' for a disclosure to form part of the start of the art.[9]

Strategic approaches to patent filings at the EPO

Any disclosure concerning a drug and/or its therapeutic use will constitute prior art for a patent application related to the drug or therapy in question and therefore may be detrimental to a patent being granted. Therefore, in view of the regulatory requirements for publication of clinical trial related information, appropriate redaction of clinical trial documents as discussed above may be critical for existing and future patent applications. Additionally, the presence or absence of confidentiality agreements during a clinical trial, e.g. between the study sponsors and the patients taking part in the trial, can affect how much of the trial information becomes prior art for a patent application. As a result, effective communication amongst scientists, regulatory team members and patent counsels is essential to consider patent filing strategies.

The challenge of determining the optimum time to

9. EPO Guidelines (March 2024), G-IV, 1; Article 54 (1) & (2) EPC.

CLINICAL TRIAL DISCLOSURES AND PATENTABILITY AT THE EPO – PART 1

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file a patent application is a balance between filing before clinical trial documents are published, as these documents could become prior art[10] against the application relevant for the assessment of novelty and inventive step, and providing sufficient data in the application to meet disclosure requirements. In the context of a medical use claim, if a therapeutic application is to be accepted as sufficiently disclosed, the application and/or the common general knowledge has to provide some information rendering it 'technically plausible for the skilled person that the claimed compounds can be applied for the claimed therapeutic use'.[11] Applicants therefore must consider both the risk of additional publications being added to the state of the art when filing late and the risk of insufficiency of their own invention when filing early.

10. 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 relevant priority/filing date of the European patent application.
11. *Case Law Book*, 10th Edition, II.C.4.1 and I.C.7.2.2(a).

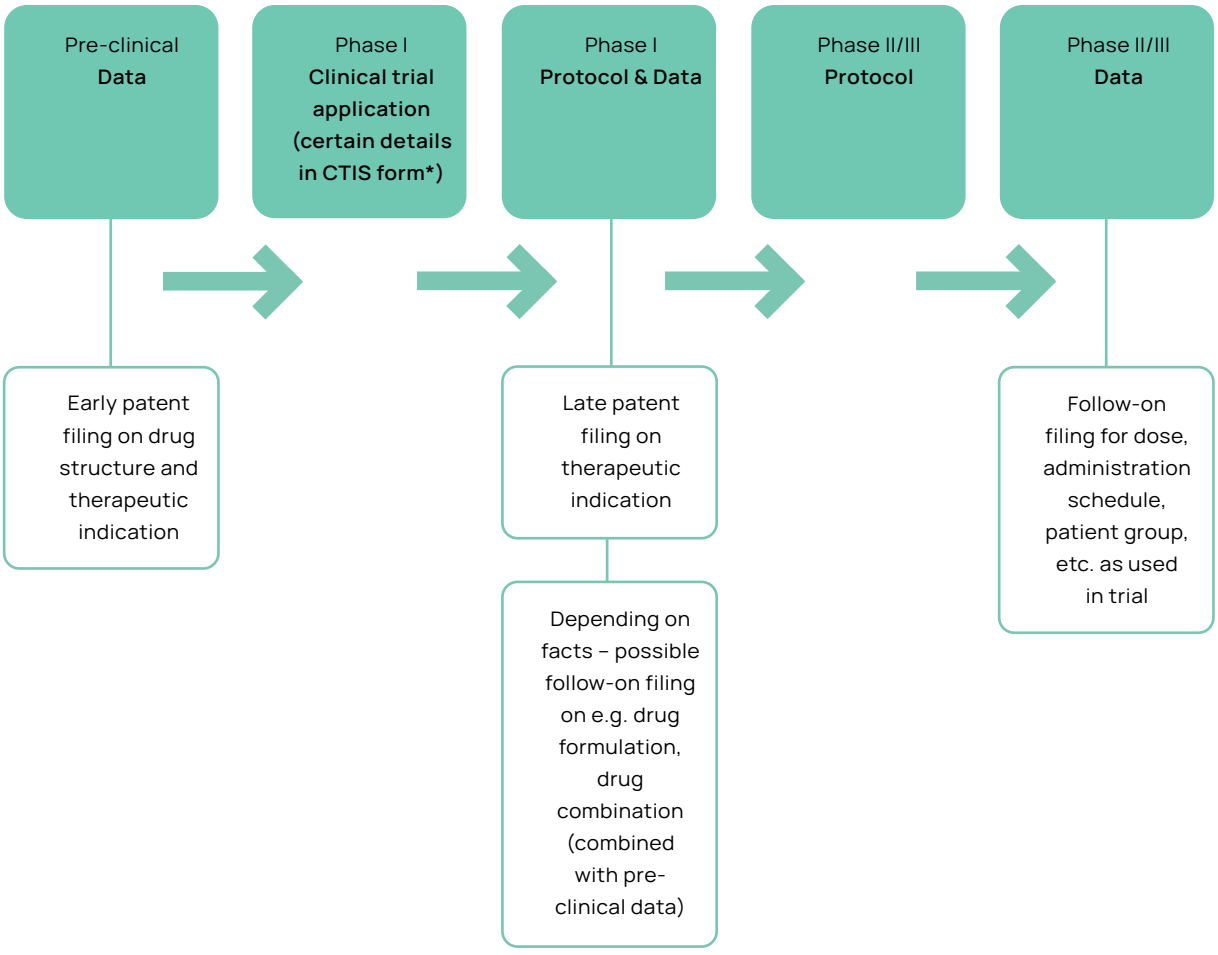
As explained above, the phase of a clinical trial will determine its category with regard to the CTIS disclosure timelines. Of course, the relevance of clinical trial related disclosures will depend on the information already in the public domain regarding the subject matter of interest, e.g. the drug and/or therapy being investigated.

