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CASE STUDY

Clinical trials for original drugs fall under experimental use exception

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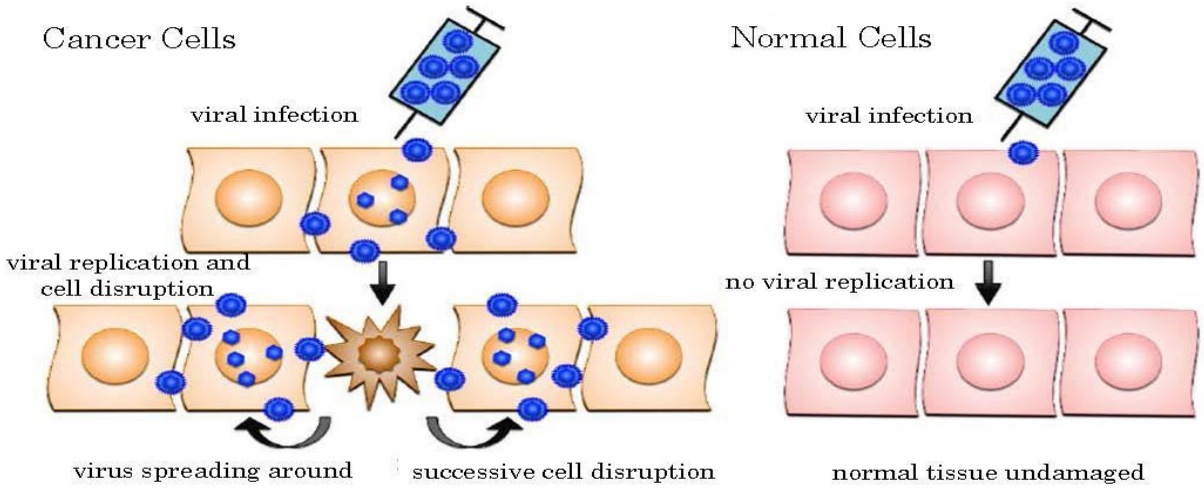
A case in Japan involving a virus therapy for brain tumours has clarified the rules around exceptions for experimental use, explains Takanori Abe of Abe & Partners.

On February 13, 2019, the University of Tokyo verified a high therapeutic effect in investigator-initiated clinical trials of a virus therapy for brain tumours. They applied for manufacturing and selling approval of the first domestic cancer treatment viral drugs.

Figure 1: The use of viruses in the treatment of cancer



Source: The University of Tokyo material

"Todo alleged that the clinical trial by Amgen using TVEC domestically fell under working of the patent."

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Summary of the case

The plaintiff, Tomoki Todo, professor of the division of Innovative Cancer Therapy, Advanced Clinical Research Center, the Institute of Medical Science, at the University of Tokyo (IMSUT), and the head of the department of Surgical Neuro-Oncology of the IMSUT hospital, owns a patent titled "viruses and their use in therapy" (JP4212897).

Using viruses in the treatment of cancer is a therapeutic method in which a virus that grows only in cancer cells is used to infect and destroy cancer cells in the patient (Figure 1). The virus of the invention is also considered as "viruses that can be used in therapeutic methods such as, for example, in the treatment of cancer" (paragraph 0015 of the specifications) and is to be used for the treatment of cancer. In the specification, G47Δ, a third-generation oncolytic herpes simplex virus, is disclosed as a specific example of the virus of the invention. Todo's research group aims to commercialise G47Δ and has been conducting phase II trials in Japan since around 2015 in treatments for glioblastoma, a type of malignant brain tumour.

The defendant, Amgen, has been conducting a clinical trial of talimogene laherparepvec, a genetically engineered herpes virus, (TVEC; brand names T-Vec or Imlygic), a regenerative medical product, domestically since March 2017, for malignant melanomas. The clinical trial is for a bridging study with foreign clinical data.

Todo alleged that the clinical trial by Amgen using TVEC domestically fell under working of the patent and infringed his patent rights and demanded an injunction against use of the virus as well as disposal of the same.

Judgment of July 22, 2020, the Tokyo District Court

The Tokyo District Court (Presiding Judge Sato) dismissed Todo's claim, holding as follows.

To decide whether the clinical trial falls under "working of the patented invention for experiment or research" of article 69(1) of the Patent Act or not, it is reasonable to consider it from the viewpoint of coordinating the interests of the patentee to be protected with the public interest, taking into account the purpose of the article 1 of the Patent Act, the legislative intent of article 69(1)

of the Patent Act, the purpose and discipline of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act), purposes and contents of the clinical trial, behaviour of the pharmaceuticals used for clinical trials, and the consistency with the patent term extension system.

