Inside The PTAB's Seagen Cancer Drug Patent Decision

By **Ryan Hagglund** (February 23, 2024, 6:20 PM EST)

Ryan Hagglund

The latest chapter in the complex and multifaceted Daiichi Sankyo Inc. v. Seagen Inc.[1] patent dispute — concerning antibody-drug conjugate technology, or ADC, and pitting Seagen against Daiichi and its collaborator, AstraZeneca — concluded recently. On Jan. 16, the Patent Trial and Appeal Board **issued** a final written decision in a post grant review proceeding, finding all challenged claims of Seagen's U.S. Patent No. 10,808,039 invalid.

The claims relate to an ADC genus incorporating a linker containing a tetrapeptide of nonmethylated amino acids in which each of the four amino acids is glycine, or Gly, or phenylalanine, or Phe, as well as certain additional elements, any drug moiety and any antibody where the drug moiety is cleaved from the antibody intracellularly in a patient.

The board found the claims unpatentable for three reasons — lack of enablement, lack of written description and anticipation on the basis that the patent was not entitled to its claimed priority date because the priority application provided inadequate written description — and rejected an indefiniteness argument.

This comes after a jury in the U.S. District Court for the Eastern District of Texas reached the contrary result and rejected Daiichi and AstraZeneca's enablement and written description arguments in April 2022 and found infringement by Daiichi and AstraZeneca's Enhertu trastuzumab-deruxtecan ADC product in Seagen Inc. v. Daiichi Sankyo Co.[2]

Seagen was awarded $41.82 million in damages and an 8% running royalty. This decision is currently on appeal.

Enablement

In finding lack of enablement, the board applied the framework articulated in 1988 by the U.S. Court of Appeals for the Federal Circuit in In re: Wands,[3] requiring consideration of factors in determining whether the specification allows an invention to be made and used without undue experimentation:

- Quantity of experimentation necessary;
- Amount of direction or guidance presented;
- Presence or absence of working examples;
- Nature of the invention;
- State of the prior art;
- Relative skill of those in the art;
- Predictability, or unpredictability of the art; and
- Breadth of the claims.

The board's decision in Seagen is not surprising. Rather, it is consistent with the U.S. Patent and Trademark Office's guidelines for assessing enablement in utility applications and patents. The PTO guidelines were issued on Jan. 10 in view of the U.S. Supreme Court's May 2023 decision in Amgen Inc. v. Sanofi.

The guidelines provide for continued application of the Wands factors in assessing enablement after the Supreme Court's decision in Amgen v. Sanofi,[4] which found claims directed to a genus of antibodies that bind specific amino acid residues on the PCSK9 protein and inhibit its binding to the low density lipoprotein receptor protein — i.e., a genus defined by function — invalid for lack of enablement.

The board found that the scope of the claims was extremely broad, encompassing ADCs composed of any antibody and any drug moiety, with the only limit being a smaller linker genus size — i.e., maleimidocaproyl group and Gly/Phe-only tetrapeptide limitations — and that the level of ordinary skill in the art was high.

There were no working examples incorporating the claimed linkers containing a Gly/Phe-only tetrapeptide unit.

While the claims cover ADCs containing any drug, the board found that the specification does not provide guidance on the attachment of drugs other than dolastatin and auristatin and their derivatives to the recited linker.

Although disclosing an extensive list of chemotherapeutic drugs and general reaction schemas for linker synthesis and attachment, the specification does not identify any specific heteroatoms or other "handles" for attachment of any other drugs to the linker or address how to place such handles on other drugs.

The board then turned to the state of the prior art and unpredictability of the art, rejecting Seagen's argument that the claims do not require any particular level of intracellular cleavage.

The board explained that the "[patent] statute and caselaw impose a 'use' requirement commensurate in scope with the claim which … requires sufficient 'intracellular cleavage in a patient' to function in the treatment of some disease or condition."

Nonetheless, the board found the prior art provided substantial details on methods for determining whether an ADC is cleaved intracellularly in vitro.