Phase 0 and I clinical trial data

A Phase 0 clinical trial is conducted to collect initial data on the behaviour of a new drug in the human body and to assess its potential harm, with no information regarding its possible therapeutic or prophylactic use. This type of trial generally involves a very small group of participants.

A phase I clinical trial typically is the first time a new treatment is tested in humans, and focuses on the drug's pharmacokinetics (its behaviour within the human body) and pharmacodynamics (its effects on the body). A phase I study may also explore drug interaction evaluations or food effect studies that examine how eating affects drug

Diagram illustrating the relationship between potential patent filing strategies at the EPO and regulatory clinical trial disclosures at the EMA



*See publication timelines table for more details.

absorption. Phase I studies are often conducted in healthy volunteers but can sometimes be conducted in patients.

Thus, phase I data may support a medical use claim, for example regarding the formulation of a drug, whether it is combined with one or more other drugs, but also the dosage of the drug, the administration schedule, the route of administration, and sometimes the patient group being treated. However, due to its exploratory nature, phase 0 data is unlikely to support a medical use claim.

Phase II and III clinical trial data

A phase II clinical trial primarily aims to evaluate a treatment's effectiveness while also continuously monitoring its safety. A phase III clinical trial involves a larger cohort of patients with the goals of confirming treatment effectiveness, monitoring side effects, and comparing outcomes with standard treatments.

Accordingly, phase II and III data may support the therapeutic effect of a drug tested in the trial. Of course, at this point the therapeutic use may be known in the art in view of preclinical and/or phase I data, and therefore the patent claim is likely to be directed to a more 'complex' medical use, such as the dosage of the drug, the administration schedule, the route of administration, as well as the patient group being treated, but also the drug formulation and whether it is combined with one or more other drugs.

Filing before the disclosure of the clinical trial

A first option is to file before a planned clinical trial is announced, and therefore for phase II and phase III trials before a clinical protocol is disclosed, such that the announcement of the clinical trial will not be prior art against the patent application. This strategy is suitable where it is sufficient to rely on, e.g. preclinical evidence (in vitro and/or in vivo in animal studies) that reflects the therapeutic application to comply with the sufficiency and inventive step requirements. In this case, post-published evidence such as clinical data may also be taken into account under certain conditions.

In this situation, although redacting clinical trial documents may not be necessary, it could still be beneficial to consider redaction to preserve potential future filings.

Filing upon completion of the clinical trial

A second option is to file upon completion of the clinical trial so that the trial data can be included in the patent application. This situation is relevant where, e.g. preclinical data is unlikely to be enough to meet the requirements of sufficiency of disclosure and/or inventive step. This would also be relevant where, upon completion of the trial, unexpected results are obtained, such as a patient sub-population responding exceptionally well, which was not anticipated at the outset.

Therefore, measures should be put in place to minimise any disclosure during the clinical trial which may be detrimental to the patent application.[12] This would include appropriate redaction of clinical trial documents, establishment of appropriate confidentiality agreements, e.g. between the study sponsors and the patients taking part in the trial, as well as limiting other disclosures such as press releases, publications in scientific journals and conferences.

Conclusion

Clinical trial disclosures play an important role in patent filing strategies. As highlighted in this article, the disclosure timelines mandated by regulatory agencies such as the EMA can be largely predicted, thus aiding navigating around these. However, due to the unpredictability of trial outcomes, a cautious approach is to always ensure appropriate redaction of clinical trial documents, as well as the establishment of appropriate confidentiality agreements. It is important to also account for other forms of disclosures, such as press releases, publications in scientific journals, and conference presentations.

As the case law indicates, addressing prior art disclosures related to clinical studies can be challenging, and we examine this topic in our EPO Boards of Appeal case law review, focusing on novelty and inventive step. Consequently, it is evident that patent filing strategies must fully consider regulatory activities throughout the entire life cycle of a drug.

12. The EPO Boards of Appeal case law supports the position that, where a clinical study is announced, there is a 'reasonable expectation of success' of achieving the therapy disclosed unless there is 'prejudice or teaching away' in the art which would have dissuaded the skilled person to put the clinical trial proposal into practice, as will be discussed in Part II of this article.

Clinical trial disclosures and their impact on novelty at the EPO

Whilst the novelty of a claim over a prior art disclosure may often appear straightforward, unique scenarios arise in the context of clinical trial prior art disclosure. Here Nadège Beynon and Sophie Skidmore provide an overview of case law in relation to two main topics: (1) whether the prior art discloses that the claimed therapeutic effect is achieved, and (2) prior art in the form of public prior use, where a duty of confidentiality is considered.

