Filed on behalf of Patent Owner by:
Jonathan B. Roses, Reg. No. 61,115
Stephen S. Rabinowitz, Reg. No. 40,286
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210
(617) 646-8000 Phone
(617) 646-8646 Fax

Paper No. __

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

_____

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

I. INTRODUCTION 1

A. Ground 1 – Obviousness Over Jung and Ton 1

B. Ground 2 – Obviousness Over Kim-741, Kim-565 and Jung 2

II. ION EXCHANGE CHROMATOGRAPHY 5

III. THE CHALLENGED PATENT 9

A. The Specification 9

B. Prosecution History 13

C. The Challenged Claims 18

IV. CLAIM INTERPRETATION AND LEVEL OF SKILL IN THE ART 20

A. "Botulinum Toxin Type A Macro Complex" and "A pH Lower Than the Isoelectric Point (PI) of Botulinum Toxin" 20

B. Level of Skill in the Art 20

V. PRIOR ART 20

A. Jung (EX1002) 20

B. Ton (EX1003) 22

C. Kim-741 (EX1004) 26

D. Kim-565 (EX1023) 28

VI. THE PETITION MUST BE DENIED BECAUSE PETITIONER FAILED TO MEET ITS BURDEN TO DEMONSTRATE A REASONABLE LIKELIHOOD OF PREVAILING AS TO ANY CHALLENGED CLAIM 29

A. Ground 1 (Jung and Ton) Fails for Three Independent Reasons 29

1. Introduction to Ground 1's Failures 29

2. Ground 1 Fails to Establish That Jung Discloses Isolating the BoNTA Macro Complex and Never Alleges That Ton Remedies That Deficiency 31

a. Petitioner Failed to Establish That Jung Discloses Isolating the BoNTA Macro Complex 32

i. The Petition Fails to Identify This Element in Jung 32

ii. Petitioner's Expert Declaration Cannot Save Ground 1 34

b. Petitioner Does Not Rely on Ton to Change the Toxin Isolated by Jung 36

3. Petitioner Established No Non-Hindsight Reason Why a POSA Would Have Combined Jung and Ton in the Manner Alleged.....36

a. Petitioner Fails to Show That a POSA Would Have Deemed the Botulinum Toxin Purified by Jung as Needing Further Purification.....37

b. Petitioner Fails to Show That a POSA Would Have Added the Binding-Mode CEX Step of Ton Even If Further Purification Were Needed.....38

c. Petitioner Ignores Teachings in Ton That Show a POSA Would Not Have Combined the CEX Step of Ton with an Upstream Acid Precipitation Step from Jung.....40

d. Petitioner Relies on Hindsight, Using the '598 Patent as a Roadmap to Select and Combine Particular Steps from Jung and Ton in a Way That Disregards Ton's Teachings 42

4. Ground 1 Fails to Establish That the Proposed Jung/Ton Combination Would Reasonably Have Been Expected to Isolate the BoNTA Macro Complex.....44

B. Ground 2 (Kim-741, Kim-565 and Jung) Also Fails 45

1. Ground 2 Should Be Discretionarily Denied under 35 U.S.C. § 325(d) 45

2. Ground 2 Fails Even If Considered on Its Merits 50

a. Petitioner Fails to Rebut Experimental Evidence of Unexpected Results, and Resorts to Mischaracterizing the Prosecution History.....51

i. Petitioner Mischaracterizes the Nature of Medytox's Unexpected Results – Efficiency of BoNTA Purification, Not Whether BoNTA Flows Through AEX Media.....53

ii. Petitioner Cannot Show the Absence of Unexpected Results by Ignoring the Evidence and Attacking a Strawman.....57

iii. The Board Routinely Denies Institution Where – As Here – The Petition Fails to Persuasively Address Objective Evidence of Nonobviousness Relied on by the Examiner....59

b. Petitioner Fails to Establish That Kim-741 Discloses Adding an Acid to the Botulinum Toxin-Containing Solution....61

c. The Portions of Kim-741 That Ground 2 Relies on Do Not Disclose the Claimed Step of "Separating" the BoNTA Macro Complex....62

i. Kim-741, ¶[0087] Does Not Disclose Separating the Macro Complex....63

ii. Kim-741, ¶¶[0117]-]0122] Relate to Collecting the Smaller 150 kDa Toxin, Not the Macro Complex....64

iii. Citation to Petitioner's Expert Declaration Cannot Save Ground 2....65

d. Petitioner's Reliance on Overlapping Ranges Fails Because It Did Not Show that pH Was Recognized as a Result-Effective Variable That Affects BoNTA Recovery....67

e. Petitioner Fails to Address the Full Scope of Kim-741's Teachings, Which Prevent it from Demonstrating a Reasonable Expectation of Isolating the BoNTA Macro Complex....69

VII. CONCLUSION....72

TABLE OF AUTHORITIES

CASES

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH,
IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) 46

Apotex Inc. v. Celgene Corp.,
IPR2018-00685, Paper 8 (PTAB Sept. 27, 2018) 49

Arendi S.A.R.L. v. Apple Inc.,
832 F.d 1355 (Fed. Cir. 2016) 31

Catalent Pharma Solutions, Inc. v. Patheon Softgels Inc.,
IPR2018-00421, Paper 9 (PTAB Aug. 13, 2018) 66

