

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HUGEL, INC.

Petitioner,

v.

MEDYTOX INC.

Patent Owner.

Case No. IPR2023-00604

Patent No. 11,331,598

PETITION FOR *INTER PARTES* REVIEW

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EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 11,331,598 (“the ’598 Patent”)
1002	U.S. Patent No. 8,993,268 (“Jung”)
1003	U.S. Patent No. 8,932,827 (“Ton”)
1004	U.S. Patent Publication No. 2018/0251741 (“Kim ’741”)
1005	U.S. Patent Publication No. 2015/0337281 (“Kim ’281”)
1006	’598 Patent Prosecution History
1007	Lu et al. <i>Purification of hemoglobin by ion exchange chromatography in flow-through mode with PEG as an escort</i> . Artificial cells, blood substitutes, and biotechnology 32.2 (2004): 209-227 (“Lu”)
1008	Certified English Translation of KR10-2015-0168196
1009	Ozturk and Hu, eds. <i>Cell culture technology for pharmaceutical and cell-based therapies</i> . CRC press, 2005, Chapter 13 (Ronald C. Bates) (“Bates Chapter”).
1010	Sugiyama. <i>Clostridium botulinum neurotoxin</i> . Microbiological reviews 44.3 (1980): 419-448.
1011	Park et al. <i>Binding of Clostridium botulinum type B toxin to rat brain synaptosome</i> . FEMS microbiology letters 72.3 (1990): 243-247.
1012	Montecucco and Schiavo. <i>Tetanus and botulism neurotoxins: a new group of zinc proteases</i> . Trends in biochemical sciences 18.9 (1993): 324-327.
1013	Poulain et al. <i>Neurotransmitter release is blocked intracellularly by botulinum neurotoxin, and this requires uptake of both toxin polypeptides by a process mediated by the larger chain</i> . Proceedings of the National Academy of Sciences 85.11 (1988): 4090-4094.

Exhibit	Description
1014	Schantz and Johnson. <i>Properties and use of botulinum toxin and other microbial neurotoxins in medicine</i> . Microbiological reviews 56.1 (1992): 80-99.
1015	U.S. Patent No. 6,558,926
1016	Amersham Biosciences, Ion Exchange Chromatography & Chromatofocusing: Principle and Methods, No. 11-0004-21, Amersham Biosciences Limited (GE Healthcare) (Ed. AA) (2004)
1017	Reserved
1018	<i>Curriculum vitae</i> of Ronald C. Bates, Ph.D.
1019	Korean Patent Application No. KR10-2015-0168196
1020	POROS™ HS Analytical Columns for Cation Exchange Chromatography Technical Sheet
1021	Expert Declaration of Dr. Ronald Bates in Support of Petition for Post-Grant Review of U.S. Patent No. 11,331,598 (“Bates Declaration”)
1022	Table Comparing Jung Example 3, ’598 Patent Example, and Inventor Declaration Submitted During Prosecution of the ’598 Patent
1023	International Patent Application Publication No. WO2016175565 (“Kim ’565”)
1024	Liu et al. Recovery and purification process development for monoclonal antibody production. MABs. Vol. 2. No. 5. Taylor & Francis, 2010.
1025	Fahrner. <i>Industrial purification of pharmaceutical antibodies: development, operation, and validation of chromatography processes</i> . Biotechnology and Genetic Engineering Reviews 18.1 (2001): 301-327.

Exhibit	Description
1026	Gasteiger et al. <i>ExPASy: the proteomics server for in-depth protein knowledge and analysis</i> . Nucleic acids research 31.13 (2003): 3784-3788.
1027	Binz et al. <i>The complete sequence of botulinum neurotoxin type A and comparison with other clostridial neurotoxins</i> . Journal of Biological Chemistry 265.16 (1990): 9153-9158.
1028	GE Healthcare Ion Exchange Instructions 56-1191-00 AF (2004)
1029	GE Healthcare BPG Column Data File 18-1116-23 AD
1030	Amersham Biosciences, Ion Exchange Chromatography: Principle and Methods, No. 18-1114-21, Amersham Biosciences Limited (GE Healthcare) (Ed. AB) (2002)
1031	Kang et al. <i>Development of a novel and efficient cell culture flocculation process using a stimulus responsive polymer to streamline antibody purification processes</i> . Biotechnology and Bioengineering 110.11 (2013): 2928-2937.

I. INTRODUCTION

Hugel, Inc. (“Hugel” or “Petitioner”) files this petition for *inter partes* review (“Petition”), seeking cancellation of claims 1-9 (“Challenged Claims”) of U.S. Patent No. 11,331,598 (“the ’598 patent”) (EX1001), assigned to Medytox Inc. (“Patent Owner”). This Petition is supported by the expert declaration of Dr. Ronald C. Bates (EX1021), and other exhibits submitted herewith.

The Challenged Claims should never have issued. They are directed to well-known and routine methods for purifying botulinum toxin from a culture of *Clostridium botulinum*, including the steps of (i) culturing *Clostridium botulinum*, (ii) removing *Clostridium botulinum* cells from the culture, (iii) adding an acid to precipitate the botulinum toxin, (iv) dissolving the precipitate, (v) filtering the solution, and (vi) conducting (a) anion exchange chromatography and (b) cation exchange chromatography.

The alleged inventive concept is that the anion exchange chromatography is performed “at a pH lower than a pI of botulinum toxin” resulting in the toxin flowing through the matrix. EX1006, 12-20-2021 Response, 12 (Exhibit Page 619). Indeed, the claims were allowed based on this limitation. *Id.*, 1-21-2022 Notice of Allowance, 3 (Exhibit Page 627). Patent Owner, however, publicly disclosed this purportedly novel subject matter eight years before the earliest alleged priority date in its application that led to U.S. Patent No. 8,993,268 (“Jung”) (EX1002). Despite

Jung sharing four inventors in common with the '598 patent, while clearly disclosing the majority of the elements of its claims, Patent Owner failed to disclose this reference to the Office.

As detailed herein, each of the claimed steps, and the use of them together, in the recited order, was well known in the art as of the priority date and would have been obvious to a POSA. In particular, Jung discloses a method for purifying botulinum toxin from a culture of *Clostridium botulinum*, including the steps of (i) culturing *Clostridium botulinum*, (ii) removing *Clostridium botulinum* cells from the culture, (iii) adding an acid to precipitate the botulinum toxin, (iv) dissolving the precipitate, (v) filtering the solution, and (vi) conducting anion exchange chromatography at pH 5.5. The only difference between the claimed method and Jung is the inclusion of a cation exchange chromatography step “at a pH lower than a PI of botulinum toxin.” This additional step, however, was well known and does not save the Challenged Claims from being unpatentable.

U.S. Patent No. 8,932,827 (“Ton”) (EX1003), filed by Allergan in 2009, describes purifying botulinum toxin from *Clostridium botulinum* comprising conducting anion exchange chromatography followed by cation exchange chromatography at pH 4.8. As set forth in detail below, a POSA would have been motivated to combine the teachings of Jung and Ton to arrive at the claimed method with a reasonable expectation of success, at least because a POSA would have

known to combine anion exchange chromatography with cation exchange chromatography to purify botulinum toxin from *Clostridium botulinum*.

U.S. Publication No. 2018/0251741 (“Kim ’741”) (EX1004), filed in 2015 by Daewoong, is another prior art publication that describes a method of purifying botulinum toxin from *Clostridium botulinum*. Kim ’741 discloses conducting anion exchange chromatography and cation exchange chromatography at pH ranges that overlap with “a pH lower than a PI of botulinum toxin.” As set forth in detail below, Patent Owner cannot overcome the presumption of obviousness based on this overlap in pH range because “a pH lower than a PI of botulinum toxin” is not critical to the claimed invention nor does it produce unexpected results. And while Kim ’741 was considered by the Examiner, this Petition demonstrates that the Examiner erred in crediting Patent Owner’s alleged evidence of unexpected results.

As detailed herein, Petitioner has shown that that there is a reasonable likelihood that at least one claim of the ’598 patent is unpatentable. Moreover, there are no persuasive grounds for denying institution under § 325(d). Petitioner respectfully requests that the Board institute review and cancel claims 1-9 of the ’598 patent.

II. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

Ground	Basis	References	Claims
1	Obviousness	Jung and Ton	1-9

2	Obviousness	Kim '741, Kim '565 and Jung	1-9
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III. GROUNDS FOR STANDING (37 C.F.R. § 42.204(A))

Petitioner certifies that the '598 patent is available for *inter partes* review, having issued on May 17, 2022, *i.e.*, this Petition is filed nine months after the grant of the patent. Petitioner hereby certifies that it is not barred or estopped from requesting review of the grounds identified.

IV. MANDATORY NOTICES

A. Real Parties-In-Interest (§ 42.8(b)(1))

Petitioner is the sole real-party-in-interest.

B. Related Matters (§ 42.8(b)(2))

The '598 patent is not currently the subject of any litigation or post-grant proceedings.

C. Identification of Counsel (§ 42.8(b)(3))

Petitioner designates Dion M. Bregman (Reg. No. 45,645) as lead counsel, and Guylaine Haché (Reg. No. 76,083) and Charles H. Rexer Jr. (Reg. No. 76,145) as back-up counsel.

Petitioner consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below.

dion.bregman@morganlewis.com

guylaine.hache@morganlewis.com

charles.rexer@morganlewis.com

MLB-Hugel-IPR-Team@morganlewis.com

D. Service Information (§ 42.8(b)(4))

This Petition is being served by Federal Express Next Business Day Delivery to the correspondence address of record for the '598 patent: Potomac Law Group, PLLC, 1300 Pennsylvania Avenue, NW, Suite 700, Washington, DC 20004, UNITED STATES.

V. POWER OF ATTORNEY (§ 42.10(B))

The Petitioner's Power of Attorney form is filed concurrently in accordance with 37 C.F.R. § 42.10(b).

VI. FEE PAYMENT (§ 42.15(A))

The required fee described in § 42.15(a) is paid under § 42.103, and the Commissioner is hereby authorized to charge all fees pertaining to this matter to Attorney Deposit Account 50-0310 (docket number 133493-0003).

VII. BRIEF BACKGROUND OF THE STATE OF THE ART

The claims of the '598 patent relate to a method of isolating a botulinum toxin type A macro complex comprising routine protein purification steps, including culturing *Clostridium botulinum* in a suitable media, followed by, *inter alia*, centrifugation, acid precipitation, filtration, and ion exchange chromatography. EX1021 ¶33.

Ion exchange chromatography separates biomolecules (e.g., proteins, peptides, nucleotides) on the basis of charge. *Id.* ¶37. Every biomolecule has an isoelectric charge. *Id.* The overall isoelectric charge and the surface charge of a biomolecule will vary with the pH of its environment. *Id.* For example, at a pH at which a biomolecule carries no net charge (i.e., its isoelectric point (pI)), the biomolecule is not expected to strongly interact with a charged separation matrix (i.e., ion exchanger). *Id.* However, at a pH above its pI, a biomolecule will carry an overall negative charge, and thus, is expected to bind to a positively charged separation matrix (i.e., anion exchanger); whereas it is expected to flow through (e.g., not bind to) a negatively charged matrix (i.e., cation exchanger). Conversely, at a pH below its pI, a biomolecule will carry an overall positive charge, and is expected to flow through a positively charged matrix; whereas it is expected to bind to a negatively charged matrix. *Id.*

Interactions between charged biomolecules, and an oppositely charged ion exchange chromatography matrix can therefore be modulated by adjusting the pH to favor either binding of biomolecules to the separation matrix or the flow of biomolecules through the separation matrix (while unwanted impurities remain bound to the separation matrix), thereby separating the biomolecule from other contaminants or impurities. *Id.* ¶38.