Attaining the claimed therapeutic effect

It is established case law that to be novelty destroying, a prior art disclosure must meet the standard of direct and unambiguous disclosure of the claimed subject matter. Additionally, a disclosure destroys novelty only if the teaching it contains is reproducible, i.e. if the information provided is sufficient to enable the skilled person, at the relevant date and taking into account the common general knowledge in the field at that time, to practise the technical teaching.[1]

In relation to medical use claims, achieving the therapeutic effect is a functional technical feature of the claim (T 209/22). Therefore, as acknowledged in a number of Board of Appeal decisions, for assessing the novelty of a medical use claim it has to be examined whether or not the same therapeutic effect has been credibly achieved in the prior art disclosures.[2] According to the case law of the Boards of Appeal,[3] 'if a prior art document disclosed clinical investigations such as phase I, II or III studies (or stated that these investigations were ongoing), but failed to disclose the final result of these studies, it was not novelty-destroying'.[4] Further, in T 2506/12, the Board held in relation to a combination therapy that 'the aspects of both efficacy and safety have to be taken into account to determine whether an effective treatment is (implicitly) disclosed in the prior-art citations', since '[a] treatment which caused unacceptable harm to patients would not be considered an effective treatment within the usual meaning of the term' (s.2.8[5]).

In T 209/22, the Board held that a phase I clinical study in healthy volunteers did not anticipate a claimed use for the treatment of chronic obstructive pulmonary disease ('COPD') and/or asthma since the subjects treated did not suffer from COPD and/or asthma. The Board found that the prior art did not meet the criterion of direct and

In relation to medical use claims, achieving the therapeutic effect is a functional technical feature of the claim. Therefore, for assessing the novelty of a medical use claim it must be examined whether the same therapeutic effect has been credibly achieved in the prior art disclosures.

1 *Case Law Book*, 10th Edition, I.C.4.1 and I.C.4.11; T 108/21.
2 E.g. T 158/96, T 1437/21 and T 2506/12.
3 E.g. T 1859/08, T 158/96 and T 715/03.
4 *Case Law Book*, 10th Edition, I.C.4.1.
5 In this article, references after the quotes refer to the relevant section of the Reasons.

unambiguous disclosure with regard to attaining the claimed therapeutic effect (s.5.6.1).

Interestingly, in T 158/96, the Board considered that the disclosure of a phase II trial 'implicitly taught' the skilled person that 'the tested substance must have complied with all the requirements of the previous clinical phase I and pre-clinical investigation'. The Board considered that if the claimed therapeutic effect had already been proven in phase I trials or during pre-clinical experimentation, then the teaching of the prior art disclosing a phase II study directed to the claimed subject-matter but lacking any data would have been regarded as prejudicial to the novelty of the claimed subject-matter. As discussed below, this was not the case in T 158/96, however, since the claimed therapeutic use had not been shown or proven during phase I trials or during pre-clinical experimentation. Therefore, whether the claimed therapeutic effect had already been 'shown or proven' will depend on the evidence on file, e.g. on positive results from preclinical or earlier clinical studies relating to the therapeutic application. Considerations in this respect include whether the preclinical studies have been conducted using an appropriate animal model of the disease, and/or whether the earlier clinical studies have been conducted in a patient population having the disease and demonstrated that the claimed therapeutic effect has been achieved. Thus, whilst the announcement of a clinical trial implies that previous steps, such as preclinical studies and/or earlier clinical studies, have been complied with, it is by no means sufficient in itself to destroy the novelty of a therapeutic use claim.

In T 799/16, the Board considered that the claimed dosage was novel over the disclosure of the results of a phase II clinical study because the results were not conclusive for the particular claimed dosage. Notably, the Board commented on the design of the prior art clinical study, stating that '[i]f the study had been intended to compare the efficacy of individual dosages, it would not have been designed as a dose-escalation study with only a short period of time on any one dose'. The Board also considered that the number of participants and placebo control in the study was relevant to draw conclusions on the efficacy of a dosage. In relation to a particular graph relied on by the opponents, data relating to 25 patients receiving the drug was not considered sufficient. The Board considered that this small number would 'increase the risk that the data would be distorted by noise, in particular since only one measurement per dose was taken'. Additionally, the data relied on by the opponents did not include results from placebo patients, and therefore 'placebo effect, known to be prominent in [multiple sclerosis], was not eliminated by comparison with a placebo control group' (s.5.5.3).

Therefore, in the case of medical use claims where the novelty relies on a feature other than the condition being treated, e.g. dose or patient population, whether the same therapeutic effect has been shown in a prior art document will heavily depend as to whether the prior art disclosure is conclusive for said feature.

Selection of decisions of the Boards of Appeal[6]

Prior art disclosure of a phase I clinical study in healthy volunteers

In **T 209/22**, the claims were directed to a once daily combination therapy for the treatment of chronic obstructive pulmonary disease (COPD) and/or asthma. The patent provided data for each of the claimed drugs as monotherapies in COPD patients. The patent also provided data for the claimed combination in healthy volunteers. However, no data was provided for the claimed combination in patients having COPD or asthma.

A clinical trial protocol disclosing a phase I clinical study in healthy volunteers corresponding to the experimental set-up on healthy volunteers described in the patent was full prior art against the claims of the patent.

The Board stated that in accordance with well-established case law of the Boards of Appeal, 'where a therapeutic application is claimed in the format provided in Article 54(5) EPC (as is the case for present claim 1), attaining the claimed therapeutic effect is regarded as a functional technical feature of the claim that may establish novelty or inventive step' (s.2.2). Accordingly, the Board considered that a clinical trial prior art in healthy volunteers could not have anticipated the claimed combination therapy for the treatment of chronic obstructive pulmonary disease (COPD) and/or asthma 'simply because the study subjects did not suffer from COPD or asthma' (s.4.2).

