OPENING INFRINGEMENT EXPERT REPORT OF PROFESSOR MICHAEL BUTLER, PH.D.

I, Michael Butler, declare as follows:

I. Qualifications

1. I am a Distinguished Professor in the Department of Microbiology at the University of Manitoba in Winnipeg, Canada. My research focuses, among other things, on bioprocess development (including the development of cell culture media) and the effect of cell culture media on the metabolism of cells and the glycosylation of the proteins the cells produce. I am also the director of MabNet (the Strategic Network for the Production of Single-type Glycoform Monoclonal Antibodies), a collaboration among academics, industry, and government in Canada focused on the development of monoclonal antibodies.

2. I have conducted research in the area of cell culturing and antibody production, and the development of cell culture media, for over 35 years, beginning in the early 1980s. In
80. As discussed below, laboratory testing confirms this. The laboratory results confirm that the differences in amounts of L-arginine·HCl in the Celltrion Media compared to the claim are insubstantial, and that L-arginine·HCl in the amounts in the Celltrion Media performs substantially the same (if not the identical) function in substantially the same (if not the identical) way with substantially the same results as in media in which L-arginine is supplied by the claimed amount of L-arginine·HCl.

e. L-Asparagine·H2O

81. Claim 1 requires between 40-250 mg/L of L-asparagine·H2O. CGM contains 3.22 mg/L of L-asparagine·H2O and CPM contains 3.27 mg/L of L-asparagine·H2O.

82. In addition to L-asparagine·H2O, CGM and CPM also contain L-asparagine free base. This ingredient provides the same active component (L-asparagine) as L-asparagine·H2O. When both sources of L-asparagine are considered, the total amount of L-asparagine in the Celltrion Media is within the range achieved by claim 1 of the '083 patent. A comparison of the total molar amount of L-asparagine supplied by L-asparagine·H2O and L-asparagine free base in the Celltrion Media with the range of total amount supplied by the claimed ingredient (L-asparagine·H2O) is shown in Table 8 below.

**Table 8.** A Comparison of the Total Molar Amounts of L-Asparagine Supplied by L-Asparagine·H2O and L-Asparagine Free Base in Claim 1, CGM, and CPM

<table>
<thead>
<tr>
<th></th>
<th>'083 Patent Claim 1</th>
<th>CGM</th>
<th>CPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient</td>
<td>Amount (per liter)</td>
<td>Amount (per liter)</td>
<td>Amount (per liter)</td>
</tr>
<tr>
<td>L-asparagine·H2O (MW: 150.13 mg/mmol)</td>
<td>40-250 mg (0.266-1.665 mmol)</td>
<td>3.22 mg (0.021 mmol)</td>
<td>3.72 mg (0.025 mmol)</td>
</tr>
<tr>
<td>L-asparagine (MW: 132.12 mg/mmol)</td>
<td>N/A</td>
<td>167.61 mg (1.269 mmol)</td>
<td>193.88 mg (1.467 mmol)</td>
</tr>
</tbody>
</table>
83. As shown in Table 8, the total molar amounts of L-asparagine supplied by L-asparagine•H2O and L-asparagine free base in the Celltrion Media fall within the range of molar amounts of L-asparagine supplied by the claimed amount of L-asparagine•H2O.

84. The function the L-asparagine•H2O ingredient performs in the context of claim 1 is to provide an amount of the amino acid L-arginine for the cells in culture, which they use to make proteins. In my opinion, the differences in the concentration between the L-asparagine•H2O in the Celltrion Media and in claim 1 are insubstantial. Furthermore, L-asparagine•H2O in the amounts in the Celltrion Media performs substantially the same function in substantially the same way as L-asparagine•H2O in the claimed amount. This is because the ingredient in the Celltrion Media is identical to the claimed ingredient, and the literal differences in concentration are small; indeed there is no difference at all in the total concentration of L-asparagine. I would expect, subject to experimentation, that mammalian cells would perform similarly in the Celltrion Media as in media in which the same total concentration of L-asparagine was supplied by an amount of L-asparagine•H2O within the claimed concentration range.