Cisco Systems, Inc. v. C-Cation Technologies, LLC,
IPR2014-00454, Paper 12 (PTAB Aug. 29, 2014) 65

Coalition for Affordable Drugs V LLC v. Hoffmann-LaRoche Inc.,
IPR2015-01792, Paper 14 (PTAB Mar. 11, 2016)..... 4, 60

Cradlepoint, Inc. v. Sisvel International SA,
IPR2020-01069, Paper 11 (PTAB Jan. 12, 2021) 66

E.I. DuPont de Nemours & Co. v. Synvina C.V.,
904 F.3d 996 (Fed. Cir. 2018) 67, 68, 69

Ex Parte Blak,
Appeal No. 2019-006661, 2020 WL 4200052 (PTAB July 14, 2020) 68

Genentech, Inc. v. Hospira, Inc.,
946 F.3d 1333 (Fed. Cir. 2020) 58

Gilead Sciences v. Regents of the University of Minnesota,
IPR2017-01753, Paper 42 (April 22, 2020) 41, 42, 70

Gilead Sciences, Inc. v. United States of America,
IPR2019-01454, Paper 15 (PTAB Feb. 20, 2020) 60

Gillette Co. v. S.C. Johnson & Son, Inc.,
919 F.2d 720 (Fed. Cir. 1990) 62

Graham v. John Deere Co.,
383 U.S. 1 (1966) 43

Harmonic Inc. v. Avid Tech., Inc.,
815 F.3d 1356 (Fed. Cir. 2016) 34, 35, 45, 61

Henny Penny Corp. v. Frymaster LLC,
938 F.3d 1324 (Fed. Cir. 2019) 42

Hospira v. Genentech,
IPR2016-01837, Paper 40 (PTAB Mar. 6, 2018).....58

In re Applied Materials, Inc.,
692 F.3d 1289 (Fed. Cir. 2012) 58, 59

Kartri Sales Co, Inc. v. Zahner Design Group, Ltd.,
IPR2016-01327, Paper 13 (PTAB Jan. 3, 2017) 33

Kennametal, Inc. v. Ingersoll Cutting Tool Co.,
780 F.3d 1376 (Fed. Cir. 2015) 62

KSR Int'l Co. v. Teleflex, Inc.,
550 U.S. 398 (2007) 43

Leo Pharm. Products, Ltd. v. Rea,
726 F.3d 1346 (Fed. Cir. 2013) 59

Lower Drug Prices for Consumers, LLC v. Forest Labs. Holdings Ltd.,
IPR2016-00379, Paper 14 (PTAB July 1, 2016).....48

Metalcraft of Mayville, Inc. v. The Toro Co.,
848 F.3d 1358 (Fed. Cir. 2017) 43

NanoCellect Biomedical, Inc. v. Cytonome/ST, LLC,
IPR2020-00548, Paper 15 (PTAB Sept. 1, 2020) 64

Procter & Gamble Co. v. Teva Pharms. USA, Inc.,
566 F.3d 989 (Fed. Cir. 2009) 44

South-Tek Sys., LLC v. Engineered Corrosion Sols., LLC,
748 F. App'x 1003 (Fed. Cir. 2018).....38

Vanguard Products Group, Inc. v. InVue Security Products, Inc.,
IPR2020-00014, Paper 8 (PTAB Apr. 1, 2020) 37

Xerox Corp. v. Bytemark, Inc.,
IPR2022-00624, Paper No. 9 (PTAB Aug. 24, 2022)..... 35, 61

STATUTES

35 U.S.C. § 103 17

35 U.S.C. § 312(a)(3).....34

35 U.S.C. § 314(a) 29

35 U.S.C. § 325(d) 2, 45, 46, 48

REGULATIONS

37 C.F.R. § 42.104 (b)(4)..... 31, 32, 64

37 C.F.R. § 42.108(b) 45

37 C.F.R. § 42.22(a)(2).....34

37 C.F.R. § 42.6(a)(3).....65

37 C.F.R. § 42.65(a).....65

LISTING OF EXHIBITS

Exhibit	Description
2001	U.S. Patent No. 9,480,731
2002	U.S. Patent No. 9,206,409 ("Ton-409")

I. INTRODUCTION

Patent Owner Medytox Inc. ("Medytox" or "Patent Owner") submits this Preliminary Patent Owner Response to the Petition by Hugel, Inc. ("Petitioner") seeking *inter partes* review of claims 1-9 of U.S. Patent No. 11,331,598 (the "'598 Patent," EX1001). The Petition should be denied because both of its Grounds are fatally flawed.

A. Ground 1 – Obviousness Over Jung and Ton

Ground 1 fails for multiple reasons.

First, the claims are directed to isolating a specific-sized complex – the "macro complex" – of botulinum toxin type A ("BoNTA"). The Petition alleges that Jung discloses isolating the BoNTA macro complex. That is manifestly untrue. Jung only discloses isolating a BoNTA toxin of unspecified size and it is undisputed that other molecular weight forms of the toxin existed that were not the macro complex. Jung's disclosure of isolating some unidentified member of the genus of BoNTA toxins does not, as Petitioner alleges, disclose isolating the specifically-claimed species – the macro complex. That is fatal to Ground 1.