In this case, sufficiency of disclosure and an alleged squeeze with novelty as argued by the appellants (opponents) was also discussed.

To meet the requirements of sufficiency of disclosure, it needs to be assessed whether the claimed combination therapy for the treatment of COPD and/or asthma by once-daily administration was credible at the effective date, based on the information provided in the patent application together with the common general knowledge then available to the skilled person. As noted above, whilst the patent application did not provide any data for the claimed combination in patients having COPD or asthma, the application provided data for each of the claimed drugs making the combination as monotherapies in COPD patients, as well as for the claimed combination in healthy volunteers. The Board considered that based on these data, there was 'a strong presumption' that the claimed combination therapy 'would be effective in the treatment of asthma or COPD, and that a dosage regimen of once-daily administration would be feasible' (s.5.4.5).

Regarding the alleged sufficiency and novelty squeeze,

6 The Reasoning of the Boards for the decisions discussed in this section is provided in relation to novelty only. Where applicable, the Boards' reasoning in relation to inventive step will be discussed in the second part of this article to be published in the next issue of the *CIPA Journal*.

the Board held that '[t]o be novelty-destroying, a prior-art disclosure must meet the standard of direct and unambiguous disclosure of the claimed subject-matter. This criterion was not met by [the clinical trial prior art] with regard to attaining the claimed therapeutic effect, because the study was performed with healthy subjects' (s.5.6.1). In contrast, the assessment as to whether the claimed therapeutic effect was credible at the effective date and thus sufficiently disclosed 'is by no means restricted to the description of the combination study [in healthy volunteers in the application] but can be based on any pertinent content in the application as filed, in view of common general knowledge at the effective date' (s.5.6.3).

Prior art disclosure of a phase I clinical study in patients

In **T 2506/12**, the claims were concerned with the further therapeutic application of ET-743 (claim 1) or PLD (Pegylated Liposomal form of the anthracycline Doxorubicin) (claim 2) in the treatment of cancer of the human body by combination therapy employing an effective therapeutic amount of ET-743 with an effective therapeutic amount of PLD. Since both ET-743 and PLD were already known, the novelty could only derive from the therapeutic application (s.2.3).

The prior art disclosed a phase I clinical trial for the claimed combination in human cancer patients (s.2.5). Since the prior art did not disclose results of the trial, there was no explicit disclosure of the claimed therapeutic application. The Board considered whether there was an implicit disclosure of an effective treatment. With reference to T 1859/08, the Board said that the 'relevant criterion is whether it is accessible, i.e. disclosed, rather than hidden' (s.2.6). Whilst PLD was already known to have efficacy in the relevant therapeutic application, it was not previously known that ET-743 used alone provided efficacy combined with acceptable safety; nor was it disclosed in the prior art that the combination treatment provided efficacy combined with acceptable safety (s.2.7). However, ET-743 in combination with another drug was reported in the prior art to have shown favourable preliminary results in clinical phase II studies (s.2.10). The Board found that 'the aspects of both efficacy and safety have to be taken into account to determine whether an effective treatment is (implicitly) disclosed in the prior-art citations', since '[a] treatment which caused unacceptable harm to patients would not be considered an effective treatment within the usual meaning of the term' (s.2.8). Since 'nothing was known or disclosed about the safety of the combination therapy', the Board considered that the skilled person would not have been able 'to exclude the possibility that ET-743 and PLD might interact to produce unacceptable adverse effects, and in combination might reach dose-limiting toxicity before reaching the threshold of pharmacological efficacy' (s.2.12). Therefore, the Board found the claimed therapeutic use novel over the phase I clinical trial disclosure.

Prior art disclosure of a phase II clinical study

T 158/96 relates to an appeal of an Examination Division's decision to refuse the application. In this decision, the Board considered whether the disclosure of a phase II clinical trial protocol would anticipate a claimed medical use. The claims were directed to the use of a compound, sertraline, for the manufacture of a medicament to treat or prevent obsessive-compulsive disorder ('OCD') (medical use claim in 'Swiss type' format under EPC 1973). The prior art disclosed that the claimed compound was undergoing phase II clinical trials for OCD, but no results were provided. The Board noted that '[o]nly the successful approval of the drug in the subsequent phase evaluation, namely phase III, would imply an implicit positive answer' (s.3.4.1).

The Board explained that the claim was 'to be construed as implicitly including the functional technical feature that sertraline achieves a therapeutic effect'. 'For the purpose of assessing novelty, it thus has to be examined whether or not the same therapeutic effect has been shown in the prior art documents' (s.3.1).

The Board considered that the disclosure of the phase II trial 'implicitly taught' the skilled person that 'the tested substance must have complied with all the requirements of the previous clinical phase I and pre-clinical investigation' (s.3.5). However, in this case the Board '[recognised] as plausible the appellant's arguments, though not confirmed by documents, that experimentation in animals was not indicative of any therapeutic effectiveness of sertraline for OCD since no animal model for OCD actually existed [at the effective date], but was simply intended to prove the lack of any form of toxicity and to gain early knowledge about the metabolism of the substance'. In addition, no conclusion could be drawn from the results of the phase I clinical trial (s.3.5.2 and s.3.6.2). In particular, the Board noted that it is 'not exceptional that a pharmacological effect observed in an early investigation may directly and unambiguously reflect a therapeutic effect, thus underlying a therapeutic application', but that this is 'not a general or absolute rule'. In this case, the Board considered that there was no evidence at the priority date showing that the mechanism of action evidenced by the phase I pharmacological data had a 'clear and accepted relationship' with OCD. As a result, the skilled person 'had no means of concluding with the required certainty that any evidence of a therapeutic effect in relation to OCD could have been produced by the results of the pharmacological studies carried out in clinical phase I'. (s.3.5.2). Therefore, the claimed therapeutic use was found novel over the cited art.