Accordingly, it was well understood by a POSA that pH, during ion exchange chromatography, was an important parameter to optimize in order to achieve effective separation of biomolecules. As noted above, the surrounding pH can impact the overall surface charge of biomolecules, which will in turn affect their ability to associate with an ion exchange chromatography matrix. Accordingly, a POSA would have been familiar with selecting the proper pH so that the desired biomolecule will either bind or flow through the separation matrix. *Id.* ¶¶39-42.

VIII. BACKGROUND OF THE '598 PATENT

A. Brief Description of the '598 Patent

The '598 patent was filed as a national stage application of PCT/IB2017/057476 on April 1, 2019. PCT/IB2017/057476, filed on November 29, 2017, and claims priority to KR10-2016-0127540, filed on October 4, 2016. The '598 patent thus has an earliest possible priority date of October 4, 2016.¹

The '598 patent issued with 9 claims. Claim 1 is the sole independent claim. Independent claim 1 relates to “[a] method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution” by culturing *Clostridium botulinum*, removing the *Clostridium botulinum* cells from the culture, precipitating botulinum toxin by adding an acid to the culture, diluting the

¹ Petitioner does not concede this date.

precipitate, filtering the resulting solution, and conducting ion exchange chromatography to purify the toxin.

The specification includes a single example titled “Culture of *Clostridium botulinum* and Purification of *Clostridium botulinum* Toxin.” EX1001, 7:17-10:16. In that example, “a large amount of *Clostridium botulinum* type A toxin was expressed outside cells by culturing *Clostridium botulinum* in an animal product-free medium.” *Id.*, 7:23-25. Following culturing, *Clostridium botulinum* was purified from the culture medium by (1) acid purification, (2) concentration and filtration, (3) anion exchange chromatography, (4) concentration and filtration, and (5) cation exchange chromatography. *Id.*, 8:14-10:16.

B. Summary of the Prosecution History of the ’598 Patent

On May 18, 2020, the Examiner rejected the claims as obvious over U.S. 9,206,409 (“’409 patent). EX1006, 5-18-2020 Office Action, 4 (Exhibit Page 329).² The Examiner stated that the ’409 patent

teaches a purification method for obtaining botulinum neurotoxin type A from a mixture of botulinum toxins using a chromatographic process. ... Briefly, a harvested fermentation medium is loaded onto an anion exchange column, subsequently onto a cation exchange column, and

² The ’409 patent is a continuation of Ton (EX1003).

finally eluted from the cation exchange column for further downstream purification.

Id. The Examiner explained that the '409 patent “teaches that botulinum neurotoxin type A is known to be soluble a pH 4-6.8” and that “one of ordinary skill in the art would find it advantageous to maintain the harvested fermentation medium containing botulinum neurotoxin type A at a pH that would maintain its solubility in buffer (i.e., at pH 4-6.8).” *Id.* The Examiner concluded that the '409 patent “reads on the claimed limitations of contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than an isoelectric point of botulinum toxin; contacting the solution which is not bound to the anion exchange chromatography medium with a cation exchange chromatography medium at a pH lower than the PI of botulinum toxin.” *Id.*, 4-5 (Exhibit Pages 329-330) (emphasis original).³

In response, Patent Owner argued that the '409 patent “only discloses ‘(d) eluting the captured botulinum neurotoxin from the anion exchange medium to obtain a first eluate’ and subsequent steps of processing the first eluate.” EX1006, 9-18-2020 Response, 8 (Exhibit Page 485) (emphasis original). According to Patent Owner:

³ Emphasis added unless noted otherwise.

one of ordinary skill in the art would not have a reason to modify “(d) eluting the captured botulinum neurotoxin from the anion exchange medium to obtain a first eluate” of [the ’409 patent] into “contacting flow-through portion of the botulinum toxin-containing solution, which is not bound to the anion exchange chromatography medium, with a cation exchange chromatography medium at a pH lower than the PI of botulinum toxin” of claim 1 (a) ... Further [the ’409 patent] does not disclose “a pH lower than the PI of botulinum toxin” as claimed.

Id., 10 (Exhibit Page 487) (emphasis original). Patent Owner further stated that the ’409 patent “does not disclose ‘a pH lower than the PI of botulinum toxin’ as claimed.” *Id.*⁴

On November 6, 2020, the Examiner again rejected the claims as obvious, this time over Kim ’741 (EX1004). The Examiner explained that

KIM ’741 discloses a method for producing and purifying botulinum toxin ... whereby after an initial series of clarification and purification steps (steps a-e) of botulinum

⁴ This statement is false. Ton—which shares the same specification as the ’409 patent—discloses purifying botulinum toxin by conducting *cation exchange chromatography at pH 4.8* (EX1003, 40:26-31), which is below the admitted 6.06 pI of botulinum toxin.

toxin produced from culture ..., subsequent anion exchange (AEX, step f) and cation exchange (CEX, step h) purification steps are practiced. The AEX chromatography step f is performed at a pH of 3-8, and botulinum toxin is collected in a flow-through fraction from the AEX column ... After diluting in a buffer in step g, the CEX chromatography step h is performed at a pH of 3-8 whereby botulinum toxin is collected at a fraction containing the botulinum toxin bound to the CEX resin ... Given the 6.06 isoelectric point (pI) of botulinum toxin type A, the taught pH ranges of 3-8 during AEX and CEX chromatography steps f and h overlap with the claimed ranges of ‘a pH lower than the pI of botulinum toxin’ and therefore, establishes cases of prima facie obviousness.

EX1006, 11-6-2020 Office Action, 4-5 (Exhibit Pages 499-500).

Patent Owner filed a response on February 8, 2021, in which they admitted that “KIM discloses a broad pH range of 2-9, preferably 3-8, for anion and cation exchange chromatographies.” *Id.*, 2-8-2021 Response, 8 (Exhibit Page 533). However, Patent Owner argued that “in the Examples, the actual pH during the anion and cation exchange chromatographies was higher than the PI of botulinum toxin in AEX.” *Id.* (emphasis original). According to Patent Owner, “[t]he general disclosure in KIM of a pH of 2-9, preferably 3-8, in which the AEX and CEX can

be performed does not provide a reason for one of ordinary skill in the art to select ‘a pH lower than the PI of botulinum toxin.’” *Id.*, 9 (Exhibit Page 534).

The Examiner rejected that argument in the next Office Action. The Examiner reiterated that Kim ’741 discloses pH ranges for the anion exchange and cation exchange steps that overlap with the claimed range of “a pH lower than the pI of botulinum toxin” and therefore “establishes cases of *prima facie* obviousness,” and that “[a]bsent showings of significance or criticality to the claimed ‘a pH lower than the pI of botulinum toxin,’ the disclosure of KIM would render the claimed invention obvious to one of ordinary skill in the art.” *Id.*, 4-22-2021 Office Action, 3 (Exhibit Page 546).

In response, Patent Owner submitted a “Declaration signed by a co-inventor, Jung Hyun SONG” which compared “the relative efficiency of botulinum toxin recovery between an AEX using a pH lower than the PI of botulinum toxin and an AEX using pH higher than the PI of botulinum toxin.” *Id.*, 7-22-2021 Response, 9 (Exhibit Page 567). “In the experiments, pH 5.5 and pH 6.5 were selected as a pH lower than the PI of botulinum toxin and a pH higher than the PI of botulinum toxin, respectively.” *Id.* (emphasis original).

Patent Owner pointed to Figure 1 of the Declaration which “shows a chromatogram for flow through solution and eluted solution from the AEX [anion

exchange] using pH 5.5, which is a pH lower than the PI of botulinum toxin.” *Id.* (emphasis original). According to Patent Owner:

As shown in FIG. 1, the botulinum toxin containing sample was detected immediately after loading the sample. ... On the contrary, no significant peaks were (*sic*) appeared in the eluted solution with buffer B (pH 6.5). There was no significant fluctuation of the blue line at retention time between about 30 ml to 150 ml, i.e., there was no significant fluctuation of the absorbance at UVA278 when buffer B started to flow. This indicates that the botulinum toxin is contained in the flow through solution.”

Id. Patent Owner next pointed to Figure 3 of the Declaration which “shows a chromatogram for a flow through solution and eluted solution from the AEX using pH 6.5, which is a pH higher than the PI of botulinum toxin.” *Id.* (emphasis original).

According to Patent Owner:

As shown in FIG. 3, the botulinum toxin containing sample was detected at about 50 ml retention time and after starting the elution with buffer B after loading the sample. This indicates that the botulinum toxin is not contained in the flow through solution, but contained in the eluted solution with buffer B. Thus, the claimed method would not work at a pH higher than the PI of botulinum toxin, as taught by KIM.

Id., 9-10 (Exhibit Page 567-568).

Patent Owner stated that “[t]hese results from using pH 5.5 and pH 6.5 show that 19S [*e.g.*, macro complex of botulinum toxin] can be purified from the flow through solution when pH 5.5 is used but at pH 6.5, 19S was not present in the flow through solution but present in the eluted solution.” *Id.*, 10. According to Patent Owner, the “unexpected benefit of the claimed invention” is that “when pH 5.5 is used, 19S can be simply purified from the flow through solution with high purity and there is no need to add an additional eluting step.” *Id.*

The Examiner again rejected the claims based on Kim '741 in an Office Action dated August 18, 2021. The Examiner explained:

[B]ased on the principles of ion exchange chromatography, a protein or target of interest will bind to either a cation or anion exchange resin based on its overall charge. In a buffered solution below the protein's pI, the protein is positively charged and will bind to the negatively charged functional groups of a cation exchange resin and will not bind to the positively charged functional groups of an anion exchange resin. Because the claimed inventive method requires taking the flow-through portion of botulinum toxin-containing solution *not bound to* an anion exchange chromatography medium and separating botulinum toxin type A macro complex *bound to* a cation exchange chromatography medium, one of ordinary skill

in the art of chromatography would find it obvious to perform such a method at a lower pH range to maximize the flow-through of botulinum toxin type A macro complex through the AEX resin and to maximize the binding of botulinum toxin type A macro complex of the CEX resin. Thus, it would be obvious to one of ordinary skill in the art at the time of filing of the invention to use the lower end of the KIM '741 disclosed pH 3-8 range in AEX and CEX chromatography steps f and h, which overlaps with the claimed ranges.

Id., 8-18-2021 Office Action, 2-3 (Exhibit Pages 586-587) (emphasis original). As to the inventor declaration, the Examiner stated that, “Applicant has only provided comparisons of botulinum toxin recovery between pH lower than the pI and pH higher than the pI *for only AEX chromatography*, i.e., *no nexus* has been shown between the provided data and the claimed inventive method.” *Id.*

In response, Patent Owner amended claim 1 to add a series of steps prior to the ion exchange chromatography steps. *Id.*, 12-20-2021 Response, 2 (Exhibit Page 609). Patent Owner argued that Kim '741 did not disclose or suggest the additional claimed steps. *Id.*, 5-8 (Exhibit Page 612-615). Patent Owner also reiterated the arguments regarding the inventor declaration that was presented in the previous response. *Id.*, 8-13 (Exhibit Pages 615-620).