However, the board found significant unpredictability in attaching drugs to the claimed linker that the prior art does not resolve. The board pointed to references indicating that a certain type of linker worked for doxorubicin but was inapplicable to most other classes of drugs and explained that numerous attempts to target tumors with ADCs have met with limited success.

For most of the many drugs covered by the claims, no specific method of attachment to a linker was predictably provided in the prior art. Thus, "ADCs are not mix-and-match" and ADCs with certain drugs would be understood to have different properties that may make them incompatible with the claimed tetrapeptide linkers.

Finally, the board found that a large quantity of experimentation is required to create any particular ADC while retaining intracellular cleavage, let alone to enable the broad scope of the claims. It remains unknown how to attach many drug moieties to ADCs.

No reference disclosed a toolkit for ADC preparation widely available to many drugs. References showed that many ADCs were less potent than non-conjugated drugs and had no selectivity for antigen-expressing cells. Also, the specification disclosed many more drugs than the four types of cancer drugs that the prior art disclosed in ADCs.

The board then analogized the facts to those in Amgen where the Supreme Court found lack of enablement, where the claimed class of antibodies included a vast number that were not described, noting that the '039 patent describes ADCs with two drug classes and no linkers in the scope of the claims while encompassing a vast number of additional drugs that were not described.

Furthermore, the board reasoned that as in Amgen, the specification leaves readers to "random trial-and-error discovery" where much of the selection of the optimal antibody, ideal linker-drug chemistry and optimal number of payload molecules are determined empirically.

The board then explained that considering the Wands factors as a whole, the large breadth of the claims, absence of working examples, limited amount of direction and guidance, unpredictability in synthesizing antibody-drug linker conjugates and extensive quantity of experimentation were balanced against the high level of skill in the art and predictability in testing intracellular cleavage.

Accordingly, the board found that undue experimentation was required to make and use the claimed invention.

Written Description

Additionally, the board found that the patent was anticipated because the priority applications did not provide adequate written description for the claimed ADCs. The specification disclosed a genus of linkers containing peptides 1-12 amino acids long, including both methylated and nonmethylated amino acids, containing 83 potential alternatives for each nonmethylated amino acid.

Thus, even if limited to nonmethylated tetrapeptides, the disclosed genus would cover over 47 million species. The claims cover a subgenus limited to nonmethylated tetrapeptides where each amino acid is glycine or phenylalanine which constitute 81 species. The priority applications disclose no example tetrapeptides containing only glycine and/or phenylalanine amino acids.

The board found disclosure of a selection of peptide length, stereochemistry, methylation and side chain selection for each amino acid of the peptide from 39 possibilities insufficient because it did not describe the actual functioning invention that those limitations together define.

Further, there was no disclosure that either glycine or phenylalanine were preferred amino acids. Indeed, there was no guidance to make the particular selections chosen by the inventors, rather than making any other selection.

While Gly/Phe tetrapeptides might have been obvious after optimization for selectivity for cleavage by a particular enzyme, the possibility of which is disclosed, disclosure merely rendering the invention obvious does not satisfy the written description requirement.

The board explained that the priority applications contained an undifferentiated description that "failed to provide sufficient 'blaze marks' to guide a reader through the forest of disclosed possibilities toward the claimed compound" and that the Federal Circuit had used the same reasoning in finding that generic disclosure did not support subgeneric claims.

For the same reasons, the board also independently found the claims invalid for lack of written description with respect to the Gly/Phe tetrapeptide element.

However, while having no impact on the outcome of lack of written description, the board found adequate support for the broad generic language covering ADCs with any drug moiety.

The specification disclosed many cancer chemotherapeutic agents. Structures of such compounds, ADCs containing multiple drugs and several linkages to various groups in a drug were known in the prior art.

The board distinguished Juno Therapeutics Inc. v. Kite Pharma Inc.,[5] in which the Federal Circuit found lack of written description with respect to an antibody fragment element where which fragments bound which targets was not disclosed, because here, many drugs in different classes that would be expected to kill cancer cells in an ADC were disclosed.