The case was remitted to the first instance for further prosecution and a patent was granted. The patent was then revoked in opposition proceedings in view of a different prior document disclosing effective treatment of OCD with the claimed compound. The Opposition Division's decision was not appealed.

Interestingly, in this decision the Board noted that if the skilled person faced with the information that sertraline was undergoing phase II trials for OCD 'was in a position to conclude with the required certainty that the anti-OCD activity of sertraline, or any other pharmacological effect, i.e. indisputably underlying such a therapeutic application, had already been shown or proven during phase I trials or during pre-clinical experimentation, then the teaching of [the prior art disclosing the phase II study] would have been regarded as prejudicial to the novelty of the claimed subject-matter' (s.3.5).

T 715/03 and T 239/16 both cite T 158/96 and refer to this point. In T 715/03 the Board similarly noted that '[t]he fact that phase II studies are running also means that phase I studies are concluded. However, from this information the skilled person can only conclude that the results on safety and tolerability in humans, as well as the pharmacokinetics studies, were positive. However, there is no information about a possible beneficial effect on [Tourette syndrome] patients. Indeed, the phase I studies may be those made within the framework for the investigation of the neuroleptic and antipsychotic activity' (s.2.2). In T 239/16, the Board considered that '[t]here is no explicit or implicit indication in any of [the evidence on file] that effects of animal models… can be directly transferred to the treatment as disclosed in [a phase II clinical trial protocol]. There remains a certain residual doubt that the [therapeutic effect] is/will be achieved' (s.5.2).

However, none of the decisions citing T 158/96 concluded that an implicit disclosure of success of earlier preclinical or clinical studies based on an announcement of a clinical trial for the claimed therapy led to a lack of novelty.

In **T 799/16**, the claims were directed to a 'sustained release 4-aminopyridine composition for use in a method of increasing walking speed of a patient with multiple sclerosis, wherein said composition is administered twice daily in a dose of 10 milligrams of 4-aminopyridine'. Since the therapeutic efficacy of sustained-release 4-aminopyridine administered at 10 mg bid is a functional technical feature of the claims, this feature must be taken into account in the assessment of novelty (s.5.1). In this case, the issue was 'whether the therapeutic efficacy of the 10 mg bid dosage is specifically disclosed in the prior art' (s.5.2).

The prior art was a conference abstract reporting on a completed double-blind phase II clinical trial 'escalating-dose study of a sustained-release formulation of 4-aminopyridine, starting from 20 mg/day (10 mg bid), increased in weekly increments of 10 mg/day to 80 mg/day and administered orally to 25 multiple sclerosis patients. 11 patients received placebo treatment. The results relating to therapeutic efficacy are described as follows:

> 'The fampridine-SR group showed statistically significant improvement from baseline compared to placebo in functional measures of mobility (timed 25 walking speed; p = 0.04) and lower extremity strength (manual muscle testing; p= 0.01). Dose response curves showed increasing benefit in both measures in the 20 to 50 mg/day range.' (s.5.4).

The Board considered that '[i]t cannot be inferred from this statement in a direct and unambiguous manner that a statistically significant therapeutic benefit for walking speed was attained, specifically, with the (lowest) dosage of 20 mg/day (10 mg bid)' (s.5.4.1). The Board noted that whilst the 'first sentence does not refer to dosage at all', the 'second sentence is also consistent, for instance, with a situation where there is no improvement in efficacy relative to placebo at 20 mg/day but increasing improvement from 30 to 50 mg/day'. The disclosure was therefore not conclusive regarding the efficacy of each dosage individually.

A similar disclosure relating to the same phase II clinical trial was presented on a poster which was admitted in the proceedings as prior art against the patent. The conclusion section of the poster stated that there was 'evidence of dose-response in 20-40 mg/day range' (s.5.5.1). For the same reason as noted above, the Board found that '[t]his statement alone does not imply that therapeutic efficacy was actually shown individually at the lowest dosage of 10 mg/bid'.

Separately, the opponents attempted to argue that a graph on the poster showing a dose response curve for walking speed versus drug dosage disclosed the claimed treatment. This data related to data from patients administered the drug and not those given placebo. The opponents argued that a 'drop from about 16 seconds to about 13.5 seconds between run-in and 20 mg disclosed treatment efficacy at 20 mg/day (10 mg bid)' (s.5.5.3). However, the Board found that 'there [were] several serious reasons to doubt the significance of the drop depicted in the dose-response curve', noting, *inter alia*, that fluctuations are common and well known in MS patients, and the lack of data from patients given placebo. In addition, the Board held that 'it is not credible that the study with only 36 participants, 25 of whom received drug, was powered to enable conclusions about the efficacy of individual doses to be drawn'. 'The small sample size would increase the risk that the data would be distorted by noise, in particular since only one measurement per dose was taken. Furthermore, potential placebo effect, known to be prominent in MS, was not eliminated by comparison with a placebo control group'. The Board stated that

'[i]f the study had been intended to compare the efficacy of individual dosages, it would not have been designed as a dose-escalation study with only a short period of time on any one dose' (s.5.5.3).