The Examiner allowed the claims on January 21, 2022. In the Reasons for Allowance, the Examiner stated:

Applicant has also provided a declaration by co-inventor SONG (22 July 2021) comparing the relative efficiency of botulinum toxin recovery from an anion exchange process between using a pH lower than the pI of botulinum toxin and a pH higher than the pI of botulinum toxin, thereby showing the criticality of such a claimed limitation. ***This showing of criticality was persuasive to overcome the 35 USC 103 rejection of claim 1 as being unpatentable over KIM.***

Id., 1-21-2022 Notice of Allowance, 3 (Exhibit Page 627). As shown below, the Examiner erred in finding that the declaration showed the criticality of the pH claim limitation.⁵

⁵ The Examiner must have also overlooked that Kim '741 discloses conducting ***flow-through anion exchange chromatography at pH 6.4-6.6***. EX1004 ¶¶[0107]-[0108] (“***pH was maintained at 6.4-6.6***” and “it was shown that the botulinum toxin was ***not adsorbed*** onto the TQ resin”). Therefore, the claimed range of “a pH lower than the PI of botulinum toxin” “cannot be critical to practicing the alleged invention if the sole alleged benefit ***is also achieved [above] the range, at [pHs] disclosed in the***

IX. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art (“POSA”) to whom the ’598 patent is directed would have been an individual with at least a graduate degree, such as a masters or Ph.D., in a relevant discipline such as biochemistry, process chemistry, protein chemistry, chemical engineering and/or biochemical engineering, among others, with at least four years of experience in those areas after receiving the graduate degree. EX1021 ¶22.

X. CLAIM CONSTRUCTION

Any term not expressly discussed should be given its ordinary and customary meaning to a POSA as of the earliest priority date of the ’598 patent, which Petitioner assumes, for purposes of this Petition only, to be October 4, 2016.

A. Botulinum Toxin Type A Macro Complex

Independent claim 1 recites “[a] method of isolating a botulinum toxin type A macro complex.” According to the specification, “botulinum toxin type A macro complex, *i.e.*, **900 kDa** may be efficiently isolated from the botulinum toxin-containing solution.” EX1001, 6:56-60. Thus, the term “botulinum toxin type A macro complex” should be construed to include *a botulinum toxin type A of 900*

prior art.” *Hospira, Inc. v. Genentech, Inc.*, IPR2016-01837, Paper 40, 24-25 (PTAB Mar. 6, 2018).

kDa. EX1006, 1-21-2022 Notice of Allowance, 2 (under “Claim Interpretation” the Examiner noting that “[a]s noted in paragraph 6 of the Specification, a botulinum toxin macro complex is 900 kDa and includes 150 kDa of botulinum toxin (A-G) and a complex of a variety of non-toxic proteins.”); EX1021 ¶44.

B. A pH Lower than the PI of Botulinum Toxin

Independent claim 1 recites conducting anion and cation exchange chromatography “at a pH lower than the PI of botulinum toxin.” According to the specification:

An isoelectric point of botulinum toxin A may be about 6.06. Therefore, the “pH lower than the isoelectric point” may differ depending on the type of the toxin to be isolated. For example, in the case of type A toxin, the pH may be 6.06 or lower ...

EX1001, 4:16-23. Thus, the term pH lower than the pI of botulinum toxin should be construed to mean a *pH lower than 6.06*. EX1006, 1-21-2022 Notice of Allowance, 2 (under “Claim Interpretation” the Examiner noting that “[a]s noted in paragraph 21 of the Specification, the isoelectric point (pI) of botulinum toxin Type A is about 6.06.”); EX1021 ¶45.

XI. DETAILED EXPLANATION OF GROUNDS

A. Asserted Prior Art⁶

1. Jung

Jung (EX1002), assigned to Patent Owner and entitled “Method of producing *Clostridium botulinum* toxin using media containing plant-derived components and flexible closed container,” is a national stage application of PCT/KR2008/003897, filed on July 2, 2008, and published as WO2009/142352 on November 26, 2009.⁷ Jung issued on March 31, 2015, which is before October 4, 2016, the presumed effective filing date of the ’598 patent. Therefore, Jung is prior art to the ’598 patent under 35 USC § 102(a)(1).⁸

2. Kim ’741

Kim ’741 (EX1004), entitled “Method for producing botulinum toxin,” is a national stage application of PCT/KR2016/013506, filed on November 23, 2016, published as WO2017/095062A1 on June 8, 2017, and names different inventors to

⁶ The ’598 patent qualifies as a post-AIA patent because its earliest effective filing date is after March 16, 2013.

⁷ Jung shares four common inventors with the ’598 patent: Hyun-Ho Jung, Gi-Hyeok Yang, Hack-Woo Kim, and Hyung-Pyo Hong.

⁸ Jung was not considered by the Examiner during prosecution.

the challenged patent. PCT/KR2016/013506 claims priority to KR10-2015-0168196 filed on November 30, 2015, which is before October 4, 2016, the presumed effective filing date of the '598 patent. EX1004 at Cover. Therefore, Kim '741 is prior art to the '598 patent under 35 USC § 102(a)(2) as of its priority filing date of November 30, 2015.⁹

3. Kim '565

Kim '565 (WO2016/175565, EX1023), entitled "Medium composition for preparing botulinum toxin," was filed on April 28, 2016, published on November 3, 2016, and names different inventors to the challenged patent. EX1023 at Cover. Kim '565's filing date of April 28, 2016 is before October 4, 2016, the presumed effective filing date of the '598 patent. Therefore, Kim '565 is prior art to the '598 patent under 35 USC § 102(a)(2).¹⁰

⁹ Petitioner has provided a certified translation of Kim '741's priority application KR10-2015-0168196 (EX1008) as well as the original document. EX1019. The citations to EX1008 throughout this Petition are to show that Kim '741 is prior art to the '598 patent as of its priority filing date.

¹⁰ Kim '565 was not considered by the Examiner during prosecution.

4. Ton

Ton (EX1003), entitled “Process and system for obtaining botulinum neurotoxin,” issued January 13, 2015, before the October 4, 2016, the presumed effective filing date of the ’598 patent. Ton is therefore prior art to the ’598 patent under 35 USC § 102(a)(1).¹¹

B. Ground 1: Claims 1-9 Would Have Been Obvious Over Jung In Combination With Ton

1. Independent Claim 1

- a) “A method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution”

Jung discloses “*a method of producing Clostridium botulinum toxin* by using a media containing plant-derived components.” EX1002, Abstract. Jung states that “[t]he *Clostridium botulinum* toxin may be one selected from the group consisting of *botulinum* toxin A, B, C, D, E, F, and G, and *preferably, botulinum toxin A.*” *Id.*, 6:36-38. Jung explains that “[e]ach toxin has about 150 kDa of toxin protein, and naturally comprises a complex with a variety of non-toxic proteins bound thereto. An intermediate complex (300 kDa) comprises toxin protein and non-toxic non-hemagglutinin protein, and a large complex (500 kDa) and *a macro*

¹¹ U.S. 9,206,409, which is a continuation of Ton, was asserted in a rejection during prosecution.

complex (900 kDa).” *Id.*, 1:43-49. Moreover, according to the ’598 patent, “the botulinum toxin-containing solution may be a *culture of Clostridium botulinum.*” EX1001, 3:28-30. Jung discloses that “the *toxin existing in the culture* from which the cell is removed is isolated.” EX1002, 4:37-38. Therefore, Jung discloses “[a] method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution.” EX1021 ¶64.

b) “culturing *Clostridium botulinum* in an animal product-free medium to obtain a culture”

Jung discloses that “*Clostridium botulinum* was cultured using the medium 5 of Example 1 or 2.” EX1002, 11:28-29. Medium 5 of Example 1 or 2 is *animal product-free*. *Id.*, Table 1; *id.*, 8:21-25 (“The fact that a large amount of *Clostridium botulinum* type A toxin was expressed outside the cell in a *media containing no animal-derived components* was confirmed using a variety of plant media.”); *id.*, 3:7-10 (“In the method of present invention, *Clostridium botulinum* is cultured in the *media containing plant-derived components* to express *Clostridium botulinum* toxin outside the cell.”)

Moreover, the “culturing” step in Jung Example 3 is essentially the same as that disclosed in the ’598 patent:

Jung Example 3	’598 Patent Example
“ <i>Clostridium botulinum</i> was <i>cultured</i> using the medium 5 of Example 1 or 2.” EX1002, 11:28-	“In this Example, a large amount of <i>Clostridium botulinum</i> type A toxin was expressed outside cells by

29. “The culturing conditions and time and the cell removal process were the same as those in Example 1.” <i>Id.</i>, 11:29-32. Medium 5: <i>phytone peptone 1%; yeast extract 1%; glucose 0.5%.</i> <i>Id.</i>, Table 1. In Example 1, “200 ml of each of the media of Table 1 and the control media was filtered through a sterilized single use microfiltration system ... so as to be injected into Cultibag™ ... <i>Then, each media was inoculated with 1ml of a seed inoculum including Clostridium botulinum type A with a concentration of 10⁶-10⁷ cells/ml through a sample injection port.</i> Cultibag™ is a disposable bioreactor that may use rocking motion in order to cause mixing.” <i>Id.</i>, 8:56-9:2.	<i>culturing Clostridium botulinum</i> in an animal product-free medium.” EX1001, 7:23-25. “The used medium was a medium containing 4% <i>yeast extract and 0.5% glucose.</i>” <i>Id.</i>, 7:26-27; <i>id.</i>, 3:43-45 (“The medium containing plant-derived components may include <i>phytone peptone.</i>”) “200 ml of the medium thus prepared was filtered through a sterile single use microfiltration system ... and injected into Cellbag™ ... <i>Then, the medium was inoculated with 1 ml of a seed culture of Clostridium botulinum at a density of 10⁶ cells/ml – 10⁷ cells/ml through a sample injection port.</i> Cellbag™ is a disposable bioreactor that uses rocking motion in order to cause mixing under low shear stress.” <i>Id.</i>, 7:31-39.
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Therefore, Jung discloses the step of “culturing *Clostridium botulinum* in an animal product-free medium to obtain a culture.” EX1021 ¶65.

c) **“removing *Clostridium botulinum* cells from the culture to obtain a botulinum toxin-containing solution”**

Jung discloses that “operation (b) may include ***removing the cells from the culture***, adding an acid to obtain a precipitate.” EX1002, 6:45-47. Moreover, the “removing *Clostridium botulinum* cells” step in Jung Example 3 is essentially the same as that disclosed in the ’598 patent:

Jung Example 3	'598 Patent Example
“After the culturing was terminated, a sterile connector QDC connector (manufactured by Satorious) was connected to the sample port of the bag ... and <i>the culture was filtered through depthfilter and the microfilter to remove the cell.</i> ” EX1002, 9:36-46.	“After the culturing was terminated, a QDC connector (manufactured by Satorious) which is a sterile connector was connected to the sample port of the bag... and <i>the culture was filtered therethrough to remove the cells.</i> ” EX1001, 8:1-9.

Therefore, Jung discloses the step of “removing *Clostridium botulinum* cells from the culture to obtain a botulinum toxin-containing solution.” EX1021 ¶66.

d) “adding an acid to the botulinum toxin-containing solution to precipitate the botulinum toxin and obtain a precipitate”

Jung discloses that “*sulfuric acid was added* to a bag including 20 L of a culture supernatant to adjust the pH of the resulting solution to be in the range of 3.0 to 4.5, and as a result, *toxin protein was precipitated.*” EX1002, 11:33-36. Moreover, the “acid precipitation” step in Jung Example 3 is essentially the same as that disclosed in the '598 patent:

Jung Example 3	'598 Patent Example
“ <i>[S]ulfuric acid was added</i> to the bag including 20 L of a culture supernatant to adjust the pH of the resulting solution to be in the range of 3.0 to 4.5, and as a result, <i>toxin protein was precipitated.</i> ” EX1002, 11:33-36.	“ <i>[S]ulfuric acid was added</i> to a bag containing 20 L of the culture supernatant obtained as above to adjust pH from 3.0 to 4.5, and as a result, <i>toxin protein was precipitated.</i> ” EX1001, 8:19-21.