Second, the Petition reconstructs the claims in hindsight by combining disparate disclosures from Jung and Ton in a manner that is totally unsupported. The claims require isolating the BoNTA macro complex using two chromatographic purification techniques in series in a manner never described in

the prior art. Petitioner found one of the techniques in Jung and the other in Ton, then stated conclusorily that it would have been obvious to use them together as claimed. Neither Jung, Ton nor any other evidence supports that combination.

Ton uses a particular anion exchange ("**AEX**") chromatography technique to remove ***positively***-charged impurities and a subsequent cation exchange ("**CEX**") chromatography technique that removes ***negatively***-charged impurities. Petitioner's challenge relies on the combination of Ton's latter CEX process (which removes negatively-charged impurities) with the AEX chromatography step disclosed by Jung. But the AEX chromatography technique of Jung ***already removes*** negatively-charged impurities. A person of ordinary skill in the art ("POSA") motivated to further purify Jung's output would have added a chromatography technique to filter out positively-charged impurities to complement the chromatography technique Jung already uses. A POSA would not have added Ton's CEX chromatography technique because it would have been cumulative of Jung's chromatography technique. The Jung/Tom combination is an unsupported attempt to reconstruct the claims in hindsight, and fails for this additional reason.

B. Ground 2 – Obviousness Over Kim-741, Kim-565 and Jung

Ground 2 should be discretionarily denied under 35 U.S.C. § 325(d) and rejected if considered on its merits.

A central aspect of the claimed invention was the discovery that AEX chromatography at a pH below the isoelectric point ("pI") of botulinum toxin ("BoNT") was critical and provided unexpected benefits. During prosecution, the Examiner rejected the claims over the same Kim-741 reference that Petitioner relies on in Ground 2. Kim-741 discloses AEX chromatography at a broad pH range extending from below the pI of BoNT to above it. The Examiner initially found this to be an "overlapping range" that rendered the claimed pH range presumptively obvious. However, the Examiner ultimately withdrew that rejection, finding that evidence submitted by Medytox – a sworn declaration and data – demonstrated the criticality of using a pH below the pI of BoNT for efficiency of purification.

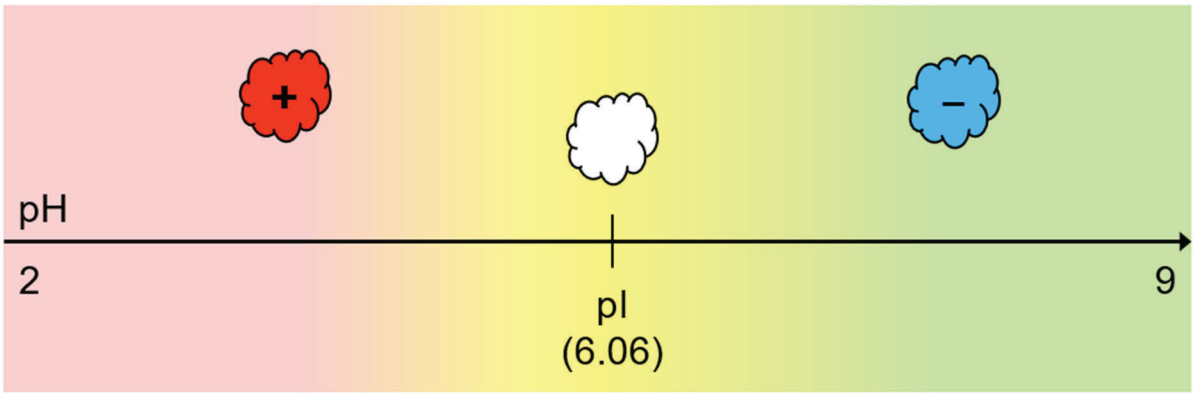
Ground 2 parrots the very same rejection, relying on the same Kim-741 disclosure and alleging the broad pH range "overlaps" the claimed range, rendering it obvious. Thus, Ground 2 seeks to relitigate the issues addressed during prosecution on the same factual record because Petitioner submitted ***no new evidence*** on this issue. Petitioner did no testing to rebut Medytox's data, and Petitioner's expert never disputes the criticality of using a pH below the pI of BoNT for the reason the Examiner found – efficiency of purification. The Board should decline Petitioner's unwarranted invitation to rehash the main issue addressed during prosecution and discretionarily deny Ground 2.

Even if the Board considers the merits, Petitioner's failure to submit any expert or other evidence refuting the data that the Examiner found proved the criticality of the claimed pH range is fatal to Ground 2. Without such evidence Petitioner has not shown it is reasonably likely to prevail on this issue. *Coalition for Affordable Drugs V v. Hoffmann-LaRoche*, IPR2015-01792, Paper 14, at 18 (PTAB Mar. 11, 2016) ("CFAD").