Of note, the prior art also disclosed 'a late phase 2 clinical trial assessing the efficacy and safety of three doses of sustained-release 4-aminopyridine (10, 15 and 20 mg bid)', including '206 subjects' (s.5.3). However, no data from this trial was disclosed in the prior art. Rather, the data obtained in this trial was discussed in the Examples of the patent in suit.

Accordingly, the Board found the claims to be novel.

Prior art disclosure of a phase III clinical study

In **T 108/21**, an appeal of an Examination Division's decision to refuse the application, the claims were concerned with fingolimod for use in the treatment of relapsing-remitting multiple sclerosis ('RRMS'), at a daily dosage of 0.5 mg p.o..

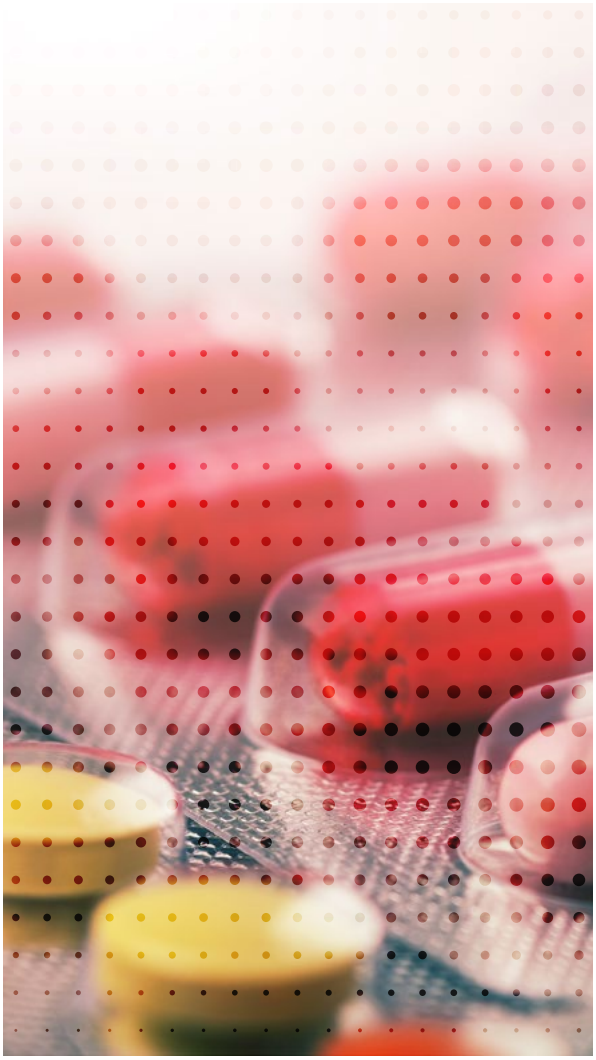
The prior art was a press release disclosing '[r]esults from a clinical phase II study showing sustained efficacy and good tolerability over 18 months in RRMS patients treated with an oral daily dose of 1.25 mg fingolimod'. The press release also disclosed 'the announcement of a clinical phase III study including more than 1000 patients with RRMS to be equally randomised to receive either 1.25 mg or 0.5 mg of oral fingolimod or placebo once daily for up to 24 months' (s.6.2).

The Board explained that 'for prior art to anticipate the subject-matter of a claim, it must, as a first requirement, disclose directly and unambiguously all the technical features of this claim in combination. As a further requirement, this disclosure must be enabling, in the sense that the skilled person must be able to carry out this disclosure on the basis of the information provided in this prior art, if required, by using common general knowledge, at the date of public availability of this prior art' (s.6.4.1). In this case, the Board considered that the prior art did 'not anticipate the subject-matter of claim 1 for failure to meet the first requirement'. The Board held that there was no mention of the therapeutic efficacy of the claimed dosage regimen. Therefore, the Board found that there was no direct and unambiguous disclosure of the effective therapeutic treatment of RRMS using the claimed dosage regimen and the claimed therapy was novel over the prior art.[7]

In **T 1437/21**, the patent claimed the use of empagliflozin for the treatment of diabetes in a sub-population of patients having moderate renal impairment.

A prior art press release disclosed results of a phase III clinical trial patient population having mild, moderate or severe renal impairment as a whole. Whilst the press releases indicated the total number of patients, no 'specific information regarding the number of participating patients with moderate renal impairment' was provided. The Board concluded that '[w]ithout this information the positive comments on the results from the trial expressed in the press releases [...] do not provide any basis for the skilled reader to conclude that as a matter of fact the [treatment] must also have been effective in the patients with moderate renal impairment' (s.3.3).

The Board found that the skilled person could not directly and unambiguously derive from the press releases that the treatment with empagliflozin was effective for 'each separate subgroup of patients defined by the mentioned levels of renal impairment', and therefore for patients with moderate renal impairment specifically (s.3.3).



7 This prior art was also discussed in the context of inventive step, as will be discussed in Part II of this article. The case was remitted to the Examination Division, and a patent was granted on 12 October 2022. The patent is currently the subject of opposition proceedings.

