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PTAB's Decision on Obviousness of Eye Drop Patent

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Inter partes reviews (IPRs) held in the Patent Trial and Appeal Board (PTAB) of the U.S. Patent and Trademark Office are frequently associated with contemporaneous patent infringement litigations in district courts. The case, *Akorn, Inc. v. Senju Pharmaceutical Co., Ltd.*, discussed in the current post is an example of such a scenario. After Akorn, Inc. ("Akorn") was sued for infringement of U.S. Patent No. 6,114,319 ("the '319 patent") owned by Senju Pharmaceutical Co., Ltd., and Mitsubishi Chemical Corporation, Akorn petitioned for IPR of the '319 patent in the PTAB on the grounds that some of the claims of the patent were unpatentable for obviousness over the prior art, U.S. Patent 5,556,848 ("the '848 patent") and international patent application publication WO 95/31211 ("Ding"). The PTAB issued a Final Written Decision in the IPR on November 22, 2016, (Case IPR2015-01205) holding that Akorn had shown that the challenged claims were unpatentable under 35 USC §103(a) as obvious over the prior art.

The challenged claims of the '319 patent were directed toward an emulsion of difluprednate, which is a steroid. Claim 1 and 18 are representative and are summarized below. For the sake of brevity, the claim elements are not reproduced in their entirety.

1. A difluprednate emulsion in the form of an eye drop, nasal drop or ear drop comprising (a) difluprednate, (b) an oil recited in the claim, (c) water and (d) an emulsifier.

Claim 18 is also directed toward a difluprednate emulsion similar to the emulsion of claim 1, wherein the oil is castor oil and the emulsifier is polyoxyethylene (20) sorbitan monooleate. Because claim 18 is narrower than claim 1 so that claim 1 would be invalid if claim 18 is found invalid, the PTAB concentrated on claim 18 in its analysis.

Akorn's Petition cites the '848 patent for disclosing that difluprednate is an anti-inflammatory steroid useful for treating various eye disorders including inflammation of the conjunctiva (a mucous membrane covering the white of the eye), inflammation of the uvea (the middle layer of the eye ball), and inflammation of the edge of an eyelid. Ding is cited for formulating drugs, such as steroids, which are poorly soluble in water as an ophthalmic emulsion with castor oil, water, and polyoxyethylene (20) sorbitan monooleate as an emulsifier with low irritation potential. Ding mentions several examples of steroids including prednisolone acetate that can be formulated in the emulsion, but Ding does not specify difluprednate as one of the steroids. However, Akorn noted that difluprednate is a derivative of prednisolone acetate. Akorn pointed out that the '848 patent teaches an aqueous solution of difluprednate containing difluprednate particles as large as 75 µm, which according to an expert of Akorn were known to cause eye irritation. Akorn argued that the challenged claims in the '319

patent would have been obvious because one of ordinary skill in the art would have expected difluprednate to be suitable for formulation as an ophthalmic emulsion as taught by Ding. The PTAB was persuaded by the arguments of Akorn because difluprednate is taught by the '848 patent to be useful for treating eye disorders and Ding teaches that the ophthalmic emulsion could solve the formulation problems of similar steroids.

The Patent Owners argued that Akorn relied on improper hindsight because there would have been no reason for the artisan to use difluprednate in the emulsion because other steroids are more desirable than difluprednate. The PTAB was not persuaded by the hindsight argument because the challenged claims are not directed toward a method of treating eye disorders, so whether other steroids would have been more desirable than difluprednate in treating eye disorders was not relevant to the claimed emulsion. Furthermore, the '848 patent does teach that difluprednate is useful for treating eye disorders.

Similarly, the Patent Owners argued that there would have been no reasonable expectation of success in combining the teachings of the '848 patent and Ding because the artisan would not have chosen difluprednate since difluprednate would have been expected to raise intraocular pressure, which is not desirable. The Patent Owners noted that "there were many possible active ingredients and potential delivery approaches." The PTAB was not persuaded by the argument because the claims of the '319 patent are not directed toward a method of treating a certain disease with an emulsion of difluprednate. "Whether or not skilled artisans would have chosen difluprednate is not the issue to be addressed in evaluating whether there would have been a reasonable expectation of success in formulating it as an emulsion." There are no limitations in the challenged claims that recite choosing difluprednate for a specific purpose. Therefore, even if difluprednate is not a drug of choice for treating a disease, it would have been obvious to formulate difluprednate in an emulsion as taught by Ding.

In addition, the Patent Owners argued that there would have been no reasonable expectation of success with a difluprednate formulation in the form of Ding's emulsion due to the high concentration of the surfactant because high surfactant concentrations were known to lead to irritation and change the physical properties of the membrane of eye tissues. However, the problems alleged to be caused by high surfactant concentrations do not appear to be of a concern for Ding because Ding teaches that its ophthalmic emulsion has "high comfort level and low irritation potential." As a result, the PTAB was not persuaded by the argument pertaining to the high concentration of the surfactant.

The Patent Owners also argued that there would have been no reasonable expectation of success in formulating difluprednate in an emulsion because "emulsions were not known to provide superior drug delivery." The PTAB did not find this argument persuasive because Ding does teach that its ophthalmic emulsion can deliver drug to the eye tissues. Thus, the artisan would have reasonable expectation of success in delivering difluprednate to the eye tissues of interest with the ophthalmic emulsion taught by Ding.

The Patent Owners also argued that there were other ophthalmic formulations such as solutions that could be used instead of emulsions. The PTAB was not persuaded by this argument because the challenged claims are not directed toward methods of delivering a drug to the eye, so whether other formulations for drug delivery would have been better is not relevant to whether the claimed emulsion would have been obvious. The PTAB noted that Ding discloses that formulations in the form of emulsions were known for delivery of poorly soluble drugs to the eye.