85. As discussed below, laboratory testing confirms this. The laboratory results confirm that the differences in amounts of L-asparagine•H2O in the Celltrion Media compared to the claim are insubstantial, and that L-asparagine•H2O in the amounts in the Celltrion Media performs substantially the same (if not the identical) function in substantially the same (if not the identical) way with substantially the same results as media in which L-asparagine is supplied by the claimed amount of L-asparagine•H2O.
NaH2PO4•H2O in the claimed amount. This is because the ingredient in the Celltrion Media is identical to the claimed ingredient, and the literal differences in concentration are small. I would expect, subject to experimentation, that mammalian cells would perform similarly in the Celltrion Media as in media that were otherwise identical but had NaH2PO4•H2O within the claimed concentration range.

90. As discussed below, laboratory testing confirms this. The laboratory results confirm that the differences in amounts of the NaH2PO4•H2O ingredient in the Celltrion Media compared to the claim are insubstantial, and that the NaH2PO4•H2O amounts in the Celltrion Media perform substantially the same (if not the identical) function in substantially the same (if not the identical) way with substantially the same result as the claimed amount of NaH2PO4•H2O.

b. Na2HPO4

91. Claim 1 requires between 30-100 mg/L of Na2HPO4, while CGM contains 374.15 mg/L and CPM contains 432.64 mg/L.

92. The primary function the Na2HPO4 ingredient performs in the context of claim 1 is to provide an extracellular amount of the phosphate nutrient. Again, cells have a minimal phosphate requirement to create high-energy molecules that they use to generate the energy needed to grow, survive, and produce the proteins the cell is engineered to produce. Cells also require phosphate as a building block of DNA, needed for new cellular DNA as the cells divide. In my opinion, the differences in the concentration between the Na2HPO4 in the Celltrion Media and in claim 1 are not substantial. Furthermore, Na2HPO4 in the amounts in the Celltrion Media performs substantially the same function in substantially the same way as Na2HPO4 in the claimed amount. This is because the ingredient in the Celltrion Media is identical to the claimed ingredient, and the literal differences in concentration are small. I would expect, subject to
experimentation, that mammalian cells would perform similarly in the Celltrion Media as in media that were otherwise identical but had Na2HPO4 within the claimed concentration range.

93. As discussed below, laboratory testing confirms this. The laboratory results confirm that the differences in amounts of the Na2HPO4 ingredient in the Celltrion Media compared to the claim are insubstantial, and that the Na2HPO4 amounts in the Celltrion Media perform substantially the same (if not the identical) function in substantially the same (if not the identical) way with substantially the same result as the claimed amount of Na2HPO4.

4. Sodium Chloride

94. Claim 1 requires a concentration of NaCl (sodium chloride) between 5000-7500 mg/L. CGM literally meets this limitation. However, the concentration of NaCl in CPM is about 10% below the claimed range, as shown in Table 10.

Table 10. Concentration of NaCl in Claim 1 and the Celltrion Media

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>'083 Patent Claim 1</th>
<th>CGM</th>
<th>CPM</th>
</tr>
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<tbody>
<tr>
<td>NaCl</td>
<td>5000-7500 mg</td>
<td>5582.73 mg</td>
<td>4556.83 mg</td>
</tr>
</tbody>
</table>

95. The difference in NaCl concentration in CPM from the claimed range is insubstantial. The function of the amount of NaCl in a medium is to make it approximately isosmotic (having the same osmolality) with physiological fluids. Osmolality is a measure of the number of particles dissolved in solution. Physiological osmolality, that is, the osmolality in living systems, is about 300 mOsm/kg, plus or minus about 10%. Cell culture media are typically maintained at an osmolality in the neighborhood of physiological. NaCl is a non-nutritive ingredient that is used to balance the osmolality of the medium.8 One of ordinary skill

8 Burgener et al., supra, at 52; R. Ian Freshney, Culture of Animal Cells, 106 (6th ed. 2010).
X. **Compensation**

137. I am being compensated for my time at my usual rate of $350 per hour.

XI. **Other Cases in Which I Have Testified**

138. I have not given testimony in any case.

XII. **Signature**

Dated: August 31, 2016

[Signature]

Professor Michael Butler, Ph.D.