Prior art in the form of public prior use, where a duty of confidentiality is considered

As discussed below, where patients are provided with information relating to the conduct of a clinical trial, e.g. a clinical trial protocol and/or information on the drug being investigated, ensuring appropriate redaction of clinical documents and establishing confidentiality agreements between the sponsor and the patients can be deciding factors for the validity of a patent.

It is established case law that if a single member of the public who is not under an obligation to maintain secrecy has the possibility to access particular information, this information is considered as being available to the public within the meaning of Article 54(2) EPC.[8] Therefore, to establish whether a disclosure has been made available to the public within the meaning of Article 54(2) EPC, it may be necessary to assess whether a duty of confidentiality was imposed on the person receiving the disclosure.

In the situation of patients in a clinical trial, it may need to be determined whether the patients participating in the trial and in possession of the disclosure had entered into a special relationship with the study sponsor.

In T 239/16 and in T 670/20, the Boards considered that patients receiving information for a clinical trial giving, *inter alia*, information on the set-up of the study including details of the treatment to be given, were considered members of the public within the meaning of Article 54(2) EPC. In particular, there was no explicit or implied obligation to maintain confidentiality between the study sponsor and the patients. Instead, patients participating in the study were actively encouraged to discuss the contents of the patient information received with 'anyone' (s.4 T 239/16).

In T 670/20 and T 7/07, the Boards considered whether distribution of medicinal tablets to trial participants and the failure of the participants to return all unused medicinal tablets amounted to a prior art disclosure for the purpose of novelty. In T 670/20, the Appeal Board found that patients participating in a trial had entered into a special relationship with the investigators of the trials with regard to the medicinal tablets. Thus, the patients were not free to dispose of the medicinal tablets. As a result, the internal structure of the medicinal tablets had not been made available to the public by patients taking part in clinical trials. However, in T 7/07 the Board found that the sponsor of the trial had effectively 'lost control' over the drugs after these had been handed out to the participants of the trial as members of the public who were not bound to secrecy.

Separately, in relation to prototype devices, the Board in T 906/01 held, in line with T 152/03, that there is a *prima facie* assumption that any person involved in a medical process is obliged to confidentiality, given the

In the situation of patients in a clinical trial, it may need to be determined whether the patients participating in the trial and in possession of a disclosure (e.g. information relating to the trial and/or medicinal tablets) were under a duty of confidentiality.

8 *Case Law of the Boards of Appeal*, 10th Edition 2022, I.C.3.3.

need for patient confidentiality and the need to protect the development and testing of prototype devices. Any evidence proving the contrary must be produced as soon as possible, i.e. as soon as the party making the prior use allegation is in possession of it, otherwise, it may be disregarded by the Board (T 152/03).

Indeed, regarding allegations of public prior use of an invention, it is well established jurisprudence of the Boards of Appeal that certain strict requirements must be met for the respective ground of opposition to be deemed admissible in accordance with Rule 76(c) EPC:

> '(a) the date on which the alleged use occurred, i.e. whether there was any instance of use before the date on which the application for the relevant European patent was filed,
> (b) what has been used, in order to determine whether the object in prior use is identical with or similar to the subject-matter of the contested patent,
> (c) all the circumstances relating to the use, by which it was made available to the public, as for example the place of use and the form of use.' (s.3.2 T 152/03 and s.3.3 T 328/87).

Selection of decisions of the Boards of Appeal[9]

In **T 906/01**, the claimed subject matter related to a medical apparatus for use internally in the human body to retain spinal elements. The alleged prior use related to surgery concerning 'the implantation of a correction device (Isola Spinal System) into a patient' as part of an investigation conducted by AcroMed Corporation (s.3.2 and s.3.3). Evidence in the proceedings indicated that 'AcroMed submitted to the FDA an application for conducting Investigational Device Exemption ('IDE') studies of its Isola Spinal System' and that this was provisionally approved by the FDA. The surgeon taking part in the IDE clinical study was bound by AcroMed's Investigator's Agreement which required, *inter alia*, 'to consider as confidential any knowledge of product development and marketing information and not to disclose any information known to him by virtue of his participation in this study' (s.3.4).

The Board considered that 'a device having an investigational status, being implanted and tested within the restricted area of an hospital, under the responsibility of a surgeon operating within the frame of an investigator's agreement provided with a clause of confidentiality, must be regarded as a prototype device'. The Board held that 'the clinical tests performed on the Isola Spinal System under the conduct and responsibility of [the surgeon] conferred to the overall operation an implicit obligation of confidentiality which had to be extended to the whole team involved in said operation'. The Board additionally noted that 'the device was implanted at least partly under the patient's skin and, therefore, not immediately visible from the outside' (s.3.5). Therefore, the Board found that the alleged prior use of the Isola Spinal System during the surgery was not made available to the public and was not state of the art within the meaning of Article 54(2) EPC. The patent was maintained as granted.

In **T 7/07**, the claimed subject matter related to a pharmaceutical composition comprising, *inter alia*, drospirenone (first active agent) and ethinylestradiol (second active agent). Novelty of the claimed composition was in question in view of alleged public prior use. A prior art document disclosed the conduct of clinical trials with contraceptives containing the claimed composition. The trials took place before the priority date of the contested patent. 'The participants [in the trials] were informed of the ingredients but had not signed a confidentiality agreement, and not all unused drugs had been returned' (s.3.1).

