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CASE STUDY

Rituximab biosimilar patent infringement lawsuit

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The direction of drug discovery has moved from focusing on low molecular weight compounds to biopharmaceuticals, and the percentage of biopharmaceuticals being sold is increasing. This is the third biosimilar patent infringement lawsuit. Takanori Abe of Abe & Partners reports.

SUMMARY OF THE CASE

Biogen is the owner of patents titled "Combination therapies for B-cell lymphomas comprising administration of anti-CD20 antibody", JP6226216 (Patent 1), JP6241794 (Patent 2) and JP6253842 (Patent 3), and Genentech is an exclusive licensee of these patents.

Zenyaku Kogyo and Chugai Pharmaceutical sold rituximab (genetical recombination) preparation, an antibody pharmaceutical of anti-CD20 monoclonal antibody (Rituxan preparation) in Japan.

Sandoz and Kyowa Kirin, the defendants, manufactured and sold their preparation (a biosimilar of Rituxan preparation, including rituximab as an active ingredient).

Genentech sought an injunction on manufacturing and selling, etc, of the defendants' preparation and damages, alleging that the defendants' preparation falls within the technical scope of the Invention, and the manufacturing, selling, etc, of the defendants' preparation infringe the licensed patents. Zenyaku Kogyo and Chugai intervened in the litigation in order to support Genentech.

The invention of Claim 1 of Patent 1 (Invention 1) is as follows:

"A pharmaceutical composition for use in combination with a chemotherapy regimen for human patient in a treatment of low grade/follicular non-Hodgkin's lymphoma (NHL), including rituximab, wherein a therapeutically effective amount of the pharmaceutical composition is administered to the patient during a chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)."

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The inventions of Claims 1 to 3 of Patent 2 (Invention 2-1 to Invention 2-3) are as follows:

a) Invention 2-1

"A pharmaceutical composition for use in combination with a chemotherapy regimen for human patient in a treatment of low grade/follicular non-Hodgkin's lymphoma (NHL), including rituximab, wherein a therapeutically effective amount of the pharmaceutical composition is administered to the patient during the chemotherapy, and the chemotherapy is CVP therapy."

b) Invention 2-2

"The pharmaceutical composition of Claim 1, wherein the therapy with rituximab and the chemotherapy provides an effective synergistic effect."

c) Invention 2-3

"The pharmaceutical composition of Claim 1 or Claim 2, wherein rituximab is administered with a dose of 375 mg/m2."

The invention of Claim 1 of Patent 3 (Invention 3) is as follows:

"A pharmaceutical composition for use in combination with a chemotherapy regimen for human patient in a treatment of intermediate grade or high grade/follicular non-Hodgkin's lymphoma (NHL), including rituximab, wherein a therapeutically effective amount of the pharmaceutical composition is administered to the patient during a chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and the pharmaceutical composition, the cyclophosphamide, the doxorubicin, the vincristine, and the prednisone are administered to the patient on Day 1 of each cycle of the chemotherapy with CHOP."

Judgment of May 29, 2019, Tokyo District Court

The Tokyo District Court (Presiding Judge Yamada) dismissed Genentech's claim, holding as follows. Genentech did not appeal to the IP High Court, and this case became final.

(1) Patents 1 and 3

The wording "during" of the Element 1B was the wording "at the same time" at the time of the divisional application of Patent 1. This "at the same time" includes a mode in which each drug of CHOP therapy and rituximab is alternately administered, that is, administration during rest period is included, and this mode is described in Genentech's Exhibit No. 38.

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After being notified of the reason for refusal because of lack of novelty and inventive step, etc, with the wording "at the same time", the wording "during" was introduced by amendment to avoid the reason for refusal. The written opinion by the applicant Biogen indicates that Invention 1 became an invention different from those disclosed in Genentech's Exhibit No. 38 by the amendment.