In the judgment of April 16, 1999, the Supreme Court of Japan states, concerning generic drugs, as follows. If a third party produces the chemical substance or pharmaceutical product which falls within the technical scope of the patented invention during the patent term and uses it for necessary experiments to obtain materials to be attached to the application for the manufacturing approval in order to apply for the approval as provided by article 14 of the Pharmaceutical Affairs Act (at that time), aiming at manufacturing and selling generic drugs which have the same ingredients as the pharmaceutical product resulting from the patented invention after the patent expires, the working falls under "working of a patented invention for experiment or research" as provided by article 69(1) of the Patent Act and should not constitute an infringement.

TVEC, the subject of the clinical trial, is an original drug approved for manufacturing by foreign drug regulatory authorities and is undergoing a bridging study in Japan. It is understood that the purpose of the 1999 Supreme Court judgment also applies to the trials.

The Supreme Court noted on the reason why the generic drugs fall within the "working of the patented invention for experiment or research" as provided by article 69(1) of the Patent Act. In order for generic drugs, as well as the other pharmaceutical products, to apply for manufacturing approval, necessary experiments within a specified time should be conducted in advance. These experiments need to use the chemical substance or pharmaceutical product that falls within the technical scope of the patented invention of the patentee.

As with generic drugs, in order for TVEC to apply for manufacturing and sales approval, necessary experiments within a specified time should be conducted

"A phase I clinical trial as stipulated in the PMD Act is ongoing."

in advance, for which producing the chemical substance or pharmaceutical product that falls within the technical scope of the patented invention and using it are needed.

The Supreme Court held that, while people can freely use inventions for public interest reasons after the patent expires (a fundamental of the patent system), if manufacturing a chemical substance or pharmaceutical product which falls within the technical scope of the patented invention during the patent term is not possible, the invention will not be freely available to third parties during a considerable period even after the patent expires, which is contrary to the fundamental of the patent system.

In order for TVEC to apply for manufacturing and sales approval, necessary experiments within a specified time should be conducted in advance. If manufacturing pharmaceutical products which falls within the technical scope of the patented invention during the patent term are not possible, the invention will not be freely available during a considerable period even after the patent expires, which is contrary to the fundamental of the patent system as is held by the 1999 Supreme Court judgment.

The Supreme Court also held that if a third party, during the patent term, produces the generic drugs to be sold after the patent term, or produces or uses the chemical substance resulting from the patented invention as ingredients of the drugs, exceeding the scope necessary for the experiments in order to apply for manufacturing approval based on the Pharmaceutical Affairs Act (at that time), such workings constitute a patent infringement, which is not allowed.

A phase I clinical trial as stipulated in the PMD Act is ongoing, and there is no evidence indicating that Amgen produces or is likely to produce TVEC during the patent term, intending assignment after the expiration of the patent term, exceeding the scope necessary for the experiments in order to apply for manufacturing approval based on the act.

Todo alleges, based on an understanding that a clinical trial needs to aim to advance technologies to fall under "working of the patented invention for test or research" of article 69(1) of the Patent Act, that Amgen's clinical trial was conducted with an aim to domestically sell TVEC (being already approved in the US and Europe) and not aiming at the advance of technologies.

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However, there is no reason that "experiment or research" under article 69(1) of the Patent Act should necessarily be limited to those aiming at the advance of technologies. In addition, the clinical trial is recognised as a study to evaluate the efficacy and safety among Japanese people by administering TVEC to Japanese subjects to conduct a clinical trial within a specified time. Even if it is construed that "experiment or research" under article 69(1) of the Patent Act should aim at the advance of technologies, the clinical trial falls under those aiming at the advance of technologies.

Todo alleges that the clinical trial is conducted with the aim of starting manufacture and sale of clinical trial drugs within the patent term, which does not fall under the "experiment or research" of article 69(1) of the Patent Act. However, Amgen argues that it does not intend to launch TVEC within the patent term and there is no evidence indicating that Amgen is likely to manufacture or sell TVEC during the patent term exceeding the scope necessary for the experiments in order to apply for manufacturing approval based on the PMD Act.

In addition, Todo alleges that Amgen could obtain manufacturing and sales approval to start manufacturing and selling the product within the patent term, and in such a condition, it can be deemed that it has the intention of manufacturing and selling within the patent term. However, even if a third party could obtain manufacturing and sales approval for a pharmaceutical product that falls within the technical scope of the patented invention during the patent term, the third party will not necessarily start manufacturing and sales of the product during the patent term.