Numerous additional flaws doom Petitioner's Ground 2. In particular, Petitioner relies on Kim-741 as purportedly disclosing "separating the **macro complex** from the [CEX] chromatography medium," but Kim-741 simply fails to do so. Kim-741 only obtained a smaller form of BoNT from the CEX chromatography step – not the macro complex as required by the challenged claims. Ground 2 also relies on Kim-741 as purportedly disclosing "adding an acid to the [BoNT]-containing **solution**" but Kim-741 only discloses adding an acid to the bacterial **culture**, not the "solution" specified in the claims. Moreover, Petitioner fails to show that a POSA would have been motivated to modify the pH of Kim-741's AEX step, which was not known to affect efficiency of BoNT recovery, or have reasonably expected that doing so would isolate the macro complex. Ground 2 fails for these additional reasons.

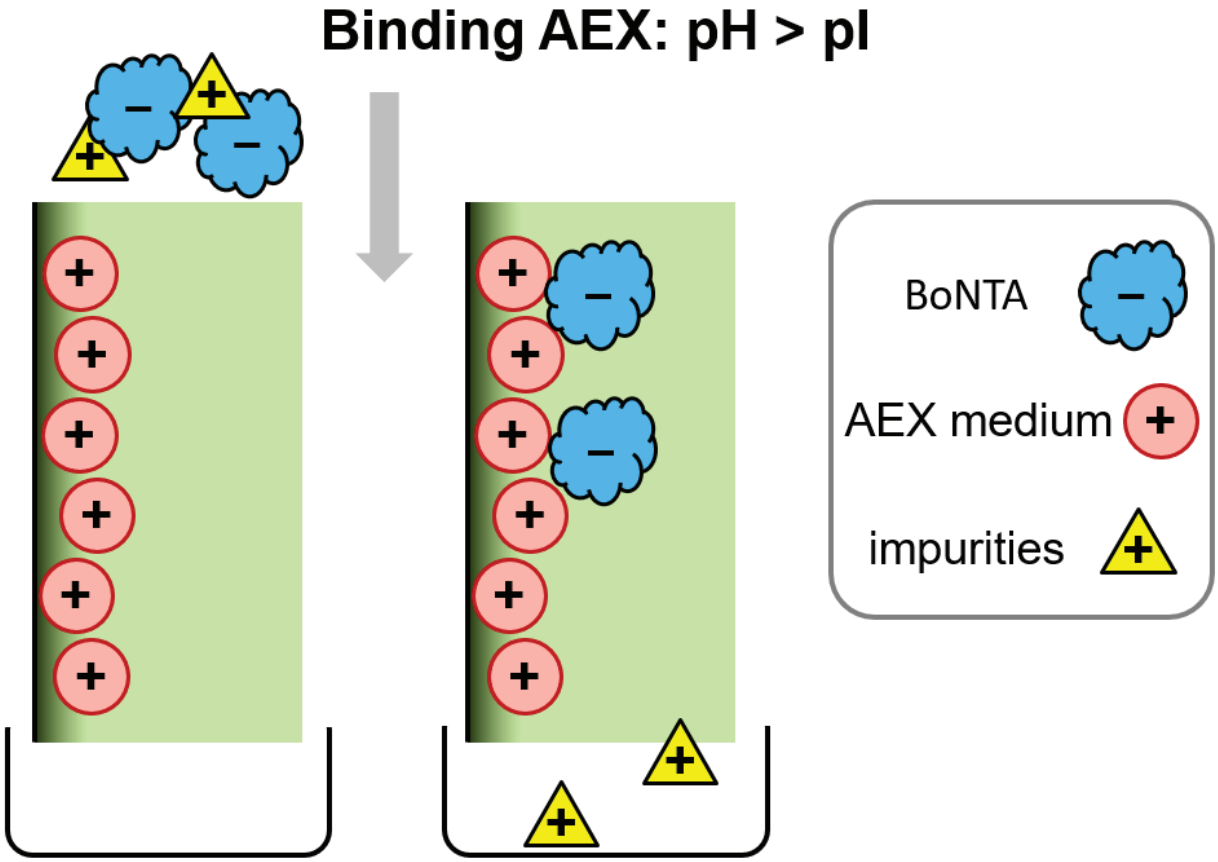
II. ION EXCHANGE CHROMATOGRAPHY

Ion exchange chromatography separates molecules based on differences in net surface charge. EX1016, 13. The net surface charge of a protein changes as the pH of its environment changes, and each protein has its own relationship between charge and pH. *Id*. At a pH equivalent to its isoelectric point ("**pI**"), a protein has no net charge and will not interact with a charged medium. *Id*. A protein is negatively charged at a pH above its pI, and positively charged at a pH below its pI. *Id*., Fig. 2. As illustrated below, BoNTA's charge is negative (blue) above the pI (6.06), neutral (white) at the pI, and positive (red) below the pI. EX1006, 626.

