UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NALOX-1 PHARMACEUTICALS, LLC,
Petitioner,
v.
ADAPT PHARMA OPERATIONS LIMITED, AND
OPIANT PHARMACEUTICALS, INC.
Patent Owners.

CASE IPR2019-00685
U.S. Patent No. 9,211,253

PETITIONER NALOX-1 PHARMACEUTICALS, LLC's MOTION FOR OBSERVATIONS ON THE SECOND DEPOSITION OF PATENT OWNERS' EXPERT DR. STUART ALLEN JONES

Pursuant to 77 Fed. Reg. 48,767-68, Petitioner Nalox-1 Pharmaceuticals, LLC ("Petitioner") submits this motion for observations regarding cross-examination of Patent Owners' sur-reply declarant Dr. Stuart Allen Jones, following his deposition on May 1, 2020 (Nalox1252).

Observation 1: Relevant to Patent Owners' argument that, "Surfactants, like BZK [benzalkonium chloride], are particularly known to facilitate drug degradation." Paper 49 at 4.

Dr. Jones testified:

> Q. …[Tsuji (Exhibit 2309)] says, [t]he previous and present studies revealed a marked stability of penicillins in acid solutions with both cationic and nonionic micelles. Do you see that?
>
> A. Yes, I see those words on the page.
>
> Q. And then three lines down, starting "These stabilization," it says, *These stabilization effects are attributed to incorporation of the penicillin molecules into both types of micelles*. Do you see that?
>
> A. Yes, I see those words on the page.
>
> Q. *Tsuji states that using cationic and nonionic surfactant micelles stabilized penicillins, correct*?
>
> . . . .
>
> A. So what Tsuji has shown here is that *certain types of chemicals can be stabilized to a certain degree by ionic and nonionic micelles*, but other chemicals are not stabilized. *And what Tsuji says is this is dependent upon how much of the molecule is incorporated within the micelle. And those chemicals which are not incorporated within the micelle are not stabilized. And those*

> *which are incorporated into the micelle to a high degree seem to show some stability in this particular study.*

Nalox1252 at 41:19–43:25 (emphases added).

Dr. Jones also testified:

> Q. [Yoshioka (Exhibit 2301)] says . . . [t]he observation that *alkaline hydrolysis* of acetylcholine is *decreased by dodecyltrimethylammonium chloride (DTAC)* as shown in Figure 114, has been explained by assuming that *the drug molecule penetrates the micellar phase and is shielded from the attack of hydroxide ion*. Do you see that?
>
> A. Yes.
>
> Q. And then two lines down, it says, *Alkaline hydrolysis* of benzocaine is *inhibited by cetyltrimethylammonium chloride (CTAC)*. Do you see that?
>
> A. Yes.

Nalox1252 at 49:15–50:3 (emphases added).

The preceding testimony contradicts Patent Owners' argument that, "Surfactants, like BZK, are particularly known to facilitate drug degradation," (Paper 49 at 4), because it demonstrates the knowledge in the prior art that *various cationic surfactants* (including the quaternary ammonium compounds DTAC and CTAC) were shown to *enhance drug stability*. This testimony is also relevant because the proposed mechanism by which the surfactants are stated to enhance drug *protection* in the prior art—*i.e.*, incorporation of the drug into the micellar phase—is the *same mechanism* proposed by Dr. Jones for BZK's *degradation* of

naloxone (*see* Nalox1252 at 98:23–100:1), further undermining Dr. Jones's opinion that BZK facilitated naloxone degradation.

Observation 2. Relevant to Dr. Jones's opinion that CTAB (which, Dr. Jones opined, has "similar properties" as BZK (*see* Exhibit 2300 at ¶ 16, n.2)) can enhance drug degradation.

Dr. Jones testified:

> Q. You say, CTAB and BZK are both quaternary ammonium compounds that the POSA would have recognized as having similar properties. Do you see that?
>
> A. Yes, and I finish then, including with respect to their ability to act as surfactants and preservatives, yes.
>
> . . . .
>
> Q. …[Yoshioka (Exhibit 2301)] says, [a]s shown in Figure 116, acid *degradation* of propicillin in solutions *was inhibited by* polyoxyethylene 23 lauryl ether, a nonionic surfactant, and *CTAB, a cationic surfactant*. Do you see that?
>
> A. Yes.
>
> …
>
> Q. [Y]ou chose to only include references to CTAB degrading drugs, specifically cefaclor and indomethacin, but you chose not to include from the same exact reference in the same exact part of the reference that you're quoting from, disclosure that the same compound, CTAB, could inhibit degradation of a compound, didn't you?
>
> A. I stated in my declaration two quotes from this reference. The first was the effect of surfactants on degradation, in quotes, can be, in quotes, difficult to interpret. These two quotes give an overall

> view of the reference. And the reference in a number of places provides examples of where surfactants can have an effect on degradation and how this can be difficult to interpret. I then go on to talk about cefaclor, an aminophenyl cephalosporin, and how the degradation was enhanced by CTAB, a well-known surfactant. And this was an appropriate example because this does not include within micelles, which, therefore, is appropriate from the description of BZK surfactant properties increasing naloxone degradation because it's not discussing the inclusion of naloxone in micelles, rather it's discussing the inclusion of oxygen in micelles, and, therefore, including drugs which themselves go into micelles -- discussing drugs which themselves penetrate into micelles and are protected from degradation as a consequence to this discussion which is moving toward the effect of surfactants to solubilize oxygen and, therefore, the oxygen is within the micelles. And, therefore, these citations are appropriate within the wider section of BZK's surfactant properties would increase naloxone degradation observed in Wyse.

Nalox1252 at 44:19–25; 79:4–82:24 (emphases added) (Patent Owners' objections omitted). This testimony is relevant because it contradicts Dr. Jones's opinion that CTAB (which, Dr. Jones opined, has "similar properties" as BZK (*see* Exhibit 2300 at ¶ 16, n.2)) can enhance drug *degradation*—since the *same prior art reference* cited by Dr. Jones shows that CTAB also can enhance drug *stability*.

Observation 3. Relevant to Patent Owners' argument that, "BZK's surfactant properties could indirectly increase naloxone degradation … by solubilizing oxygen in lipophilic micelles…." Paper 49 at 4.

Dr. Jones testified:

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