Therefore, Jung discloses the step of “adding an acid to the botulinum toxin-containing solution to precipitate the botulinum toxin and obtain a precipitate.” EX1021 ¶67.

e) “dissolving the precipitate in a medium to obtain a solution”

Jung discloses that “10 L of a 25 mM citrate buffer (pH 5.5) was added to the collected precipitation to *re-dissolve toxin protein existing in the precipitation.*” EX1002, 11:51-53. Moreover, the “dissolving” step in Jung Example 3 is essentially the same as that disclosed in the ’598 patent:

Jung Example 3	’598 Patent Example
“10 L of a 25 mM citrate buffer (pH 5.5) was added to the collected precipitation to <i>re-dissolve toxin protein</i> existing the precipitation.” EX1002, 11:51-53.	“10 L of citrate buffer (25 mM, pH 5.5) was added to the collected precipitate to <i>redissolve toxin protein</i> existing in the precipitate.” EX1001, 8:37-39.

Therefore, Jung discloses the step of “dissolving the precipitate in a medium to obtain a solution.” EX1021 ¶68.

f) “filtering the solution to obtain a botulinum toxin-containing solution”

Jung discloses that a “sterilized disposable filtration system ... was connected to the bag including the redissolved toxin protein and *filtration was performed on the toxin protein.*” EX1002, 11:54-57. Moreover, the “filtering” step in Jung Example 3 is essentially the same as that disclosed in the ’598 patent:

Jung Example 3	'598 Patent Example
<i>“[F]iltration was performed on the toxin protein through the system not in contact with the outside. As a result, the supernatant was collected in a sterilized disposable bag and insoluble impurities were removed.”</i> EX1002, 11:57-12:1.	<i>“[F]iltration was performed without being in contact with the outside. As a result, the supernatant was collected in a sterile disposable bag and insoluble impurities were removed.”</i> EX1001, 8:43-46.

Therefore, Jung discloses the step of “filtering the solution to obtain a botulinum toxin-containing solution.” EX1021 ¶69.

- g) **“contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than an isoelectric point (PI) of botulinum toxin”¹²**

Jung discloses a buffer exchange step after the filtration step “using a 25 mM citrate buffer (**pH 5.5**).” EX1002, 11:65-12:1 (“Then, the sample was filtered with no contact with the outside to be enriched, and a **buffer exchange** was performed on the enriched resultant by using a **25 mM citrate buffer (pH 5.5)**.”). Jung discloses applying the buffer-exchanged toxin containing solution to an anion exchange

¹² Claim 1 of the '598 patent recites an element (b) as an alternative to element (a). A claim element reciting alternatives is disclosed if the prior art discloses one of the alternatives. *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1297-98 (Fed. Cir. 2009).

chromatography resin: “Then, *DEAE anion exchange chromatography* and membrane chromatography were performed on the sample ...” *Id.*, 12:9-12.

While not expressly stated in Jung, a POSA would understand that Jung equilibrated the anion exchange resin with *citrate buffer pH 5.5* prior to applying the sample. EX1021 ¶70. For example, as explained in the 2002 GE Handbook on Ion Exchange Chromatography, “[t]he first stage is *equilibration* in which the ion exchanger is brought to a *starting state*, in terms of pH and ionic strength, which allows the binding of the desired solute molecules.” EX1030, 12; *id.*, 83. And the POSA would have known to equilibrate the resin with the same buffer as the buffer containing the botulinum toxin. *Id.*, 87 (“The ionic composition [of the sample] *should be the same* as that of the starting buffer.”); EX1028, 6 (GE Healthcare’s Instructions for DEAE anion exchange from the relevant time period; DEAE being the very medium described as being used in Jung) (“To equilibrate, pump approximately 100 ml of start buffer through the column at a flow rate of 8-10 ml/min. The column is fully *equilibrated* when the *pH and/or conductivity of the effluent is the same as the start buffer.*”); EX1021 ¶70.¹³

¹³ EX1028 and EX1030 are not expressly relied upon in Ground 1. To the extent Patent Owner argues that Petitioner’s reliance on these references is improper for failure to provide an analysis to combine these references with Jung, Petitioner

Therefore, a POSA would have understood that the anion exchange chromatography step in Jung was performed at *pH 5.5* since the buffer containing the toxin prior to conducting anion exchange chromatography was *buffer exchanged with a citrate buffer pH 5.5*, and the column was *equilibrated with citrate buffer pH 5.5* prior to sample application. EX1021 ¶70. A pH of 5.5 is “lower than an isoelectric point (PI) of botulinum toxin” as that term is properly construed (*i.e.*, lower than pH 6.06).

Moreover, the “anion exchange chromatography” step in Jung Example 3 is essentially the same as that disclosed in the ’598 patent:

Jung Example 3	’598 Patent Example
“Then, the sample was filtered with no contact with the outside to be enriched, and a <i>buffer exchange</i> was performed on the enriched resultant by using <i>a 25 mM citrate</i>	“ <i>DEAE anion exchange chromatography was performed ...</i> In detail, the <i>citrate buffer (25 mM pH 5.5)</i> was passed through a column packed with a DEAE anion

submits that (1) EX1028 and EX1030 are analogous art to the ’598 patent (they relate to ion exchange chromatography), (2) a POSA would have been motivated to consult these references, particularly because Jung expressly states that he used the GE Healthcare DEAE anion exchange resin (EX1002, 12:5-6), so a POSA would have looked to those manuals when modifying Jung in view of Ton, and (3) a POSA would have had a reasonable expectation of success since Jung itself discloses that the purification was successful. *Id.*, 12:30-34.

buffer (pH 5.5). ... Then, DEAE anion exchange chromatography and membrane chromatography were performed ... After the sample was loaded on the system, the <i>Clostridium botulinum type A toxin protein in the sample was not bound to a column</i> while other impurities [<i>sic</i>] were bound to the column, and <i>thus a fraction flowing out of the system was collected.</i> EX1002, 11:65-12:16.	exchange resin <i>to equilibrate the column</i> , and the toxin-containing <i>citrate buffer (25 mM pH 5.5)</i> was passed through the column. In this process, <i>Clostridium botulinum type A toxin was not adsorbed to the anion exchange resin</i> , and most impurities were adsorbed thereto and removed.” EX1001, 8:60-9:2. “Next, <i>a fraction containing Clostridium botulinum type A toxin was collected from the flow-through solutions</i> which were not bound to the anion exchange resin during the anion exchange chromatography.” <i>Id.</i> , 9:5-8.
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Therefore, Jung discloses the step of “contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than an isoelectric point (PI) of botulinum toxin.” EX1021 ¶70.

- h) “contacting a flow-through portion of the botulinum toxin-containing solution, which is not bound to the anion exchange chromatography medium, with a cation exchange chromatography medium at a pH lower than the PI of botulinum toxin”

Jung discloses that “[a]fter the sample was loaded on the system [containing the anion exchange chromatography column], ***the Clostridium botulinum type A toxin protein in the sample was not bound to a column*** while other impurities [*sic*] were bound to the column, ***and thus a fraction flowing out of the system was***

collected.” EX1002, 12:12-19. In other words, the anion exchange step in Jung is operated in *flow-through* mode. EX1021 ¶71.

Jung does not disclose the subsequent claimed step of applying the flow-through fraction of the anion exchange chromatography step to a cation exchange chromatography medium. However, that limitation would have been obvious in view of Ton, as shown below. EX1021 ¶¶72-78.

Ton discloses “*high purity*, highly potent *botulinum neurotoxins* obtainable by rapid, smaller scaled, commercially useful, high yield, *animal protein free, chromatographic systems and processes.*” EX1003, 6:60-64. According to Ton, “[a]n important aspect of our invention is use of an anion exchange (capture) media chromatography *followed by use of cation exchange (polishing) media chromatography* to purify botulinum neurotoxin from an APF fermentation medium in which *Clostridium botulinum* bacterium have been fermented.” *Id.*, 24:33-38. Ton states “that use of *anion exchange followed by use of cation exchange chromatography* media provides an effective and rapid method for obtaining *high purity, high yield botulinum neurotoxin.*” *Id.*, 24:38-41. Therefore, Ton discloses the combination of anion exchange chromatography and cation exchange chromatography for the purification of botulinum toxin from *Clostridium botulinum*. EX1021 ¶73.

In a specific example, Ton discloses that “[f]ollowing the run-through of the anion exchange column, *cation exchange chromatography operation was undertaken.*” EX1003, 40:25-26. Specifically:

The cation exchange column (e.g. Poros® 20HS) was *equilibrated* with a minimum of 5 CVs of *equilibration buffer* (50 mM sodium acetate, *pH 4.8*). After equilibration, the diluted *eluate pool from the anion exchange column was loaded onto the cation exchange column.*¹⁴

Id., 40:8-31; EX1021 ¶74. A pH of 4.8 is “a pH lower than the PI of botulinum toxin” as that term is properly construed. Therefore, Ton discloses conducting cation exchange chromatography at “a pH lower than the PI of botulinum toxin.” EX1021 ¶74.

It would have been obvious to a POSA to modify Jung’s teachings by conducting the cation exchange chromatography step disclosed in Ton, downstream

¹⁴ The eluate pool of the anion exchange chromatography of Ton is at *pH 4.8*. EX1021 ¶74; EX1003, 40:8-24 (“The next step was the elution step, where *elution buffer (e.g. 50 mM sodium acetate, pH 4.8)* was pumped onto the anion exchange column. ... [T]he *eluate pool* from the anion exchange column was diluted with 1 CV of *50 mM sodium acetate, pH 4.8.*”).

of Jung's anion exchange chromatography step. Ton expressly states "that use of *anion exchange followed by use of cation exchange chromatography* media provides an effective and rapid method for obtaining *high purity, high yield botulinum neurotoxin*." EX1003 at 24:38-41; *id.* at 24:47-49 ("*Another important aspect of our invention is that it results in high purity* botulinum neurotoxin"); EX1021 ¶75. Therefore, a POSA wanting to improve the purity and yield of the collected botulinum neurotoxin in Jung, and do so effectively and rapidly, would have looked to Ton to add a cation exchanger in series after an anion exchanger.

Motivation would further come from a POSA's general knowledge that to achieve a high level of purity, it is generally necessary to use more than one chromatographic step. *Id.* ¶¶75-76; EX1009, 461; EX1024, 484-487; EX1025, 305-308. Thus, a POSA, seeking to develop a method for purifying botulinum toxin type A with high purity,¹⁵ would have been motivated to modify Jung by adding a further chromatography step, such as the cation exchange chromatography step disclosed in Ton. EX1021 ¶76.

¹⁵ See EX1001, 10:20-22 (The alleged "Industrial Applicability" of the '598 patent is that "according to the purification method, a macro complex of botulinum toxin type A which is not dissociated *may be isolated with high purity*.")

Finally, a POSA would have had a reasonable expectation of success in making that modification. For example, Ton teaches that combining anion and cation exchange chromatography results in a “**high purity, high yield botulinum neurotoxin.**” EX1003, 24:38-41. Reasonable expectation of success would further come from the general knowledge in the art that more than one chromatography steps is typically required to achieve a high level of purity in the purification of therapeutic proteins. EX1021 ¶ 77.

