IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Inter Partes* Reexamination of U.S. Patent No. 8,030,348

Entitled: NATURAL MARINE SOURCE PHOSPHOLIPIDS COMPRISING POLYUNSATURATED FATTY ACIDS AND THEIR APPLICATIONS

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Examiner: Bruce Campbell

DECLARATION OF RICHARD B. VAN BREEMEN, PH.D., IN SUPPORT OF INTER PARTES REEXAMINATION OF U.S. PATENT NO. 8,030,348

EFS WEB Filed

Mail Stop Inter Partes Reexam
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I, Richard B. van Breemen, Ph.D., hereby declare and say:

1. I am Professor of Medicinal Chemistry and Pharmacognosy at the College of Pharmacy of the University of Illinois at Chicago. I was promoted to this position in 2000. I hold the administrative position of Assistant to the Director of the Research Resources Center at the University of Illinois at Chicago. In this position, I provide advice regarding campus needs in the area of mass spectrometry, and my laboratory serves as a central campus resource in mass spectrometry. I am also on the editorial boards of the scientific journals *Biomedical Chromatography* and *Assay and Drug Development Technologies*. A copy of my Curriculum Vitae is attached as Exhibit 1 and sets forth my education, teaching positions, honors, various memberships in professional societies, selected speaking engagements, listing of my previous

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and present graduate students and postdoctoral research associates, and listings of my patents and publications.

2. I was asked by Aker Biomarine ASA to review Declarations and references submitted by Neptune Bioresources and Technologies (Neptune) in the re-examination proceedings referenced above and to review U.S. Pat. No. 8,030,348. I was also asked to use ultrahigh performance liquid chromatography-tandem mass spectrometry (UHPLC-MS-MS) to analyze lipid fractions prepared from two species of krill, *Euphausia superba* and *E. pacifica*. I am being compensated for this analysis.

The 2011 White Declaration Demonstrates the Presence of the Claimed Phospholipid Species in Beaudoin Krill Extracts

3. Tables 1 and 2 of the 2011 White Declaration demonstrate the presence of phospholipids species detected as protonated molecules of *m/z* 826 and *m/z* 852 in fractions from each of the sample sets tested. These masses are consistent with phosphatidylcholines containing two eicosapentainoic acid groups (PC-EPA/EPA) (*m/z* 826) and one EPA group plus one docosahexaenoic acid group (PC-EPA/DHA) (*m/z* 852), respectively. Neptune's experts, Dr. Yeboah and Dr. Shahidi both recognize and acknowledge this fact. As stated by Dr. Yeboah in ¶36 of his Declaration:

> The species detected at *m/z* values of 826 and 852 represent amounts in a range on the order of only 0.1 to 2.8% of the phospholipids of the oil. I understand that phospholipids represent about 40% of the total lipids in krill oil and therefore, the raw data of Tables 1 and 2 of the White Declaration shows that the amount of phospholipids carrying two and EPA and DHA in the total Beaudoin oil is only about 0.05 to 1.1%.

Likewise, Dr. Shahidi stated in ¶22 of his Declaration:

> As Beaudoin reports an oil potentially with a small amount of the phospholipid containing two of EPA and DHA (i.e. about 0.1 to 1%), it is my opinion that this is not a biologically effective amount. As the claims of the' 348 patent are directed to biologically effective amounts of this composition, they are distinct from Beaudoin.

Both Dr. Yeboah and Dr. Shahidi agree that the Beaudoin samples generated by Neptune and analyzed by Dr. White contain the claimed phospholipid species with two of EPA and DHA (PC-EPA/EPA and PC-DHA/DHA).

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4. Dr. Yeboah and Dr. Shahidi both argue that amounts of the claimed phospholipid species detected by Dr. White are *de minimis* or not a "biologically effective amount." However, the 2011 White Declaration provides no data comparing the amount of the claimed phospholipid species in extracts produced according to the '348 Patent to those present in the Beaudoin extracts. Likewise, the '348 patent itself contains no disclosure or data that can be used to determine the amount of the claimed phospholipid species in the '348 patent extracts.

5. The '348 patent contains no data that identifies the presence or amount of any particular phospholipid species such a phospholipid containing EPA and/or DHA at both sn-1 and sn-2 positions. Tables 2-5 of the '348 patent (as well as Claim 15) clearly show that phospholipids of the krill extracts contain a complex mixture of fatty acids. The only reasonable assumption from these data is that only a small percentage of the phospholipids in the extracts actually produced and described in the '348 Patent contain two of EPA and DHA as claimed. Krill phospholipid extracts are complex mixtures of many different phospholipid species. The identities of these species is described in a recent paper, Winther et al., Elucidation of Phosphatidylcholine Composition in Krill Oil Extracted from *Euphausia superba*, *Lipids* 46(1):25-36 (2011). I note that Neptune's expert, Dr. Yeboah (Yeboah Declaration ¶34), relied on this paper in his analysis of the fatty acid content of the phospholipids in the 2011 White Declaration. As can be seen in Table 2 of Winther et al., there are many different phospholipids in a krill extract, including phospholipids with one of either DHA or EPA at one of the sn-1 or sn-2 positions and another non-omega 3 fatty acid at the other position, as well as phospholipids that do not have an omega 3 fatty acid attached. Phospholipids with two of EPA or DHA at the sn-1 and sn-2 positions (i.e., phospholipid species corresponding the claims) make up only a very small portion of the total phospholipid species in the extract. Winther et al., which was relied on by Dr. Yeboah for calculation of fatty acid percentages in the 2011 White declaration, corroborates the fact the claimed phospholipid species are only a few of many present in krill phospholipid extracts and that the relative percentage of the claimed phospholipid species is low in a krill extract. In summary, the available data indicate that any krill oil extract will only have small amounts of phospholipids with EPA and DHA at both sn-1 and sn-2 positions. There is no information to the contrary. The *de minimis* arguments presented by Dr. Yebaoh and Dr. Shahidi are without merit because they have not addressed the issue of how much of the claimed phospholipid species is actually in the '348 extracts.