The board explained that recitation of known structures would serve no goal of the written description requirement and that this was the case here, where the claims are not focused on the particular cancer drug or the antibody, but rather focus entirely on the linker.

Takeaways

The board's detailed analysis of the Wands factors confirms the continued vitality of the Wands framework in the wake of Amgen prescribed by the guidelines.

Indeed, the board applied the enablement standard set forth in Wands requiring the specification to enable the full scope of an invention without undue experimentation without mentioning the Supreme Court's formulation of the standard as going to "reasonable experimentation" in Amgen.

While the guidelines explain that there is no meaningful difference between the two articulations of the standard, it is noteworthy that the board did not address this or even mention the Supreme Court's language here.

However, the board's decision offers little, if any, insight as to the interplay between the Wands analysis and Amgen as well as how the Wands factors pointing in different directions are weighed against each other.

With respect to the latter, the board noted which factors weighed in which direction, as explained above, and stated its conclusion that undue experimentation was necessary with no further explanation.

The board noted similarities to Amgen inasmuch as the scope of the claims was much broader than the subject matter disclosed and that the description left the reader to trial and error discovery. Thus, the decision can be taken to stand for the proposition that the board would be unlikely to find enablement in its weighing of the Wands factors under such circumstances.

Additionally, the board's Wands analysis and reliance on Amgen in the context of ADC chemistry follow the prescriptions in the guidelines that both apply in all technology areas and that the principles in Amgen apply beyond antibody claims. Thus, it appears that the board is inclined to follow the guidelines when addressing enablement.

Moreover, while not affecting the board's ultimate decision on written description, the board's reasoning in finding adequate written description of the limitation going to any drug that the claims focused on the linker rather than the particular drug is in tension with the Federal Circuit's rejection of this logic in Juno.

The Federal Circuit explained that "[t]he test is the same whether the claim element is essential or auxiliary to the invention."

Also, the Juno court found lack of written description of a functional claim element for an antibody fragment binding a target where which fragments bound which targets (or which fragments bound a particular target) and characteristics, sequences, or structures allowing determination of this were not disclosed.

Here, the board did not address the unpredictability of the scope of the claims regarding drugs and linkers and specifically whether an ADC containing a given drug and the claimed linker met the functional intracellular cleavage limitation in its written description analysis although it relied on this unpredictability in finding lack of enablement.

While the board's analysis with respect to drugs could be viewed as inconsistent with Juno, one might distinguish Juno because only two antibody fragments — which bound specific targets — were disclosed while the '038 patent discloses many drugs, a fact the board relied on.

However, the specification disclosed none of these drugs in a working example of an ADC including the claimed linker, let alone such an ADC that was shown to be cleaved intracellularly.

Thus, it appears the board is more likely to find adequate written description of a broad generic claim term where many and diverse species are disclosed.

Also, the difference in treatment here may suggest that the board might be more amenable to finding sufficient written description of generic claim elements covering chemical compounds than those to antibodies or other proteins even when functional elements are present.

The board's decision will not be the last word in this saga — Seagen has already sought director review of it, and the Texas decision is on appeal to the Federal Circuit. Indeed, the Federal Circuit will likely pass on the validity of '038 patent in one or both of these cases.

Ryan Hagglund is a partner at Loeb & Loeb LLP.

[1] No. PGR-2021-00030, 2024 Pat. App. LEXIS 189 (P.T.A.B. January 16, 2024).

[2] Seagen Inc. v. Daiichi Sankyo Co., No. 20-337 (E.D Tex. filed Oct. 19. 2020).

[3] In re Wands, 858 F.2d 731 (Fed. Cir. 1988).

[4] Amgen Inc. et al. v. Sanofi et al., 143 S. Ct. 1243 (2023).

[5] Juno Therapeutics Inc. v. Kite Pharma Inc., 10 F.4th 1330 (Fed. Cir. 2021).