In the prosecution history of Patent 1, even if rituximab is administered in the period until all is finished after cycles of prescribed administration schedule since CHOP therapy is started, such as the third and fourth administration of Rituxan in the clinical trial by Czuczman et al in Genentech's Exhibit No. 38, those administered during the rest period of each drug of CHOP therapy are reasonably understood to be excluded from "during a chemotherapy with (CHOP)".

Therefore, "during a chemotherapy with (CHOP)" of the Element 1B is reasonably understood to mean "administration period of each drug of CHOP therapy" among the period until all is finished after cycles of prescribed administration schedule since CHOP therapy is started.

As described above, the detailed description of the invention of the specifications of Patents 1 and 3 does not describe or suggest the use of Inventions 1 and 3, and even with all of the evidences of this case, it cannot be admitted that the problem to be solved by the invention, a provision of a new effective treatment method by using the pharmaceutical composition containing rituximab for the use of Inventions 1 and 3, is recognised as solvable, based on the description of the detailed description of the invention of the specifications of Patents 1 and 3, and the common technical knowledge as of the filing date of the original application.

Therefore, the claims of Inventions 1 and 3 do not satisfy article 36(6)(i) of the Patent Act, and Patents 1 and 3 violate the article.

"The claims of Inventions 1 and 3 do not satisfy article 36(6)(i) of the Patent Act, and Patents 1 and 3 violate the article."

(2) Patent 2

Multiple chemotherapies using the same combination of drugs, if their dose, administration method and administration timing, etc, differ, may be recognised as different. As of the filing date of the original application, the CVP therapy and the COP therapy were distinguished by the administration timing of cyclophosphamide, as cyclophosphamide is administered from Day 1 through to Day 5 for CVP therapy, but only on Day 1 for COP therapy. Such a distinction is reasonably admitted to be a common technical knowledge.

In light of this common technical knowledge as of the filing date of the original application, the CVP of the Element 2B means that cyclophosphamide is administered from Day 1 through to Day 5, which is reasonably admitted not to include those in which cyclophosphamide is administered only on Day 1.

The R-CVP regimen described in the label of the defendants' preparation is recognised as a regimen to administer rituximab on Day 1, cyclophosphamide (CPA) and vincristine (VCR) on Day 1, and prednisolone or prednisone (PSL) from Day 1 through to Day 5. Then, the defendants' preparation does not satisfy CVP of the Element 2B considering that the R-CVP regimen described in the label administers cyclophosphamide only on Day 1, not from Day 1 through to Day 5.

Practical tips

The biosimilar patent infringement lawsuits include Genentech and Chugai's lawsuit against Nippon Kayaku, and Genentech and Chugai's lawsuit against Daiichi Sankyo and Pfizer Japan so far regarding a Herceptin (trastuzumab) biosimilar. The former ended by waiver of claim, and the latter by withdrawal. Therefore, this case is the first judgment of a biosimilar patent infringement lawsuit.

In this case, validity of patent concerning the administration regimen in the combination therapy of rituximab and chemotherapy and whether the defendants' preparation falls within the technical scope of the Invention was disputed, and the issues specific for biosimilar patent infringement lawsuit were not disputed. Judgment in this regard was carried over to increasing biosimilar cases in the future.

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Since anticancer drugs have stronger side-effects and narrower therapeutic range than general drugs, medical accidents caused by anticancer drugs often have serious consequences. In fact, medical accidents due to overdose of anticancer drugs, such as the Dana-Farber case in 1994 and the Saitama Medical University Hospital case in 2000, occur all over the world. Therefore, a time-series treatment plan, called a regimen, combining an anticancer drug, an infusion, and a supportive care agent is created, and medical accidents are prevented by treating according to the plan.

The invention is the one relating to such a regimen. Patenting an appropriate regimen is useful from the perspective of LCM, but when patenting, it is necessary to prevent a violation of the support requirement by including in the specification a description that the regimen can solve the problem to be solved by the invention to provide an effective treatment method and the supporting data.

One example of a successful LCM by patenting an anticancer drug regimen is Eli Lilly's patent claiming the administration of a three-drug combination of pemetrexed, folate, and vitamin B12. ●

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