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6. Dr. Yeboah admits that there are several errors in the 2011 White Declaration (Yeboah Declaration ¶¶27-34). I agree with Dr. Yeboah that Figure 10 does show a positive ion electrospray tandem mass spectrum consistent with phosphatidylcholine containing EPA at both sn-1 and sn-2 positions. According to the 2011 White Declaration, Figure 10 indicates a phospholipid containing EPA (C20:5) and stearic acid (C18:0). However, when calculating the molecular mass of a phosphatidylcholine with EPA (20:5) in one position and stearic acid (18:0) in the other, the molecular mass would be 807.6, which would be detected as a protonated molecule of *m/z* 808.6. Instead, the protonated molecule of the phospholipid in Figure 10 is *m/z* 826.5, which is consistent with a phosphatidylcholine containing EPA at both sn-1 and sn-2 positions (PC-EPA/EPA). This assignment of the phospholipid PC-EPA/EPA is also supported by fragment ions of *m/z* 524.3 and *m/z* 542.3 in Figure 10 of the White Declaration, which correspond to loss of EPA (-302), $[MH-302]^+$, and loss of dehydrated EPA, $[MH-284]^+$, respectively.

7. Dr. Yeboah argues that the data in Figure 10 of the White Declaration should not be considered because the sample identified as "previous Beaudoin Oil" in the legend for Figure 10 is not actually a Beaudoin oil. Dr. Yeboah goes to great length to distinguish the protocol used to generate the oil analyzed in Figure 10 from the Beaudoin protocol used for the other samples analyzed by Dr. White. I note that all the data in the White Declaration indicate the fact that different protocols give the same result – all extracts contained the claimed phospholipid species.

8. In addition to the errors identified by Dr. Yeboah, it is my opinion that Dr. White also erred in not analyzing positive controls such as PC-DHA/DHA and PC-EPA/EPA. In ¶11, Dr. White reports that the phospholipids with protonated molecules of *m/z* 826 and *m/z* 852 were detected, which were consistent with PC-EPA/EPA and PC-EPA/DHC. However, Dr. White suggests that the tandem mass spectra of these ions were inconsistent with these structures. How does he know that the tandem mass spectra he obtained, such as that shown in Figure 11, are not PC-EPA/DHC unless he compared them with standards as positive controls? Dr. White addresses this shortcoming in his Supplemental Declaration in which he states that he did use a commercial phospholipid standard set as a positive control (White Supplemental Decl. ¶¶10-12). However, this standard set did not include the target phospholipids with two of EPA or DHA and thus have no value in establishing utility of the experimental set up to actually detect the target

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phospholipids. If a positive control of PC-EPA/EPA had been analyzed, it would have been clear that Figure 10 represents a phospholipid with EPA at both of the sn-1 and sn-2 positions (PC-EPA/EPA) and not stearic acid and EPA as concluded by Dr. White.

Dr. Gundersen's Analysis of the Beaudoin and Murayama Extracts Confirms the Presence of the Claimed Phospholipid Species

9. I have reviewed the initial Gundersen Declaration and raw data. Dr. Gundersen used LC-MS-MS with a triple quadrupole tandem mass spectrometer equipped with selected reaction monitoring (SRM; also known as multiple reaction monitoring, MRM) to confirm the presence of PC-EPA/EPA, PC-DHA/DHA and PC-EPA/DHA in lipid fractions prepared from krill. The use of LC-MS-MS with SRM to measure natural products, drug molecules, metabolites, etc., is among the most selective, specific and sensitive analytical approaches known today. Dr. Gundersen's identification of each of these phospholipid species in the krill fractions was based on the comparison of authentic standards of PC-EPA/EPA and PC-DHA/DHA with the krill samples using three highly selective and complementary analytical dimensions as follows: 1. HPLC retention time; 2. mass of the protonated molecule; and 3. structurally significant fragment ions. The use of analytical standards of PC-EPA/EPA and PC-DHA/DHA makes Dr. Gundersen's analyses more credible those carried out by Dr. White, who omitted comparison with standards. Using LC-MS-MS and authentic standards, Dr. Gundersen rigorously identified PC-EPA/EPA and PC-DHA/DHA in the krill specimens. Furthermore, his data show the presence of PC-EPA/DHA and/or PC-DHA/EPA in the krill specimens, but conclusive identification of which isomer (whether EPA is in the sn-1 or sn-2 position) would require comparison with an authentic standard.

10. The lipid fractions prepared from krill that were analyzed by Dr. Gundersen included samples from two different species, *E. superba* and *E. pacifica*, that were prepared using fractionation with different solvents and using various heat treatments. The large volume of data probably contributed to the "cut and paste" errors pointed out in the Declaration of Dr. Yeboah. Nevertheless, the data overwhelmingly support Dr. Gundersen's conclusion that PC-EPA/EPA, PC-DHA/DHA and PC-EPA/DHA are present in krill oils.

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