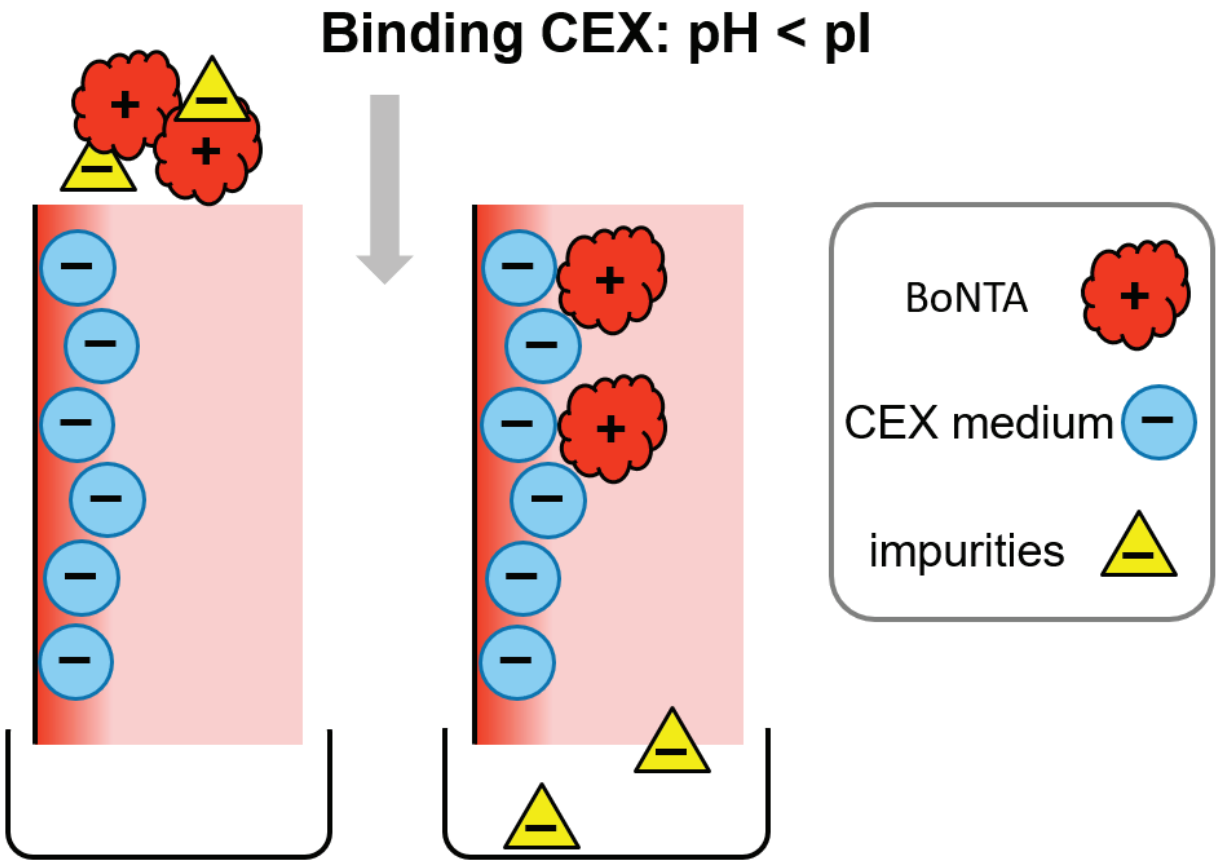


Various types of chromatography are used to separate proteins:

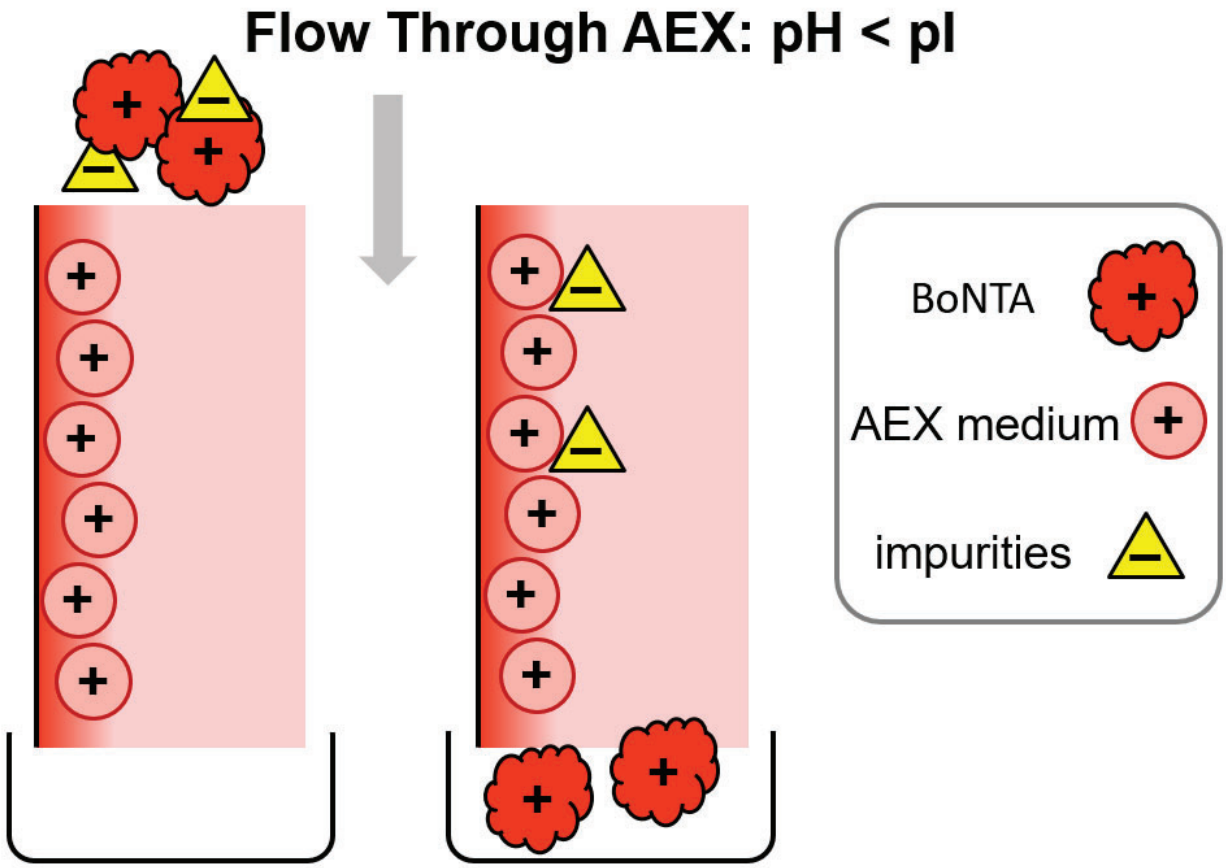
- "Binding-mode AEX chromatography" relies on a negatively charged protein (present at a pH above its pI) binding to the positively-charged AEX medium to separate out positively charged impurities, which flow through. EX1016, 13-15; EX1021, ¶¶38-39.



