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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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COALITION FOR AFFORDABLE DRUGS II LLC
Petitioner

v.

NPS PHARMACEUTICALS, INC.
Patent Owner

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Case IPR2015-01093
Patent No. 7,056,886

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**PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE**

## I. INTRODUCTION

The Board instituted this IPR proceeding because Petitioner established a reasonable likelihood in prevailing on its assertions that claims 1-27, 31-40, 44, and 45 are obvious. (Paper 26, pp. 2, 19, 20, 23). Patent Owner ("PO") does not dispute that the prior art teaches each and every element of claims 1-27, 31-40, 44, and 45.

Faced with this reality, PO resorts to baseless arguments about alleged "complexities" in stabilizing peptide formulations, interprets the claims too narrowly, improperly attempts to import stability limitations into the claims, and makes unsupported arguments concerning motivation to combine. None of these efforts can withstand scrutiny when considered in view of the '886 patent and the prior art. Moreover, the positions now taken by PO in this IPR plainly contradict two publications of PO's own expert, Dr. Carpenter.

For example, Dr. Carpenter's prior publications discredit PO's positon that stabilizing peptide formulations is unpredictable based on the number of choices and combinations of components. Dr. Carpenter's publications explain that one of ordinary skill in the art could use a "rational approach" to prepare stable formulations of GLP-2 or analogs thereof. This is particularly true given that there are a finite number of options from which to choose in view of Kornfelt. The contradictions between Dr. Carpenter's prior publications and his declaration, as

well as the lack of support for many of his current positions, all point to PO's and Dr. Carpenter's positions lacking credibility.

Furthermore, PO's improper attempts to discredit Petitioner's expert, Dr. Palmieri, are misplaced. This is because PO relies on an unnecessarily elevated level of ordinary skill in the art that ultimately disqualifies PO's own expert as one of ordinary skill in the art.

In addition, PO overlooks the well-known fact that both glucagon and GLP-2 are susceptible to *in vitro* degradation by the same mechanisms. This knowledge in combination with Kornfelt's disclosure that histidine reduces *in vitro* degradation of glucagon provides the motivation to choose histidine and develop a lyophilized GLP-2 formulation with a reasonable expectation of success.

Finally, PO's attempts to demonstrate unexpected results, commercial success, and fulfillment of a long-felt, unresolved need do not pass muster and should be disregarded.

Based on those arguments originally offered by Petitioner and the rebuttal arguments herein, Petitioner submits that claims 1-27, 31-40, 44, and 45 of the '886 patent are unpatentable as obvious under 35 U.S.C. § 103.

## II. RESPONSE TO PATENT OWNER'S ARGUMENTS

### A. The '886 patent does not recognize any of the "complexities" associated with peptide formulation alleged by PO.

PO alleges various "complexities" associated with peptide formulations in an attempt to argue that stabilizing glucagon is not predictive of stabilizing GLP-2. (Resp., 43-48). Dr. Carpenter's "complexities" include protein or peptide degradation pathways, pH requirements, pI, amino acid sequence, sensitivities to processing stresses, and responses to stabilizing excipients. (Ex. 1041, ¶ 11).

The '886 patent, however, never even recognizes these alleged complexities. This is despite the claims of the '886 patent covering the wide breadth of GLP-2 *or an analog thereof*. The failure of the '886 patent to recognize these alleged complexities suggests that one of ordinary skill in the art could have readily addressed them with what was known in the art using routine optimization.

If these complexities resulted in protein/peptide formulation science being so complex and unpredictable (Resp., 4-5), the '886 patent should have provided at least some guidance regarding these complexities in order for it to meet the requirements of 35 U.S.C. § 112, first paragraph. (Ex. 1041, ¶ 11). Logic would dictate that the '886 patent should have at least addressed these complexities to enable formulating the breadth of peptides (i.e., GLP-2 *or an analog thereof*) in the claims. (Ex. 1041, ¶¶ 11, 17). The lack of disclosure in the '886 patent suggests

the purported complexities are contrived, *post hoc* arguments designed to save the claims at issue from now being invalidated as obvious. (Ex. 1041, ¶¶ 16, 18, 19).

### B. The previous publications of PO's expert, Dr. Carpenter, contradict his declaration and support Petitioner's positions.

Dr. Carpenter has two publications directly contradicting arguments made in PO's response: Avis et al. (ed.), Biotechnology and Biopharmaceutical Manufacturing, Processing, and Preservation, (Carpenter et al.) Chapter 4, 199-263 ("Carpenter 1996"; Ex. 1049) and Carpenter et al., Pharmaceutical Research, Vol. 14, No. 8, 1997, 969-975 ("Carpenter 1997"; Ex. 1050). Dr. Carpenter's contradictions in these publications show that the basis on which PO relies to allege the non-obviousness of the claims at issue lacks credibility.

PO argues the number of components and combinations are voluminous and lead to infinite possibilities to test. (Resp., 19). In support, Dr. Carpenter claims one of ordinary skill in the art would have no idea where to start. (Ex. 1041, ¶ 22). But, Carpenter 1996 and Carpenter 1997 both describe "rational" choices for excipients in lyophilized protein formulations, describe excipients that should be avoided, and name excipients that have been proven useful in stabilizing lyophilized protein formulations. (Ex. 1041, ¶¶ 23-27; *see, e.g.,* Ex. 1049, p. 225; Ex. 1050, p. 972; Ex. 1043, p. 219, ll. 9-24 and p. 243, l. 15-p. 244, l. 13). For example, Dr. Carpenter points to using sugars, but not reducing sugars. (Ex. 1049, p. 225; Ex. 1050, p. 972). Dr. Carpenter calls out *histidine, mannitol, and sucrose*

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