Patent Owner may argue, as they did during prosecution with a related Ton patent, that Ton “teaches away” from flow-through anion exchange chromatography because Ton only discloses anion exchange chromatography in **binding** mode. EX1006, 9-18-2020 Response, 10. But “[t]o teach away ... a reference must ‘criticize, discredit, or otherwise discourage’ investigation into the invention claimed.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009). Here, no such discouragement exists. EX1021 ¶78. And Ton’s failure to disclose anion exchange chromatography in flow-through mode is not teaching away. *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (“[A] prior art reference that does not specifically refer to one element of

a combination does not, *per se*, teach away. If it did, only references that anticipate could be used to support an obviousness analysis.”¹⁶

i) **“separating the botulinum toxin type A macro complex from the cation exchange chromatography medium”**

Ton discloses that “[*e*]lution of bulk toxin complex from the cation exchange column was carried out utilizing elution buffer.” EX1003, 40:45-46; *id.*, 27:25-27 (“Unless otherwise set forth in the examples “toxin” or “botulinum toxin” means a *botulinum toxin type A complex with a molecular weight of about 900 kDa.*”) Therefore, Ton discloses “separating the botulinum toxin type A macro complex from the cation exchange chromatography medium.” EX1021 ¶79.

¹⁶ Moreover, Ton discloses *eluting* the botulinum toxin from the anion exchange resin with an elution buffer having a *pH of 4.8*, indicating that the botulinum toxin *does not bind to the anion exchange resin at pH 4.8*. EX1021 ¶78. Thus, a POSA would have understood that flow-through anion exchange chromatography *can be achieved* at “a pH lower than the PI of botulinum toxin.” *Id.* Ton, therefore, does not discourage flow through anion exchange chromatography. *Id.* Additionally, Petitioner is relying on Ton for its disclosure of a *cation exchange step at pH lower than the pI of botulinum toxin*, which was not expressly relied upon by the Examiner during prosecution.

* * *

In view of the disclosures described above, it would have been obvious to a POSA to perform the claimed method in view of Jung and Ton. EX1021 ¶¶64-82. As an initial matter, Jung and Ton are related to the same field of endeavor—botulinum toxin purification—as the '598 patent. EX1001, Title; EX1002, Title; EX1003, Title. In fact, all are classified in the same U.S. CPC class C07K. Furthermore, the methods of Jung and Ton would have been reasonably pertinent to the problems facing the named inventors, *e.g.*, how to improve the purification of botulinum toxin from *Clostridium botulinum*. EX1001, 2:50-53; EX1002, 2:45-56; EX1003, 6:52-56; EX1021 ¶80.

As discussed, Jung expressly discloses all of the limitations of claim 1, except for the cation exchange chromatography step. EX1021 ¶¶64-70. However, as explained, this limitation would have been obvious in view of Ton. Ton discloses a method for purifying botulinum toxin type A comprising anion exchange chromatography followed by cation exchange chromatography. *Id.* ¶¶71-78. A POSA would have been motivated to combine the cation exchange chromatography step of Ton with the anion exchange chromatography step of Jung, given that Ton expressly states that “use of anion exchange followed by use of cation exchange chromatography media provides an effective and rapid method for obtaining high purity, high yield botulinum neurotoxin.” *Id.* ¶75. And a POSA would have had a

reasonable expectation of success in doing so in view of Ton's successful purification method of combining anion and cation exchange chromatography to purify botulinum toxin. *Id.* ¶77.

Claim 1 is written in the alternative, and recites an alternative element (b), which recites conducting cation exchange chromatography first and anion exchange chromatography second. While not required to show that claim 1 is unpatentable, *Fresenius*, 582 F.3d, 1297-98, it would have been a matter of simple design choice to conduct the cation exchange chromatography step of Ton first and the anion exchange chromatography of Jung second. *CRFD Research, Inc. v. Matal*, 876 F.3d 1330 (Fed. Cir. 2017) (design choices are obvious where “a person of ordinary skill would have two predictable choices”); *Google LLC v. Koninklijke Philips N.V.*, 795 Fed. Appx. 840, 844-46 (Fed. Cir. 2020) (affirming obviousness where POSA would have recognized two “evident alternative[s]” even if one alternative was more efficient than the other).

As explained by Dr. Bates, a POSA would understand that for obtaining high purity, high yield botulinum toxin, what really matters is the performance of ***multiple chromatography steps***. EX1021 ¶81. Thus, a POSA would understand that the order of the ion exchange steps recited in claim 1 is immaterial to the alleged invention of the '598 patent. *Id.*

This is supported by the '598 patent itself, as it lacks any working example supporting a method that involves conducting cation exchange first and anion exchange second. EX1001, 8:56-10:5. Indeed, in describing alternative element (b), the '598 patent explains:

The contacting of the botulinum toxin-containing solution with the cation exchange chromatography medium at a pH lower than PI and the separating of the botulinum toxin from the cation exchange chromatography medium *are the same as described above, except that the botulinum toxin-containing solution is used instead of “the solution which is not bound to the medium”*. Further, “the contacting of the solution containing the toxin which is separated from the medium, with the anion exchange chromatography medium at a pH lower than PI, and the isolating of the botulinum toxin from the solution which is not bound to the medium” *are the same as described above, except that “the solution containing toxin which is separated from the medium” is used instead of “the botulinum toxin-containing solution”*.

Id., 6:31-44. Thus, the '598 patent admits that a POSA could easily implement a method of purifying botulinum toxin whereby cation exchange is conducted first and anion exchange is conducted second, because all the POSA needs to do is (i) apply the “botulinum-toxin containing solution” obtained from the *Clostridium botulinum*

culture to a cation exchange, and (ii) apply the “solution containing toxin which is separated from the [cation exchange] medium” to the anion exchange. Other than that, the steps “are the same as described above” for a method where anion exchange is conducted first, and cation exchange is conducted second. EX1021 ¶82.

For at least these reasons, claim 1 would have been obvious over Jung in combination with Ton (and regardless of the order of the anion exchange and cation exchange chromatography steps).

2. Dependent Claim 2

Claim 2 depends on claim 1 and recites four alternatives, only one of which is recited below:¹⁷

adjusting a pH of the botulinum toxin-containing solution to a pH lower than the PI of botulinum toxin,
before the contacting of the botulinum toxin-containing solution with the anion exchange chromatography

¹⁷ A claim element reciting alternatives is disclosed if the prior art discloses one of the alternatives. *Fresenius*, 582 F.3d, 1297-98. Regardless, the step of “adjusting” the pH of a solution prior to conducting any ion exchange chromatography step is a matter of routine practice to those skilled in the art of protein purification. EX1021 ¶83. Therefore, any of the recited alternatives would have been obvious to a POSA.

medium at the pH lower than the PI of botulinum toxin in
(a)

Jung discloses that the botulinum toxin-containing solution “was filtered with no contact with the outside to be enriched, and a *buffer exchange* was performed on the enriched resultant by using a 25 mM citrate *buffer (pH 5.5)*.” EX1002, 11:65-12:11. A pH of 5.5 is “pH lower than the PI of botulinum toxin” as that term is properly construed. Following the buffer exchange step, “*DEAE anion exchange chromatography* and membrane chromatography were performed on the sample not in contact with the outside.” EX1002, 12:9-11. Therefore, Jung discloses “adjusting a pH of the botulinum toxin-containing solution to a pH lower than the PI of botulinum toxin,” *e.g.*, by *buffer exchanging* the solution with a citrate buffer pH 5.5, “before the contacting of the botulinum toxin-containing solution with the anion exchange chromatography medium at the pH lower than the PI of botulinum toxin in (a).” EX1021 ¶¶83-84.

3. Dependent Claim 3

Dependent claim 3 depends on claim 2 and recites that “the adjusting comprises *mixing the botulinum toxin-containing solution*, the flow-through portion of the botulinum toxin-containing solution, or the solution containing the botulinum toxin *with a buffer having a pH lower than the PI of botulinum toxin.*” As discussed above with respect to claim 2, Jung discloses that “*buffer exchange*

was performed on the enriched resultant by using a 25 mM citrate *buffer (pH 5.5)*” prior to performing anion exchange chromatography. EX1002, 11:65-12:11. A pH of 5.5 is “lower than the PI of botulinum toxin” as that term is properly construed. Therefore, Jung discloses this limitation. EX1021 ¶86.

4. Dependent Claim 4

Dependent claim 4 depends on claim 3 and recites that “the buffer is a phosphate buffer, a *citrate buffer*, or an acetate buffer.” Jung discloses buffer exchanging the botulinum toxin-containing solution with a *citrate buffer* pH 5.5 prior to performing anion exchange chromatography. EX1002, 11:65-12:11. Therefore, Jung discloses this limitation. EX1021 ¶88.

5. Dependent Claim 5

Dependent claim 5 depends on claim 3 and recites that “the buffer has a *pH of 3.5 to 6.0*.” Jung discloses buffer exchanging the botulinum toxin-containing solution with a citrate buffer *pH 5.5* prior to performing the anion exchange chromatography step. EX1002, 11:65-12:11. Therefore, Jung discloses this limitation. EX1021 ¶90

6. Dependent Claim 6

Dependent claim 6 depends on claim 3 and recites that “the buffer comprises a 10 mM to 100 mM phosphate buffer, a *10 mM to 100 mM citrate buffer*, or a 10 mM to 100 mM acetate buffer.” Jung discloses buffer exchanging the botulinum

toxin-containing solution with a **25 mM citrate buffer pH 5.5** prior to performing the anion exchange chromatography step. EX1002, 11:65-12:11. Therefore, Jung discloses this limitation. EX1021 ¶92.

7. Dependent Claim 7

Dependent claim 7 depends on claim 1 and recites that “the anion exchange chromatography medium comprises **DEAE or Q** anion exchange resin.” Jung discloses performing **DEAE anion exchange chromatography**. EX1002, 12:4-16. Jung also discloses “Q Sepharose” and “Q sephadex.” *Id.*, 4:62-65. Therefore, Jung discloses this limitation. EX1021 ¶94.

8. Dependent Claim 8

Dependent claim 8 depends on claim 1 and recites that “the cation exchange chromatography medium comprises CM, S, or **SP** cation exchange resin.” Ton discloses conducting cation exchange chromatography using a **POROS® 20HS**. EX1003, 25:61-63 (“The cation exchange column can be a POROS® 20HS cation exchange resin from Applied Biosystems”). A POSA would have known that POROS® 20HS is a sulfopropyl (“SP”) cation exchange resin. EX1021 ¶96; EX1020.

9. Dependent Claim 9

Dependent claim 9 depends on claim 1 and recites that “the pH lower than the PI of botulinum toxin is **pH 3.5 to 6.0**,” which is a limitation of each of the anion

and cation exchange steps. Jung discloses conducting anion exchange chromatography at *pH 5.5*. EX1002, 11:65-12:11. Ton discloses conducting cation exchange chromatography at *pH 4.8*. EX1003, 40:25-32; EX1021 ¶98.

C. Ground 2: Claims 1-9 Would Have Been Obvious Over Kim '741 In View Of Kim '565 and Further In View Of Jung

1. Independent Claim 1

a) “A method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution”

Kim '741 teaches “a more efficient and safe *method for producing botulinum toxin* ...” EX1004 ¶[0023]; EX1008 ¶[28].¹⁸ “The *botulinum toxin purified according to the production method* of the present invention may have a form of 7S or 19S (*molecular weight: 150-900 kDa*).” EX1004 ¶[0046]; EX1008 ¶[48]. “[T]he term ‘botulinum toxin’ as used herein is meant to include *botulinum toxin serotypes A, B, C, D, E, F and G* ...” EX1004 ¶[0048]; EX1008 ¶[50]. Moreover, in Kim '741, the botulinum toxin is purified from a “*culture of a botulinum toxin-producing strain*.” EX1004 ¶[0026]; EX1008 ¶[31]. According to the '598 patent,

¹⁸ EX1008 is a certified English translation of Korean Patent Application No. KR10-2015-0168196 (EX1019), to which Kim '741 claims priority. As demonstrated throughout this Petition, the disclosure relied upon in Kim '741 is also found in KR10-2015-0168196.