- "Binding-mode CEX chromatography" relies on a positively-charged protein (present at a pH below its pI) binding to the negatively-charged CEX medium to separate out negatively charged impurities, which flow through. EX1016, 13-14; EX1021, ¶¶38-39.



- "Flow-through mode AEX chromatography" relies on a positively charged protein present at a pH below its pI flowing through an AEX medium to separate out negatively charged impurities, which bind to the medium. *See* EX1006, 586-87; EX1021, ¶¶38-39.



III. THE CHALLENGED PATENT

A. The Specification

The ’598 Patent marks another Medytox innovation in the field of botulinum toxins (*see, e.g.*, EX2001) – bacterial toxins useful for treating medical conditions like strabismus (EX1014, 4-5) as well as cosmetic use.

The ’598 Patent claims a method for isolating a particular high molecular weight form – the **macro complex**[1] – of BoNTA. The bare BoNTA protein “includes about 150 kDa of toxin protein” but naturally occurs as “a complex with a variety of non-toxic proteins bound thereto.” EX1001, 1:36-39. These complexes occur in different sizes: an intermediate complex of 300 kDa, a large complex of 500 kDa, and a macro complex of 900 kDa (*id*., 1:39-42), and differ in their specific toxicities and stability in therapeutic formulations. EX1010, 8. The challenged claims are directed to a method of isolating just one of those complexes – the BoNTA macro complex.

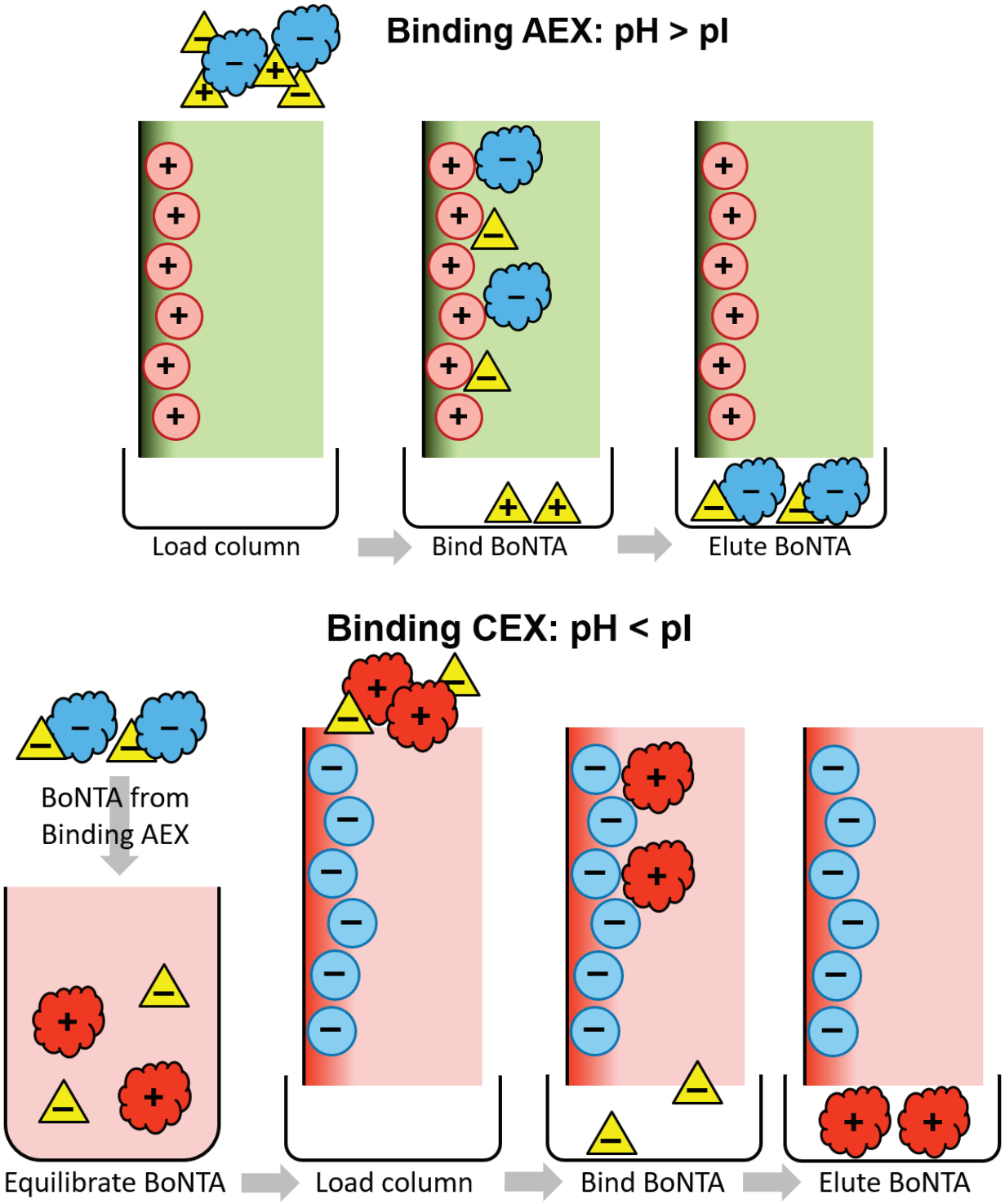
The ’598 Patent is directed to obtaining BoNTA using an “upstream” process of culturing *Clostridium botulinum* bacteria in a medium to produce the

