Paper No. ___
Filed: June 14, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

PROTIVA BIOTHERAPEUTICS, INC.,
Patent Owner.

Case IPR2018-00739
Patent No. 9,364,435

PATENT OWNER'S PRELIMINARY RESPONSE PURSUANT TO 37 C.F.R. § 42.107

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I. INTRODUCTION

The Board should not institute *inter partes* review of claims 1-20 of U.S. Patent No. 9,364,435 ("the '435 patent") because Moderna Therapeutics, Inc. ("Petitioner") fails to show that it has a reasonable likelihood of prevailing.

The '435 patent protects an important technological advance in the emerging field of gene delivery systems. It covers novel nucleic-acid lipid particle formulation that can be used, for instance, to treat cancer, liver disease, and viral infections, as set forth in the challenged claims.

Before the '435 patent, the trend was to use particles with "low levels of cationic lipid." EX1001, 2:52-56. That prevailing wisdom was understandable. Cationic liposome complexes were understood to "elicit considerable toxic side effects." *Id*. High levels of cationic lipid were also known to result in *in vivo* aggregation, immunogenicity, and rapid clearance of these particles from circulation. The prior art that Petitioner cites only confirms the community's aversion to the toxicity and poor *in vivo* efficacy associated with formulations with a high level of cationic lipid. Those concerns were so entrenched in the community that even Petitioner's expert acknowledges as much in his own publications. *See* EX2006 at 125; *see also* EX1018 at 8 (citing EX2006).

Another prior art trend was to incorporate higher than the claimed levels of conjugated lipids to stabilize the particle so that the therapeutic payload could

reach the target cells. Failing to do so was understood to cause the particles to degrade or undergo dissolution before reaching their targets, resulting in little more than a wasted effort.

The inventors solved these problems by requiring cationic lipids at "50 mol % to 85 mol %," non-cationic lipids at "13 mol % to 49.5 mol %," and conjugated lipids at "0.5 mol % to 2 mol %." This specific combination, it turns out, is surprisingly effective, stable following systemic (*in vivo*) administration, and does not elicit the feared toxic effects associated with formulations having a high level of cationic lipid. Given the innovation protected by the '435 patent, the petition is a poorly conceived challenge. It seeks troubling shortcuts to the legally mandated obviousness analysis and fails to coherently identify the specific invalidity theories it asks the Board to review in this matter.

Petitioner builds its obviousness argument of Ground 1 on a misapplication and over-reading of *In re Peterson.* 315 F.3d 1325 (Fed. Cir. 2003). Petitioner relies on *Peterson* to argue for a *prima facie* case of obviousness on a per-limitation basis for what it contends are overlapping ranges of individual claim elements. Having invoked *Peterson*, Petitioner rests on its putative "*prima facie*" case as though that alone meets its obligation to justify institution, rather than present the requisite obviousness analysis.

For starters, Petitioner fails to perform its obviousness analysis on the claim as a ***whole***, repeatedly arguing that each "limitation is *prima facie* obvious." Of course, obviousness must be performed on the full combination of a claim and not merely on a per-limitation basis. This is a fundamental, and indeed fatal, defect of the petition.

Moreover, it is well-established that, before a conclusion of obviousness is reached based on the presence of elements in the prior art, a petitioner must evaluate whether there is a motivation to combine those disclosures with a reasonable expectation of success. These critical elements of the obviousness analysis are missing from the petition.

Petitioner also attempts to side-step its legal obligation to make such showings by invoking *prima facie* obviousness of claim limitations. As a threshold matter, the concept of a *prima facie* obviousness showing is a "burden-shifting framework [that] does not apply in the adjudicatory context of an IPR." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016). Petitioner's attempt to cut corners by invoking this inapposite analytic substitute is another fatal flaw in the petition.

Beyond that, Petitioner's misguided effort to shoehorn the facts here into the holding of *Peterson* is the type of misuse of precedent that the Federal Circuit has already criticized. *Genetics Institute v. Novartis Vaccines*, 655 F.3d 1291, 1306

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