The patentee argued that 'the drug had not become publicly available before the priority date as according to established board of appeal case law any persons involved in clinical trials are (implicitly) bound to confidentiality' (s.3.3). However, the Board did not agree, noting that the present case differed from T 152/03 and T 906/01, in which patients were not in a position to inspect implanted prototype devices. In the present case, a large number of patients were given tablets to take home with them and for use over a longer period of time, and not all of the unused study drugs were returned. The Board considered that 'it appears 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'. There was indeed no obligation of confidentiality. The Board concluded that the handing out of the drugs to the participants made them publicly available. The Board found that the skilled person could discover the composition or the internal structure of the product without undue burden (s.3.6). The claimed subject matter lacked novelty.

In **T 239/16**, it was disputed amongst the parties whether a document formed part of the state of the art pursuant to Article 54(2) EPC. It was established that the document was received by patients asked to participate in a clinical study. The document provided information such as the objective of the study, the set-up of the study including details of the treatment to be given, information on possible benefits, risks and discomforts, and contra-indications.

It was thus to be determined whether the recipients of this document were considered members of the public within the meaning of Article 54(2) EPC. Specifically, it had to be established 'whether there existed a special situation or some special relationship between the sponsor of the study and the patients having the

9 The Reasoning of the Boards for the decisions discussed in this section is provided in relation to novelty only. Where applicable, the Boards' reasoning in relation to inventive step will be discussed in the second part of this article to be published in the next issue of the *CIPA Journal*.

consequence that the patients, as recipients of the information provided in [the document], cannot be considered members of the public due to an implied obligation to maintain confidentiality' (s.4).

In an affidavit by a clinical investigator for the study, a professor 'stated that he had explained the contents of [the document] to his patients and told them that, before signing the form, they should openly discuss the treatment referred to in the document with anyone, including their family and family doctor'. The Board considered that '[t]he term 'anyone' includes people who cannot be considered to be in a special relationship with the patient, let alone with the study sponsor'. Therefore, there is 'no pointer to a special situation that would lead to the conclusion that the patients were under an implied obligation to keep the information contained in [the document] secret' (s.4). As a result, the Board held that the content of the document had been made available to the public and was state of the art pursuant to Article 54(2) EPC.

The claimed subject matter was nevertheless found novel over this disclosure since no effective therapeutic treatment was disclosed in this prior art document (s.5.2).

In **T 670/20**, the question was whether the internal structure of medicinal tablets had been made available to the public by patients taking part in clinical trials involving administration of the tablets. The question of whether the protocol was made available to the public (because it was made available to the patients) was also considered.

This case related to a composition comprising a compound called 'edoxaban'. Prior art documents relating to phase IIa and phase IIb clinical trials involving administration of edoxaban for a period of up to ten days were relevant prior art documents for the assessment of novelty and inventive step of the claimed composition. Notably, the documents disclosed that 'the tablets under investigation during the trials [were provided] to the participating patients who were discharged from hospital before the end of the treatment period' (s.4.2). Therefore, the assessment of lack of novelty in view of the trials described in the prior art documents 'crucially depends on whether the participating patients who received the tablets are to be considered as members of the public who were free to dispose over the provided tablets and thus theoretically in a position to investigate the internal structure of the tablets'.

Notably, the clinical trials described in the prior art documents were carried out in accordance with the European Medicines Agency Guidelines for Good Clinical Practice. These guidelines explicitly require 'adherence to the prescribed protocol' and 'assurance of drug accountability'. This 'implies that the patients who decided to participate in the trials agreed, following their informed consent, to use the provided medication according to instruction or to return the unused medication' (s.4.3). 'Accordingly, the participating patients who were provided with the tablets under investigation entered into a special relationship with the investigators of the trials and were with regard to the provided tablets not members of the public that could freely dispose over these tablets' (s.4.3). The Board noted that 'the patients' agreement to use the provided medication according to instruction or to return the unused medication obliges the patients irrespectively of any sanction on non-compliance' (s.4.5).

The Board noted that the circumstances in this case differed from that of T 7/07 where 'the sponsor of the trial had effectively lost control over the drugs after these had been handed out to the participants of the trial as members of the public who were not bound to secrecy' (s.4.6).

Therefore, the Board found that 'the public did not gain access to the claimed tablets during the trials' reported in the prior art and the claimed composition was found novel (s.4.7).

Aside, in line with T 239/16, the Board found that 'the patients were not under a duty of confidence with respect to their participation to the trials and the information regarding the trial provided to them in that context' (s.4.4). In particular, statements in the prior art documents encouraged 'patients to discuss their participation in the trials'. The Appeal Board noted that 'a duty of confidence regarding such information could be considered to constrain the patients in their ability to freely decide on participating in the trials on the basis of their informed consent, which would seem contrary to the above-mentioned guidelines' (s.4.4).

Conclusion

Clinical trial prior art disclosures are highly relevant to the patentability of medical use claims. However, a prior art clinical trial disclosure should not destroy the novelty of a medical use claim at the EPO unless it is established that the claimed therapeutic effect is achieved in the disclosure. For more 'complex' medical use claims reciting, e.g., a patient population or a dosage regimen, the prior art disclosure in relation to that specific feature will be of importance. Of relevance, information received by clinical trial participants can also become prior art against a patent application. The significance of a disclosure made to a clinical trial participant, including prior use of a drug, will largely depend on whether a duty of confidentiality exists.