It is likely that the third party will start manufacturing and selling the product after the patent expires. Even if it is objectively possible to obtain manufacturing and sales approval of the product during the patent term, it should not be deemed that conducting a clinical trial necessarily means that the aim is the manufacture and sale of the product during the patent term.

"The third party will not necessarily start manufacturing and sales of the product during the patent term."

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Todo alleges that, because it takes a long time from patent application to commercialisation of a biopharmaceutical product, the interests of the patentee of the innovative biopharmaceutical product will be unreasonably damaged if a third party is allowed to conduct development or clinical trials of a similar product of the patented invention concurrently with the inventor's development.

In particular, the commercialisation of recombinant viruses for the treatment of cancer (after obtaining manufacturing and sales approval) should be when patent right expires. However, the Patent Act uniformly stipulates that "the duration of a patent right shall expire after a period of 20 years from the filing date of the patent application" (article 67[1] of the Patent Act), regardless of the type of patented invention and the magnitude of its technical value.

Even if it may take a long time for approval of a regenerative medical product, it cannot be interpreted to have the same effect as extending the patent term for a considerable period by prohibiting clinical trials of a regenerative medical product belonging to the patented invention within the patent term.

Todo alleged that the 1999 Supreme Court judgment is on the premise that the patentee can secure the profit earned by the exclusive working of the patented invention during the patent term, and that the 1999 Supreme Court judgment does not apply to this case because the patentee of a biopharmaceutical product, unlike a generic drug, has difficulty securing the profit earned by the exclusive working of the patented invention during the patent term.

As grounds for this allegation, Todo states that the manufacturer of the original drugs virtually secures the profit exclusively during the re-examination period because generic drugs are not able to obtain manufacturing and sales approval without basic studies or clinical trials.

By contrast, it should be considered that such circumstances are not applied to biopharmaceutical products (regenerative medical products). However, if the manufacturer of the original drugs could secure the profit exclusively during the re-examination period of a new drug, it is nothing more than a virtual reflexed interest by regulations of the PMD Act. It is not mentioned in the 1999 Supreme Court judgment as a factor to be considered in determining the applicability of article 69(1) of the Patent Act that the patentee may obtain a virtually exclusive profit during the said re-examination period.

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Judgment of February 9, 2021, the IP High Court

Todo appealed and amended his claim at the second instance, seeking (1) injunction against the manufacture, use, transfer, export, import, and offer to transfer, of the above-mentioned virus; (2) injunction against the application for approval of the manufacture and sale of the above-mentioned virus under the PMD Act; (3) disposal of the above-mentioned virus; and (4) payment of ¥1 million ($9,500) in damages.

The IP High Court (Presiding Judge Mori) dismissed Todo's appeal and the claims amended in the second instance. The judgment of the IP High Court corrected the judgment of the Tokyo District Court and added a judgment on Todo's claim in the second instance. Except for that, the two judgments are almost the same.

Practical tips

The 1999 Supreme Court judgment held that carrying out necessary experiments to apply for approval of generic drugs stipulated in article 14 of the Pharmaceutical Affairs Act (at that time) falls within "working of the patented invention for experiment or research", however the original drugs are not mentioned.

The present judgments of the Tokyo District Court and the IP High Court held that the purpose of the 1999 Supreme Court judgment also applies to the original drugs. The case has been appealed to the Supreme Court and attention must be paid to its future ruling.

A case prior to the 1999 Supreme Court judgment, on whether a clinical trial of an original drug would fall under "working of the patented invention for test or research" is disputed, is the consensus interferon case (*Roche v Amgen*, February 9, 1998, the Tokyo District Court). The judgment held that the clinical trial conducted by Amgen using consensus interferon is considered to be of extremely strong public interest in relation to the efficacy and safety of drugs, and that the trial would contribute to advance of technologies in the pharmaceutical industry by confirming the interferon has new efficacy not found in the existing drugs. Thus it is reasonable to understand that it

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falls under "working of the patented invention for experiment or research" of article 69(1) of the Patent Act. Infringement and validity were not decided in the judgment.

A case after the 1999 Supreme Court judgment, in which whether a clinical trial of an original drug would fall under "working of the patented invention for experiment or research" is disputed, is the Hemlibra (emicizumab) case (*Baxalta v Chugai*, October 3, 2019, the IP High Court and March 28, 2018, the Tokyo District Court).

Chugai alleged that the manufacture of its product for clinical trial falls under "working of the patented invention for experiment or research" of article 69(1) of the Patent Act and the case should be dismissed. However, the court did not adopt Chugai's argument and proceeded to infringement and validity arguments. Abe & Partners represented Baxalta in that case.

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