“the botulinum toxin-containing solution may be a *culture of Clostridium botulinum*.” EX1001, 3:28-30. Therefore, Kim ’741 discloses “[a] method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution.” EX1021 ¶100.¹⁹

b) “culturing *Clostridium botulinum* in an animal product-free medium to obtain a culture”

Kim ’741 does not disclose “culturing *Clostridium botulinum* in an animal product-free medium to obtain a culture.” However, it would have been obvious to a POSA to substitute the animal product-containing medium of Kim ’741 with the animal product-free medium of Kim ’565 for the reasons explained below. EX1021 ¶101.

As stated in Kim ’565, “Transmissible spongiform encephalopathy (TSE) is known as a neurodegenerative disorder causing serious degeneration of neurons.” EX1023 ¶[12]. Kim ’565 explains that “if an animal abnormal prion known as an agent that causes transmissible spongiform encephalopathy is contained in the animal components due to contamination, it poses problems in a process for producing botulinum toxin.” *Id.* ¶[11]; ¶[15] (“if a pharmaceutical composition is

¹⁹ To the extent Patent Owner argues Kim ’741 does not disclose this claim limitation, it is disclosed in Jung. *See* §XI.B.1.a.

prepared by drug substance produced using animal-derived components, it can subject the patient to a potential risk of receiving various pathogens or infectious agents.”). The object of Kim ’565’s invention is therefore “to provide a medium composition comprising plant-derived peptones having no risk of transmissible spongiform encephalopathy (TSE) infection.” *Id.* ¶[19]; EX1021 ¶102. Thus, a POSA, wanting to culture *Clostridium botulinum* in an effective medium and at the same time avoid TSE, would have been motivated to use an animal protein free culture medium disclosed in Kim ’565. EX1021 ¶103.²⁰

A POSA would have had a reasonable expectation that using a culture medium disclosed in Kim ’565 would be successful. EX1021 ¶104. For example, Kim ’565 states that:

[I]t could be seen that an *optimal medium composition for culturing Clostridium botulinum* is one comprising a *plant-derived peptone*, ... and a carbon source (e.g.,

²⁰ Although Kim ’741 uses casein in the culture medium, the overall goal of Kim ’741 is to provide “a method of producing botulinum toxin by *an animal product-free (APF) process ... to solve safety problems such as transmissible spongiform encephalopathy infections* caused by such animal-derived components worldwide.” EX1004 ¶[0021]; EX1021 ¶103.

glucose), *and the optimal growth of the bacterium in this medium was found.*

EX1023 ¶[39]. According to Kim '565, “*the APF medium showed an increased growth rate of the bacterium* compared to a medium that is in current use.” *Id.* ¶[37]. Thus, a POSA would have had a reasonable and better expectation of success in substituting the culture medium of Kim '741 with the animal product-free culture medium of Kim '565. EX1021 ¶104.²¹

c) “**removing *Clostridium botulinum* cells from the culture to obtain a botulinum toxin-containing solution**”

Kim '741 does not disclose removing the cells from the culture prior to adding an acid to precipitate the toxin. However, this cell removal step is trivial and would have been obvious modification of Kim '741 in view of Jung. EX1021 ¶105. Jung discloses purifying botulinum toxin from *Clostridium botulinum* by “(a) culturing *Clostridium botulinum* in a media containing plant-derived components to express *Clostridium botulinum* toxin outside a cell, and (b) *removing the cell from the obtained culture* to obtain a portion including *Clostridium botulinum* toxin expressed outside the cell and isolating the *Clostridium botulinum* toxin from the

²¹ To the extent Patent Owner argues Kim '565 does not disclose this claim limitation, it is disclosed in Jung. *See* §XI.B.1.b.

portion.” *Id.*, 2:67-3:6. According to Jung, “removing the cell may be performed using at least one method selected from the group consisting of depth filtration and microfiltration.” *Id.*, 4:49-5. A POSA, seeking to develop a method for purifying botulinum toxin from *Clostridium botulinum* would have been motivated by Jung, with a reasonable expectation of success, to remove the cells from the culture prior to adding an acid to precipitate the toxin because, as disclosed in Jung, “the inventors of the present application found that a large amount of *Clostridium botulinum* toxin was *expressed outside the cell* by using a composition of plant-derived components, and ... *Clostridium botulinum* toxin could be easily and very simply purified from the culture from which the cell was removed.” EX1002, 2:46-56. Moreover, as explained by Dr. Bates, cell removal (e.g., clarification) is a routine step in the art of protein purification. EX1021 ¶105.

d) “adding an acid to the botulinum toxin-containing solution to precipitate the botulinum toxin and obtain a precipitate”

Kim ’741 discloses “(a) treating a culture of botulinum toxin-producing strain with acid to form a botulinum toxin-containing precipitate.” EX1004 ¶[0042]; EX1008 ¶[42]. The ’598 patent states that “the botulinum toxin-containing *solution* may be a *culture of Clostridium botulinum* or a solution derived therefrom.” EX1001, 3:27-30. Therefore, Kim ’741 discloses “adding an acid to the botulinum

toxin-containing solution to precipitate the botulinum toxin and obtain a precipitate.”

EX1021 ¶106.²²

e) “dissolving the precipitate in a medium to obtain a solution”

Kim ’741 discloses “(b) adding a buffer to the botulinum toxin-containing precipitate of step (a).” EX1004 ¶[0043]; ¶[0067] (“step (b) comprises a step of *dissolving the toxin precipitate* resulting from step (a) by addition of phosphate buffer”); EX1008 ¶[44], [69]. Therefore, Kim ’741 discloses “dissolving the precipitate in a medium to obtain a solution.” EX1021 ¶107.²³

f) “filtering the solution to obtain a botulinum toxin-containing solution”

Kim ’741 discloses “clarifying” the solution in (b) “by one or more method selected from the group consisting of *depth filtration* (DF), *microfiltration* (MF), *ultrafiltration* (UF), *sterile filtration*, membrane chromatography (MC) and centrifugation.” EX1004 ¶ [0043]; EX1008 ¶ [44]. Therefore, Kim ’741 discloses

²² To the extent Patent Owner argues Kim ’741 does not disclose this claim limitation, it is disclosed in Jung. *See* §XI.B.1.d.

²³ To the extent Patent Owner argues Kim ’741 does not disclose this claim limitation, it is disclosed in Jung. *See* §XI.B.1.e.

“filtering the solution to obtain a botulinum toxin-containing solution.” EX1021

¶108.²⁴

- g) “contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than an isoelectric point (PI) of botulinum toxin”

Kim ’741 discloses subjecting the botulinum toxin solution to *anion exchange chromatography* at a pH of 2-9, preferably 3-8. EX1004 ¶[0072]. As disclosed in Kim:

The anion-exchange chromatography in step (d) may be performed at a pH of 2-9, preferably 3-8, and a conductivity of 2-40 mS/cm, preferably 3-30 mS/cm. In step (d), botulinum toxin may be collected as a botulinum toxin-containing fraction (flow-through mode) of a flow-through (FT) fraction eluted from anion-exchange chromatography or as a fraction containing the botulinum toxin bound to anion exchange chromatography resin. The finally purified botulinum toxin may have a form of 7S or 19S.

²⁴ To the extent Patent Owner argues Kim ’741 does not disclose this claim limitation, it is disclosed in Jung. *See* §XI.B.1.f.

Id.; *id.* ¶[0085]; EX1006, 2-8-2021 Response, 8 (Patent Owner admitting that “KIM discloses a broad pH range of 2-9, **preferably 3-8**, for anion and cation exchange chromatographies.”); EX1008 ¶¶[74], [77].

Thus, Kim ’741 discloses performing anion exchange chromatography at a pH range that **overlaps** with “a pH lower than an isoelectric point (PI) of botulinum toxin,” *i.e.*, a **pH of 6.06 or lower**, as this term is properly construed. EX1021 ¶¶109-110. In cases involving overlapping ranges, courts have consistently held that even a slight overlap in range establishes a prima facie case of obviousness. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). “[T]he existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious . . .” *Id.*, 1330. More recently in *E.I. DuPont de Nemours v. Synvina C.V.*, the Federal Circuit reiterated the established principle that overlapping ranges create a presumption of obviousness and concluded that the same framework governing overlapping ranges in district court adjudications and PTO examinations controls in IPR proceedings. 904 F.3d 996, 1008 (Fed. Cir. 2018).

A patentee may attempt to rebut this presumption by demonstrating that practicing the process at the claimed range produces unexpected results, and is therefore “critical.” *Id.*, 1006. As noted (§VII.B), Patent Owner submitted an inventor declaration during prosecution of the ’598 patent attempting to demonstrate the alleged criticality of the claimed pH range. Specifically, the declaration

described an experiment comparing anion exchange chromatography conducted at pH 5.5 and 6.5. According to Patent Owner, results showing that “19S can be purified from the flow through solution when pH 5.5 is used but at pH 6.5, 19S was not present in the flow through solution ... is an unexpected benefit of the claimed invention.” EX1006, 7-22-2021 Response, 10; 12-20-2021 Response, 13 (“The experiments and results provided in the SONG Declaration show the criticality of the use of ‘a pH lower than the pI of botulinum toxin.’”)

But there is *nothing unexpected* about that observation. EX1021 ¶112. Jung, Medytox’s own patent discussed in Ground 1, disclosed a method of purifying botulinum toxin type A comprising the steps of (1) culturing *Clostridium botulinum* in an animal product-free medium, (2) removing the cells from the culture, (3) adding an acid to precipitate the botulinum toxin from the culture medium, (4) dissolving the precipitated toxin with a buffer, (5) filtering the solution, and (6) *applying the solution to an anion exchange chromatography medium at a pH of 5.5*. EX1002, 11:20-12:16. As disclosed in Jung, “the *Clostridium botulinum type A toxin protein in the sample was not bound to a column* ...and thus a fraction flowing out of the system was collected.” *Id.*, 12:13-16; EX1021 ¶112. Thus, it was highly disingenuous of the Medytox inventor to swear under oath that the results described in his inventor declaration submitted during prosecution were unexpected.

Moreover, as explained by Dr. Bates, ion exchange chromatography is a chromatographic process that separates molecules, such as proteins, on the basis of surface charge. EX1021 ¶113. Each protein has an isoelectric charge. The surface charge of a protein will vary with pH. The pH at which a protein has a net charge of zero is called the isoelectric point (pI). A protein at a pH below its pI will carry a net positive charge and is less likely to interact with a positively charged separation matrix (anion exchanger). Rather, it is more likely to flow through the matrix. Conversely, a protein at a pH above its pI, *i.e.*, a pH at which the protein carries a negative charge, is more likely to interact with and remain bound to a positively charged matrix. *Id.*; EX1006, 7-22-2021 Response, 6. This is how ion exchangers work, as everyone in the industry knew from well before the '598 patent.