[1] The BoNTA macro complex is as also called “900 kDa” or “19S,” reflecting the size of the complex as measured by two different techniques. EX1001, 1:41-42; 9:62.

toxin, and then performing initial purification steps – *e.g.*, removing bacterial cells, acid precipitation and filtration – to produce a crude solution containing BoNTA. EX1001, 10:28-38. "Downstream" chromatography steps are added to obtain purified BoNTA. *Id*., 10:39-63

The '598 Patent discusses a particular prior art method for isolating BoNT from *Clostridium botulinum* that included **binding-mode** AEX chromatography followed by binding-mode CEX chromatography. EX1001, 2:28-39. As illustrated below, binding-mode AEX removes positively charged impurities, and

binding-mode CEX removes negatively charged impurities. *See* EX1016, 13-14; EX1021, ¶¶38-39.



The ’598 Patent’s inventors identified a problem with this method: the macro complex dissociated into lower molecular weight forms, preventing its recovery. *Id*., 2:40-45 (“[**D]uring purification**[2] of the [BoNT] protein, a neurotoxic component (i.e., a neurotoxic molecule of approximately 150 kDa), an intermediate complex (300 kDa), or a large complex (500 kDa) is **dissociated and removed** from the [BoNT] protein.”).

The inventors solved this problem to provide “a method of isolating a [BoNTA] **macro complex** from a botulinum toxin-containing solution.” *Id*., 2:51-53. This method uses **flow-through** AEX chromatography followed by binding-mode CEX chromatography,[3] both at a pH lower than the pI of BoNT:

> [T]he method includ[es] contacting the [BoNT]-containing solution with an [AEX] chromatography medium at a pH lower than the isoelectric point (PI) of botulinum toxin; contacting the solution, **which is not bound to the [AEX] chromatography medium**, with a [CEX] chromatography medium at a pH lower than the PI of [BoNT]; and separating the [BoNTA] **macro complex** from the [CEX] chromatography medium … .”

[2] Emphasis added throughout unless otherwise indicated.

[3] The order of these chromatography steps can be reversed. *Id*., 2:67-3:10.

Id., 1:59-67; *see also id.*, 8:66-9:2 ("In this process, [BoNTA] toxin **was not adsorbed to the [AEX] resin**, and most impurities were adsorbed thereto and removed.").

The '598 Patent provides a working example in which the BoNTA macro complex was obtained with a purity of 99.64% by the claimed process, using flow-through AEX chromatography, followed by binding-mode CEX chromatography. *Id*., 9:48-62.

B. Prosecution History

Originally-filed claim 1 recited "[(i)] contacting the [BoNT]-containing solution with the [AEX] chromatography medium at a pH lower than an isoelectric point (PI) of [BoNT and (ii)] contacting the solution, which is not bound to the [AEX] chromatography medium, with a [CEX] chromatography medium at a pH lower than the PI of [BoNT] …." EX1006, 115.

The Examiner rejected the claims as obvious over U.S. Patent No. 9,206,409 to Ton (EX2002) ("Ton-409")[4] combined with other references. EX1006, 329. The Examiner stated that Ton-409 disclosed "that during the [AEX] step, [BoNTA] complex was eluted" and found that the material, once eluted from the

[4] Ton-409 is a continuation of, and shares a specification with, Ton (EX1003) of Ground 1.

AEX column, met the claimed requirement for the "solution, which is not bound to the [AEX] chromatography medium." *Id*.

