Paper No. ___
Filed: March 31, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MODERNA THERAPEUTICS, INC.,
Petitioner,

v.

ARBUTUS BIOPHARMA CORPORATION,
Patent Owner.

Case IPR2019-00554
Patent No. 8,058,069

PATENT OWNER'S SUR-REPLY

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I. INTRODUCTION

The Reply is largely an untimely attempt to cure deficiencies identified in the Patent Owner Response (POR). Consolidated Trial Practice Guide, 73 ("Petitioner may not submit new evidence in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability."s); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("Unlike district court litigation… the expedited nature of IPRs bring with it an obligation for petitioners to make their case in their petition to institute.").

Much of the Reply relies on attacking arguments Patent Owner ("PO") never made, mischaracterizing the deposition testimony of PO's expert, and blatantly ignoring detrimental testimony from Petitioner's first expert. Beyond that, the Reply newly attempts to overstate the importance of irrelevant parameters (e.g., N/P ratio), fabricate "trends," and falsely argue non-toxic cationic lipids. These arguments not only lack any supporting evidence, but are contradicted by the references of record, including Petitioner's own publications.

First, Petitioner's anticipation charge is unaddressed in the Reply, and now appears abandoned.

As to Petitioner's obviousness assertions, PO's Response ("POR") (*e.g.*, 2-4, 11-31) laid out in detail how Petitioner failed to substantiate the "routine optimization" rationale at the heart of the cited *Peterson* and *du Pont* cases—*i.e.*,

the only obviousness theory identified in the petition and instituted by the Board under *SAS*. *E.g.*, Pet. 31-33, 38-40, 54, 56-59; Decision on Institution ("DI"), 24-27, 35-37. In fact, up until the Reply, Petitioner and its expert, Dr. Janoff, agreed on the inapplicability of routine optimization. The petition materials, presumably concerned by extensive experimental testing reported in the '069 patent, embraced the complexity of the technology and argued wild unpredictability. During cross-examination, Petitioner's expert witness repeatedly testified the prior art lipid ranges are "immense" and "would require undue experimentation, not simple optimization." EX2033, 60:5-16; 42:7-10; 19:25-20:15; POR 4, 19-27. As explained in the POR, Dr. Janoff was correct in this regard, undermining the ill-conceived obviousness case in the petition.

With the deficiencies in the petition case laid bare, Petitioner belatedly attempts to cure them—ignoring the evidence and testimony of its own witness entirely and now asserting "routine optimization."[1] Even if this untimely argument is entertained, it can be rejected on the merits for at least the reasons set forth

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[1] Even in Reply, Petitioner continues its erratic oscillation on this point. While now arguing routine optimization, Petitioner returns to embracing complexity and unpredictability when attacking the extensive experimental testing. *E.g.*, Reply 24-25; *compare* EX2006, 405:5-12.

below. The evidence is overwhelming — achieving the nucleic acid-lipid particles of the '069 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 '069 patent and numerous post-filing publications showing unexpected results, including Petitioner's own publications. As corroborated in the literature (and unrebutted by Petitioner), high-level cationic lipid formulations (*e.g.*, 50-65% cationic lipid) would have been expected to have relatively poor *in vivo* activity and elicit increased toxicity and immunogenicity compared to lower-level cationic lipid formulations. EX1006, 3315; EX1007, 745; EX1009, E96; EX2009, 30:34-41.

PO, however, found that the claimed formulations surprisingly impart increased activity of the nucleic acid payload and improved tolerability of the formulations *in vivo*, resulting in a significant increase in the therapeutic index. POR, 31-42. Moreover, the claimed formulations are stable in circulation and are substantially non-toxic when administered to mammals. These surprising results are different in kind, and the Reply fails to demonstrate otherwise.

As such, when all the evidence of record is weighed and considered, Petitioner fails to meet its burden of demonstrating the unpatentability of the

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