As such, it clearly would ***have been entirely expected*** to a POSA that anion exchange chromatography conducted at “a pH lower than the pI of botulinum toxin” (e.g., pH of 5.5) results in the toxin flowing through the matrix (*i.e.*, the fraction that does not bind to the anion exchange matrix). EX1021 ¶114. Accordingly, the claimed pH range of “a pH lower than the PI of botulinum toxin” is neither special nor critical, but instead, it is as obvious as daylight. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) (“[I]n order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were ***expected.***”)

Moreover, it is well established that evidence of criticality “must be commensurate in scope with the claims to which it pertains.” *In re Dill*, 604 F.2d 1356, 1361 (CCPA 1979). “Establishing that one (or a small number of) species gives unexpected results is inadequate proof[.]” *In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978). Here, the alleged unexpected results presented during prosecution are not commensurate in scope with the claims because the declaration relied on an experiment using a **single** pH level below (pH 5.5) and a **single** pH level above (pH 6.5) the PI of botulinum toxin. *See E.I. DuPont*, 904 F.3d at 1012 (patent owner did not show unexpected results commensurate with the scope of the claims because PO relied on experiments at **only a single pressure** within the claimed range); *In re Patel*, 566 F. App'x 1005, 1011-12 (Fed. Cir. 2014) (“Appellants cannot rely on a **single point** within a large range to prove unexpected results for the entire range.”); *In re Greenfield*, 571 F.2d at 1189 (affirming PTO determination that “there is no adequate basis for reasonably concluding that the great number and variety of compositions included by the claims would behave in the same manner as the **(single) test composition**”).

Additionally, in Kim '741's Example 2-3-1, entitled “TQ Purification (Anion Exchange Chromatography **Flow-Through (AEX FT)**),” anion exchange chromatography was performed at a **pH of 6.4-6.6**, and “it was shown that the **botulinum toxin was not adsorbed onto the TQ resin**, and most major impurities

were removed by adsorption, and thus a botulinum toxin could be produced with high purity.” EX1004 ¶¶[0102]–[0108]; EX1008 ¶¶[118]–[125]. “In addition, the resulting botulinum toxin had a form 19S (molecular weight: about 900 kDa).” EX1004 ¶[0108]; EX1008 ¶[125]. In other words, Kim ’741 successfully conducted anion exchange chromatography in ***flow-through mode at a pH higher than the pI*** of botulinum toxin (e.g., about 6.06). EX1021 ¶115.

Thus, the claimed pH range cannot be critical to practicing the claimed method if flow-through anion exchange chromatography ***can be achieved with a pH higher than the pI of botulinum toxin***. EX1021 ¶115; *Hospira*, IPR2016-01837, Paper 40, 24-25 (Board agreeing with Petitioner that “[t]he claimed range of ‘about 10° C to about 18° C’ cannot be critical to practicing the alleged invention if the sole alleged benefit ***is also achieved below the range, at temperatures disclosed in the prior art***.”); *id.*, 23 (“[W]e credit Dr. Przybycien’s testimony that ‘[t]he claimed range in the ’799 Patent is ***not critical***, because protein A chromatography ***works in the same way at the prior art temperatures*** of 4° C, 18-25° C and 20-25° C as it does at the claimed range.’”).

Moreover, as explained by Dr. Bates, a POSA would have been very familiar with optimizing pH of a protein solution such that the solution is applied to the separation matrix under conditions suitable for the protein to interact with (or flow through) the separation matrix. EX1021 ¶116. pH is easy to modulate in the context

of ion exchange chromatography, and it would have been obvious to try pHs at all points in Kim '741's disclosed range, to ensure that the toxin flowed through the matrix (as taught by Kim '741). *Id.* In other words, pH is a variable that can be optimized by routine experimentation to achieve a desired result during ion exchange chromatography. *Id.* And given that Kim '741 discloses pH ranges that overlap with the claimed pH range, that "itself provides sufficient motivation to optimize the range[]" with a reasonable expectation of success. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012); *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341-42 (Fed. Cir. 2020) (affirming Board's obviousness finding that claims directed to a method of purifying antibodies by affinity chromatography performed "at a temperature in the range from about 10 °C to about 18 °C" to reduce leaching was rendered obvious by prior art that disclosed a temperature range of 18-25 °C, explaining "that a skilled artisan would have been motivated to optimize the temperature given the teachings of the prior art, and that given the ease with which temperature can be varied, finding an optimal temperature range would have been nothing more than routine experimentation" since the evidence showed the prior art recognized that reducing the temperature reduced leaching).

Finally, Patent Owner's argument during prosecution that Kim '741 teaches away from "a pH lower than the PI of botulinum toxin" (EX1006, 7-22-2021

Response, 7-8) is factually and legally incorrect. As echoed by the Federal Circuit in *In re Urbanski*, 809 F.3d 1237, 1244 (Fed. Cir. 2016), “[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” Kim ’741 in no way instructs or suggests that a POSA should not try a pH lower than that of the pI of the toxin. And, although Example 2-3-1 of Kim ’741 uses a pH of 6.4-6.6 for anion exchange chromatography (EX1004 ¶[0107]–[0108]), Kim ’741 “does not criticize or discredit the use of” a lower pH, and, in fact, instructs a POSA to “adjust” the pH to any of the pH values from 2 to 9, of which 2 to 6.06 meet the limitation for the claim. *In re Urbanski*, 809 F.3d at 1244; EX1021 ¶117.

Therefore, Kim ’741 teaches, or at least renders obvious, the limitation of “contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than an isoelectric point (PI) of botulinum toxin.”²⁵

²⁵ To the extent Patent Owner argues Kim ’741 does not disclose or otherwise render this claim limitation obvious, it is disclosed in Jung. *See* §XI.B.1.g.

- h) “contacting a flow-through portion of the botulinum toxin-containing solution, which is not bound to the anion exchange chromatography medium, with a cation exchange chromatography medium at a pH lower than the PI of botulinum toxin”

Kim ’741 states that following the anion exchange chromatography “[i]n step (d), botulinum toxin may be collected as a botulinum toxin-containing fraction (*flow-through mode*) of a *flow-through (FT) fraction*” which is not bound to the anion exchange chromatography medium. EX1004 ¶[0072]. As disclosed in Kim ’741:

The term “FT (*flow-through*)”, “flow-through process” or “flow-through purification”, as used interchangeably herein, means a separation process in which at least one target molecule (e.g., botulinum toxin) contained in a biopharmaceutical formulation together with one or more impurities passes through a material and one or more impurities generally bind to the material and *the target molecule generally does not bind to the material (that is, flows through the materials)*.

Id. ¶[0073]; EX1008 ¶¶[74]-[75]; EX1021 ¶119.

Kim ’741 discloses that a further “*cation-exchange chromatography in step (h) may be* performed at a pH of 2-9, preferably 3-8.” EX1004 ¶[0087]; EX1008 ¶[93]. Thus, Kim ’741 discloses performing cation exchange chromatography at a pH that overlaps with “a pH lower than an isoelectric point (PI) of botulinum toxin,”

i.e., lower than pH 6.06. EX1021 ¶120. The overlap in pH range creates a presumption of obviousness. Patent Owner ***did not*** present any evidence of alleged criticality for this limitation during prosecution. Even if Patent Owner were to argue that the pH range is critical, that argument fails because Ton (Ground 1) discloses conducting cation exchange chromatography at ***pH 4.8***. EX1003, 40:26-31.

i) “separating the botulinum toxin type A macro complex from the cation exchange chromatography medium”

Kim ’741 discloses that “[i]n the cation-exchange chromatography of step (h), the botulinum toxin ***may be collected as a fraction containing the botulinum toxin bound to the cation-exchange chromatography resin.***” EX1004 ¶[0087]; ¶¶[0117]–[0122] (describing the “XS cation-exchange chromatography (CEX, binding mode)” and stating that “***the sample was eluted*** at 20 CV and 12% gradient.”); EX1008 ¶[93]. Therefore, Kim ’741 discloses “separating the botulinum toxin type A macro complex from the cation exchange chromatography medium.” EX1021 ¶122.

* * *

In view of the above, it would have been obvious to a POSA to perform the claimed method of Kim ’741 as modified by Kim ’565 and Jung. As an initial matter, Kim ’741, Kim ’565 and Jung are related to the same field of endeavor—botulinum toxin purification—as the ’598 patent. EX1001, Title; EX1004, Title;

EX1023, Title; EX1002, Title. Furthermore, the methods of Kim '741, Kim '565 and Jung would have been reasonably pertinent to the problems facing the named inventors, for example, how to improve the purification of botulinum toxin from *Clostridium botulinum*. EX1001, 2:50-53; EX1002, 2:45-56; EX1004 ¶[0023]; EX1023 ¶[19]; EX1021 ¶123.

As discussed, Kim '741 expressly teaches most of the steps of claim 1, including the steps of culturing *Clostridium botulinum*, adding an acid to the culture to precipitate the botulinum toxin, dissolving the precipitate, filtering the solution, anion exchange chromatography in flow-through mode, and cation exchange chromatography in binding mode. EX1021 ¶¶100-122. While Kim '741 does not remove *Clostridium botulinum* cells from the culture prior to adding an acid to precipitate the toxin (which the '598 patent itself admits is not a necessary step (EX1001 at 3:27-30; EX1021 ¶106)), a POSA would have been motivated, with a reasonable expectation of success, to remove the cells (and cell debris) in view of Jung expressly teaching such a step, and further explaining that “*Clostridium botulinum toxin could be easily and very simply purified from the culture from which the cell was removed.*” EX1002, 2:46-56; EX1021 ¶105. In other words, a POSA at the relevant time wanting to obtain a pure botulinum toxin preparation “easily and very simply” would have followed Jung’s teaching of removing cells prior to adding acid to precipitate the toxin. EX1021 ¶105. And a POSA would

have a reasonable expectation of success in removing the cells since cell and cell debris removal is a routine step in the art of protein purification and Jung demonstrates that such a routine step was successful. *Id.*

With respect to the limitation of conducting anion and cation exchange chromatography “at a pH lower than an isoelectric point (PI) of botulinum toxin,” Kim ’741 discloses pH ranges that overlap with the claimed range, which creates a presumption of obviousness. And Patent Owner’s evidence presented during prosecution do not overcome that presumption because a POSA would have been familiar with well-known ion exchange chromatography principles and would have expected botulinum toxin to flow through an anion exchange column at a pH lower than the pI of botulinum toxin. EX1021 ¶¶109-117. Moreover, pH is easy to modulate in the context of ion exchange chromatography, and it would have been obvious to try pHs within the range disclosed in Kim ’741, and observe whether varying the pH affected the binding of the toxin to the matrix. *Id.*

For at least these reasons, claim 1 would have been obvious over Kim ’741 in combination with Kim ’565 and Jung.

2. Dependent Claim 2

Claim 2 depends on claim 1 and recites four alternatives, only one of which is recited below:

adjusting a pH of the botulinum toxin-containing solution to a pH lower than the PI of botulinum toxin,
before the contacting of the botulinum toxin-containing solution with the anion exchange chromatography medium at the pH lower than the PI of botulinum toxin in
(a)

Kim '741 discloses a “dilution or dissolution of the botulinum toxin in step (c) compris[ing] a step of adding phosphate buffer. ... [t]he pH of the phosphate buffer is preferably about 4.0-8.5, and a base may be added to *adjust the final pH to 4.5-8, preferably 5.5-7.5, more preferably 6-7.*” EX1004 ¶[0068]; EX1008 ¶[70]. The dilution or dissolution in step (c) precedes the anion exchange chromatography step (d). The overlap in pH range creates a presumption of obviousness and as explained above, there is nothing critical about the claimed pH range of “a pH lower than the PI of botulinum toxin.” EX1021 ¶126.

3. Dependent Claim 3

Dependent claim 3 depends on claim 2 and recites that “the adjusting comprises *mixing the botulinum toxin-containing solution*, the flow-through portion of the botulinum toxin-containing solution, or the solution containing the botulinum toxin *with a buffer having a pH lower than the PI of botulinum toxin.*” Kim '741 discloses a “dilution or dissolution of the botulinum toxin in step (c) compris[ing] a step of adding phosphate buffer. ... [t]he pH of the phosphate buffer

is preferably about 4.0-8.5, and a base may be added to *adjust the final pH to 4.5-8, preferably 5.5-7.5, more preferably 6-7.*” EX1004 ¶[0068]; EX1008 ¶[70]. The overlap in pH range creates a presumption of obviousness and as explained above, there is nothing critical about the claimed pH range of “a pH lower than the PI of botulinum toxin.” EX1021 ¶128.