The Patent Owners further argued that there would have been no motivation to combine the teachings of the '848 patent and Ding because, according to the Patent Owners, Ding aims at delivering a steroid with the ophthalmic emulsion to only the lacrimal gland of the eye, which is on the exterior of the eyeball, but difluprednate is disclosed by the '319 patent to be active inside the eyeball. The Patent Owners also relied on an expert who cited to a portion of the '848 patent which teaches that difluprednate is effective in treating acute inflammation of the uvea, which is inside the eyeball. However, the PTAB was not persuaded because uvea is not the only site of inflammation that difluprednate is disclosed to be effective by the '848 patent, which teaches that difluprednate is effective in treating a number of eye disorders, including inflammation of the conjunctiva, the edge of the eyelid and uvea. Both the conjunctiva and eyelid are external to the eyeball. Thus, the PTAB was

not convinced by the arguments of the Patent Owners that difluprednate was known to be useful only inside the eyeball, so that the artisan would not have considered Ding which teaches an emulsion targeting anatomical sites outside the eyeball. The PTAB noted that Ding presents a broad teaching that the ophthalmic emulsion is for delivering a medication to ocular tissues. Ding also presents data on the delivery of a drug with the ophthalmic emulsion to the conjunctiva, cornea, ciliary body, and lacrimal gland. Thus, "the emulsion of Ding is not limited to delivering drug to the lacrimal gland, but also provides benefits for delivery to other ocular tissues, such as the conjunctiva." In view of the disclosures of the '848 patent that difluprednate is effective for treating inflammation of the conjunctiva, the PTAB concluded that there would have been motivation for the artisan to combine the teachings of the '848 patent and Ding.

Furthermore, the Patent Owners argued that there would have been no motivation to combine the teachings of the '848 patent and Ding because the '848 patent already solved the irritation problem of difluprednate by reducing the particle size. The PTAB was not persuaded by this argument of the Patent Owners. The PTAB held that even though the '848 patent had solved the irritation problem by reducing the particle size, it would still have been obvious for the artisan to use another technique known to solve the irritation problem, namely by using Ding's ophthalmic emulsion which is disclosed to have low irritation potential. In support of the holding, the PTAB cited a statement made by the Supreme Court: "[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predicted solution." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

The Patent Owners argued that emulsions were known to be absorbed and distributed throughout the body so that the artisan would not have formulated steroids in the form of emulsions. This argument did not persuade the PTAB because, although the Patent Owners had cited references that discussed systemic absorption and distribution, the Patent Owners did not point out statements in the references that caution against the use of emulsions.

The Patent Owners further argued that the artisan would have no reason to choose polyoxyethylene (20) sorbitan monooleate in an emulsion because the prior art discloses that polyoxyethylene (20) sorbitan monooleate was known to constrict blood vessels in the uvea and increased intraocular pressure which is undesirable. The PTAB was not persuaded by the argument because the prior art teaches that polyoxyethylene (20) sorbitan monooleate causes the constriction of uveal blood vessels after administering the emulsion into the artery, not topically such as in the form of an eye drop as claimed.

The Patent Owners also argued that the prior art teaches away from selecting castor oil, instead of other oils, in an emulsion because castor oil was known to increase the permeability of corneal epithelium. The PTAB was not persuaded that the prior art teaches away from castor oil because the prior art that teaches the increase of the permeability used castor oil at a concentration of at least 98%, but the emulsion of Ding uses castor oil in a much lower concentration, e.g., 1.25%, and Ding is silent on any increase in the permeability of the corneal epithelium.

Furthermore, the PTAB pointed out that the Patent Owners did not address an argument made by Akorn that the artisan would have reasonable expectation of success of formulating difluprednate in Ding's ophthalmic emulsion because prednisolone acetate was one of the steroids taught by Ding that could be formulated in the emulsion and difluprednate was known to be a derivative of prednisolone acetate. The PTAB noted that because the Patent Owners did not provide any evidence that contradicts the teachings of Ding, the PTAB held that "there would have been a reasonable expectation of success making the claimed emulsion." In accordance with the reasons discussed above, the PTAB concluded that the claims were *prima facie* obvious over the prior art.

Takeaway

This case illustrates that, according to this panel of the PTAB, it is not useful to argue that a product form as claimed, e.g., the emulsion here, or the active drug, e.g., difluprednate, in the claimed product, would have no reasonable expectation of

success because the claims are not directed toward a method of treating a disease, so that whether another product form or active drug would work better would be irrelevant to the obviousness analysis. Arguments that the claimed invention would not have been obvious over the prior art should be directed toward specific teachings of the prior art pertinent to the claims. For instance, if the prior art teaches a certain concentration, the Patent Owner should argue against the concentration taught by the prior art, not against a concentration not taught by the prior art. Any arguments against the other concentration would be regarded by the PTAB to be not germane to the obviousness analysis. Similarly, arguments that the claimed invention would not have been obvious should be relevant to the claim limitations. For example, an argument based on a route of administration different from the route in which the claimed product is administered would likely be found not pertinent to the obviousness analysis. If the Patent Owner's argument is contrary to the teachings of the prior art relied upon by the Petitioner, the Patent Owner's argument should be supported by experimental data in order to better convince the PTAB that the teachings of the prior art were wrong. Finally, the Patent Owner in an IPR should address all arguments made by the Petitioner, or else it runs the risk that the PTAB would agree with any unchallenged arguments of the Petitioner.

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