Paper No. ___
Filed: April 17, 2019

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 SUR-REPLY

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I. INTRODUCTION

This sur-reply is filed in response to Petitioner's Reply filed March 22, 2019. *See* EX2056.

The Reply illustrates precisely why attorney argument should be accorded no weight, and why such argument cannot take the place of evidence in the record. Much of the Reply relies on attacking arguments Patent Owner never made, mischaracterizing the deposition testimony of Patent Owner's expert, and flatly ignoring detrimental testimony from Petitioner's own expert. Beyond that, the Reply attempts to weave false narratives about non-toxic cationic lipids and inoperable formulations that not only lack a shred of supporting evidence, but are contradicted by Petitioner's own publications.

In the end, Petitioner's unpatentability challenges lack supporting evidence, and the Reply fails to show otherwise. Petitioner's sole remaining anticipation challenge fails in that neither the L054, nor any other composition in the '554 publication, represents ***particles*** (as opposed to starting ingredients) having a lipid composition required by the challenged claims—nor does the L054 composition or any other composition disclosed in the '554 patent encapsulate nucleic acid in the particle so as to protect the nucleic acid from enzymatic degradation.

Regarding Petitioner's obviousness assertions, Patent Owner previously pointed out those challenges fail for being premised on the false notion that

overlapping lipid ranges in the prior art alone necessarily render the '435 patent claims obvious. The Reply perpetuates this erroneous argument, now citing to *E.I. duPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996 (Fed. Cir. 2018). But *duPont*, like all other overlapping range cases, is based the specific rationale of "routine optimization"—rather than obviating the need for the critical aspects of an obviousness inquiry (*e.g.*, motivation, reasonable expectation of success). *Id.* at 1006. Petitioner has never established that formulating nucleic acid-lipid particles as claimed would have been a matter of routine optimization (or any other obviousness rationale). Here, the evidence is overwhelming — achieving the nucleic acid-lipid particles of the '435 patent was *not* a matter of routine optimization.

To the extent any *prima facie* case of obviousness was established by identification of overlapping lipid ranges in the art, that case is rebutted by the extensive experimental data in the '435 patent and numerous post-filing publications, including Petitioner's own publications. As explained previously, and as corroborated throughout the literature at the time (and unrebutted by Petitioner), high-level cationic lipid formulations (*e.g.*, 50-85% cationic lipid) were expected to have poor *in vivo* activity and elicit increased toxicity and immunogenicity relative to lower-level cationic lipid formulations. EX1005, 3315; EX1006, 745; EX1008, E96; EX2007, 30:34-41.

Patent Owner, however, found that the claimed formulations surprisingly impart increased activity of the encapsulated nucleic acid and improved tolerability of the formulations *in vivo*, resulting in a significant increase in the therapeutic index. EX1015, 38-39, 68-69. Moreover, the claimed formulations are stable in circulation and are substantially non-toxic when administered to mammals. These surprising results are different in kind, not merely degree. The Reply fails to demonstrate otherwise.

As such, when all the evidence of record is weighed and considered, Petitioner has failed to meet its burden of demonstrating unpatentability by a preponderance of the evidence, and the challenges in the Petition should be rejected and the claims of the '435 patent found *not unpatentable*.

II. CLAIM CONSTRUCTION

Petitioner now abandons the construction of the term "nucleic acid-lipid particle" that was proffered in the Petition and rejected in the Institution Decision (*e.g.*, Pet. 24; Decision 10-11). The Reply (3) instead provides a single conclusory sentence stating that the Board's preliminary construction of this term "is appropriate."[1] EX1021, ¶13. Petitioner offers no argument or analysis as to *why*

[1] This represents the third different construction for this term advanced by Petitioner.

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