4. Dependent Claim 4

Dependent claim 4 depends on claim 3 and recites that “the buffer is a *phosphate buffer*, a citrate buffer, or an acetate buffer.” Kim ’741 discloses “dilution or dissolution of the botulinum toxin in step (c) compris[ing] a step of adding *phosphate buffer*.” EX1004 ¶[0068]; EX1008 ¶[70]; EX1021 ¶130.

5. Dependent Claim 5

Dependent claim 5 depends on claim 3 and recites that “the buffer has a *pH of 3.5 to 6.0.*” Kim ’741 discloses that “the *pH of the phosphate buffer is preferably about 4.0-8.5.*” EX1004 ¶[0068]; EX1008 ¶[70]. The overlap in pH range creates a presumption of obviousness and as explained above, there is nothing critical about the claimed pH range of “a pH lower than the PI of botulinum toxin.” EX1021 ¶132.

6. Dependent Claim 6

Dependent claim 6 depends on claim 3 and recites that “the buffer comprises a *10 mM to 100 mM phosphate buffer*, a 10 mM to 100 mM citrate buffer, or a 10 mM to 100 mM acetate buffer.” Kim ’741 discloses a *phosphate buffer* having a

concentration of “*15-70 mM, preferably about 20-60 mM.*” EX1004 ¶[0075]; EX1008 ¶[77]. The overlap in concentration range creates a presumption of obviousness and Petitioner is not aware that there is anything critical about the claimed concentration range. EX1021 ¶134.

7. Dependent Claim 7

Dependent claim 7 depends on claim 1 and recites that “the anion exchange chromatography medium comprises *DEAE or Q* anion exchange resin.” Kim ’741 discloses that “the resin that is used in the anion-exchange chromatography process includes *diethylaminoethyl (DEAE)*, quaternary aminoethyl (QAE) and *quaternary amine (Q)* groups.” EX1004 ¶[0088]; EX1008 ¶[94]; EX1021 ¶136.

8. Dependent Claim 8

Dependent claim 8 depends on claim 1 and recites that “the cation exchange chromatography medium comprises *CM, S, or SP* cation exchange resin.” Kim ’741 discloses that “the resin that is used in the cation-exchange chromatography process preferably includes *carboxymethyl (CM)*, sulfoethyl (SE), *sulfopropyl (SP)*, phosphate (P), and *sulfonate (S)*.” EX1004 ¶[0089]; EX1008 ¶[95]; EX1021 ¶138.

9. Dependent Claim 9

Dependent claim 9 depends on claim 1 and recites that “the pH lower than the PI of botulinum toxin is *pH 3.5 to 6.0*,” which is a limitation of each of the anion and cation exchange steps. Kim ’741 discloses that the “anion-exchange

chromatography in step (d) may be performed at a *pH of 2-9, preferably 3-8*” and that “the cation-exchange chromatography in step (h) may be performed at a *pH of 2-9, preferably 3-8*.” EX1004 ¶¶[0072], [0087]; EX1008 ¶¶[74], [93]. The overlap in pH range creates a presumption of obviousness and as explained above, there is nothing critical about the claimed pH range of 3.5 to 6. EX1021 ¶140.

XII. NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS EXISTS

Patent Owner has not identified evidence of secondary indicia of non-obviousness for the '598 patent besides the inventor declaration allegedly showing the criticality of the claimed pH range submitted during prosecution. As explained above, however, there is nothing special or unexpected about conducting anion exchange chromatography at “a pH lower than the PI of botulinum toxin.” Accordingly, there is no objective evidence of non-obviousness that warrant a finding that the challenged claims are patentable.

XIII. SECTION 325(D) SHOULD NOT PREVENT INSTITUTION

The Board should reject any argument that Petitioner’s grounds or asserted prior art are cumulative of the '598 patent’s prosecution. The record confirms that the Examiner either (1) was not presented with the same or substantially the same art or arguments as Petitioner’s, or (2) materially erred in allowing the Challenged Claims. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*,

IPR2019-01469, Paper 6 , 8 (PTAB Feb. 13, 2020) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017)).

A. Neither the Same nor Substantially the Same Art or Arguments Were Previously Presented to the PTO

For Ground 1, Petitioner relies on Jung, Patent Owner’s own prior art patent that was not before the Examiner (nor did Patent Owner disclose to the Office this highly relevant reference). Jung expressly discloses purifying botulinum toxin by conducting flow-through anion exchange chromatography at a ***pH of 5.5*** (EX1002, 11:65-12:10)—***the exact same pH*** used in the inventor declaration submitted during prosecution to allege the criticality of the claimed pH range of “a pH lower than the PI of botulinum toxin.” EX1006, 7-22-2021 Response, 10. For this reason alone, the Board should proceed to institution.

Ground 1 also combines Jung with Ton. While a patent related to Ton was considered by the Examiner, it was never considered in combination with Jung. This favors institution. *Netflix, Inc. v. DivX, LLC*, IPR2020-00558, Paper 10, 40 (PTAB Aug. 26, 2020) (granting institution and explaining “[b]ecause the combination... was not considered by the examiner, we find consideration of the references and arguments based thereon to be materially different than the examiner’s previous consideration...”).

For Ground 2, Petitioner relies on Kim '741 in combination with Kim '565 and Jung. While Kim '741 was considered by the Examiner, Kim '565 and Jung were not, and the Examiner never considered Kim '741 in combination with Kim '565 and Jung. *Netflix*, IPR2020-00558, Paper 10, 40. This favors institution.

B. The Examiner Erred in Allowing the Challenged Claims

As discussed above, the answer to *Advanced Bionics*' first inquiry—whether the same or substantially the same art or arguments were previously presented to the Office—is clearly no. Accordingly, an allegation of Examiner error is unnecessary. Nonetheless, even if the Board were to find otherwise, discretionary denial still would not be warranted because the Examiner erred in crediting the purported evidence of criticality presented by Patent Owner during prosecution. These results were the *sole reason* the Examiner allowed the claims. EX1006, 1-21-2022 Notice of Allowance, 3 (“*This showing of criticality was persuasive* to overcome the 35 USC 103 rejection of claim 1 and being unpatentable over KIM.”).

But as explained, there is nothing special, critical, or unexpected about the pH range claimed by the '598 patent, and Patent Owner knew as much at the time. That the botulinum toxin flowed through the anion exchange chromatography column at pH 5.5 would have been entirely expected. Indeed, that is *exactly* what Jung, Patent Owner's own prior art patent, discloses. EX1002, 11:65-12:16. Moreover, Kim '741 demonstrates that flow-through anion exchange chromatography is possible at

pH 6.5, which is *higher* than the pI of botulinum toxin, and thus the claimed pH cannot possibly be critical. Thus, in crediting Patent Owner's inventor declaration during prosecution, the Examiner erred in a manner that was material to patentability. *Advanced Bionics*, Paper 6, 8. This favors institution.

XIV. CONCLUSION

For these reasons, the Challenged Claims are unpatentable, and Petitioner respectfully requests that the Board institute trial.

Dated: February 21, 2023

Respectfully Submitted,

/ Dion M. Bregman /
Dion M. Bregman, Reg. No. 45,645

Counsel for Petitioner

LISTING OF THE CHALLENGED CLAIMS

Claim No.	Claim Language
Independent Claim 1	A method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution, the method comprising: culturing <i>Clostridium botulinum</i> in an animal product-free medium to obtain a culture; removing <i>Clostridium botulinum</i> cells from the culture to obtain a botulinum toxin-containing solution; adding an acid to the botulinum toxin-containing solution to precipitate the botulinum toxin and obtain a precipitate; dissolving the precipitate in a medium to obtain a solution; filtering the solution to obtain a botulinum toxin-containing solution; and (a) contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than an isoelectric point (PI) of botulinum toxin; contacting a flow-through portion of the botulinum toxin-containing solution, which is not bound to the anion exchange chromatography medium, with a cation exchange chromatography medium at a pH lower than the PI of botulinum toxin; and separating the botulinum toxin type A macro complex from the cation exchange chromatography medium; or (b) contacting the botulinum toxin-containing solution with a cation exchange chromatography medium at a pH lower than a PI of botulinum toxin; separating botulinum toxin from the cation exchange chromatography medium;

	contacting a solution containing the botulinum toxin separated from the cation exchange chromatography medium with an anion exchange chromatography medium at a pH lower than the PI of botulinum toxin; and separating the botulinum toxin type A macro complex from a flow-through portion of the solution containing the botulinum toxin, which is not bound to the anion exchange chromatography medium.
Dependent Claim 2	The method of claim 1, further comprising adjusting a pH of the botulinum toxin-containing solution to a pH lower than the PI of botulinum toxin, before the contacting of the botulinum toxin-containing solution with the anion exchange chromatography medium at the pH lower than the PI of botulinum toxin in (a); adjusting a pH of the flow-through portion of the botulinum toxin-containing solution that is not bound to the anion exchange chromatography medium, before the contacting of the flow-through portion of the botulinum toxin-containing solution with the cation exchange chromatography medium at the pH lower than the PI of botulinum toxin in (a); adjusting a pH of the botulinum toxin-containing solution, before the contacting of the botulinum toxin-containing solution with the cation exchange chromatography medium at the pH lower than the PI of botulinum toxin in (b); or adjusting a pH of the solution containing the botulinum toxin separated from the cation exchange chromatography medium, before the contacting of the solution containing the botulinum toxin separated from the cation exchange chromatography medium with the anion exchange chromatography medium at the pH lower than the PI of botulinum toxin in (b).
Dependent Claim 3	The method of claim 2, wherein the adjusting comprises mixing the botulinum toxin-containing solution, the flow-through portion of the botulinum toxin-containing solution, or the solution

	containing the botulinum toxin with a buffer having a pH lower than the PI of botulinum toxin.
Dependent Claim 4	The method of claim 3, wherein the buffer is a phosphate buffer, a citrate buffer, or an acetate buffer.
Dependent Claim 5	The method of claim 3, wherein the buffer has a pH of 3.5 to 6.0.
Dependent Claim 6	The method of claim 3, wherein the buffer comprises a 10 mM to 100 mM phosphate buffer, a 10 mM to 100 mM citrate buffer, or a 10 mM to 100 mM acetate buffer.
Dependent Claim 7	The method of claim 1, wherein the anion exchange chromatography medium comprises DEAE or Q anion exchange resin.
Dependent Claim 8	The method of claim 1, wherein the cation exchange chromatography medium comprises CM, S, or SP cation exchange resin.
Dependent Claim 9	The method of claim 1, wherein the pH lower than the PI of botulinum toxin is pH 3.5 to 6.0.

CERTIFICATE OF COMPLIANCE

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent 11,331,598 contains 13,956 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

Dated: February 21, 2023

Respectfully Submitted,

/ Dion M. Bregman /
Dion M. Bregman, Reg. No. 45,645

Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: Petition for *Inter Partes* Review of U.S. Patent 11,331,598 and the exhibits cited therein by Federal Express Next Business Day Delivery on this day, February 21, 2023, on the correspondence address of record for the subject patent as follows: Potomac Law Group, PLLC, 1300 Pennsylvania Avenue, NW, Suite 700, Washington, DC 20004, UNITED STATES.

Dated: February 21, 2023

Respectfully Submitted,

/ Dion M. Bregman /
Dion M. Bregman, Reg. No. 45,645

Counsel for Petitioner