In response, Medytox amended claim 1 to require "contacting a flow-through portion of the botulinum toxin-containing solution[[, which]] is not bound to the [AEX] chromatography medium, with a [CEX] chromatography medium…." (*id*., 484 (emphasis original)), arguing *inter alia* that Ton-409 "does not suggest or provide a reason for 'contacting a flow-through portion of the [BoNT]-containing solution, which is not bound to the [AEX] chromatography medium, with a CEX chromatography medium'" at the claimed pH range. *Id*., 485 (emphasis original).

The Examiner withdrew the rejection based on Ton-409 (*id*., 497) and issued a new ground of rejection for obviousness over Kim-741. *Id*., 499. The Examiner stated that: "[t]he AEX chromatography step [of Kim-741] is performed at a pH of 3-8, and [BoNT] is collected in a flow-through fraction from the AEX column" (*id*.) and that "[g]iven the 6.06 isoelectric point (pI) of [BoNTA], 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 [BoNT]' and therefore, establishes cases of *prima facie* obviousness." *Id*., 500.

To overcome Kim-741, Medytox submitted a declaration by co-inventor Song that established unexpected results and criticality of using a pH ***below*** the pI

of BoNT for the AEX chromatography step. *Id*., 570-581. The Song Declaration compared results from AEX chromatography both below (at pH 5.5) and above (at pH 6.5) the pI of BoNT "**to compare the relative efficiency of [BoNT] recovery** …." *Id*., 570. The material from AEX chromatography was analyzed by CEX chromatography. *Id*., 573, 575. The data demonstrated that with AEX chromatography at pH 5.5, the macro complex was obtained from a single flow-through fraction with a purity of 91.8%, while AEX chromatography at pH 6.5 provided the macro complex in a wide band overlapping with other impurities: "[T]he purity of botulinum fraction no. 1, 3, 5, and 7, i.e., the eluted solution was about 30% to 88%. However, [the macro complex] is not purified but distributed to the all the fractions." *Id*., 575-76. Medytox argued:

> These results from using pH 5.5 and pH 6.5 show that [the macro complex] can be purified from the flow through solution when pH 5.5 is used but at pH 6.5, [the macro complex] was not present in the flow through solution but was present in the eluted solution, distributed in a wide retention time. In this regard, **when pH 5.5 is used, [the macro complex] can be simply purified from the flow through solution with high purity and there is no need to add an additional eluting step**. This is an unexpected benefit of the claimed invention.

Id., 568.

The Examiner initially maintained the rejection over Kim-741, noting from "the principles of ion exchange chromatography" that "[i]n a buffered solution

below the protein's pI, the protein is positively charged … and will not bind to the positively charged functional groups of an [AEX] resin." *Id*., 586-87. The Examiner reasoned that "[b]ecause the claimed inventive method requires taking the flow-through portion of botulinum toxin-containing solution *not bound to* an [AEX] medium … [a POSA] 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 [BoNTA] macro complex through the AEX resin …." *Id*., 587 (emphasis original).

Medytox responded by amending the claims to require upstream culture and processing steps – including acid precipitation – before the downstream chromatography steps. *Id*., 609. Medytox argued that the broad pH range of 3-8 disclosed in Kim-741 for AEX and CEX chromatography "is simply the largest pH range that can theoretically be performed" and that it would not have been obvious to select a pH lower than the pI of BoNT for both the AEX and CEX chromatography steps. *Id*., 616-617. Medytox pointed out that the working examples of Kim-741 used a pH **higher** than the pI of BoNT (*i.e*., pH 6.4-6.6) not only for the first flow-through AEX step, but also for a second binding-mode AEX step (*i.e.*, pH 7.7-7.9) and for CEX chromatography (*i.e.*, pH 6.9-7.1). *Id*., 617. Moreover, Kim-741 disclosed that the botulinum BoNT obtained from the CEX chromatography was the 150 kDa toxin, not the 900 kDa macro complex. *Id*.

Medytox also relied on the Song Declaration, which provided experimental data "to compare the relative efficiency of [BoNT] recovery between AEX using pH lower than the PI of [BoNT] and AEX using pH higher than the PI of [BoNT] …." *Id*., 619.

The Examiner then allowed the application, noting in the Statement of Reasons for Allowance that Kim-741 "discloses a broad pH range of 3-8 and provides only embodiments where the pH levels are above the pI of botulinum toxin," and finding that a POSA "would not have been motivated to select a pH lower than the pI of [BoNT] from the pH range of 3-8 disclosed by [Kim-741] because [Kim-741] does not disclose or provide any reason that the [AEX] or [CEX] process can be performed at such a lower pH level." *Id*., 627. The Examiner stated that he was persuaded by the Song Declaration "comparing **the relative efficiency of [BoNT] recovery** from an AEX process between using a pH lower than the pI of [BoNT] and a pH higher than the pI of [BoNT], thereby showing the criticality of such a claimed limitation." *Id*. The Examiner found this showing of criticality "persuasive to overcome the 35 USC 103 rejection of Claim 1 as being unpatentable over [Kim-741]." *Id*.

The prosecution history thus demonstrates that the application was allowed over Kim-741 because the Song Declaration demonstrated the unexpected result of

improved efficiency of BoNT recovery in terms of simplicity and purity that is achieved by using a pH below the pI of BoNT.

C. The Challenged Claims

Independent claim 1 is reproduced below:

A method of **isolating a botulinum toxin type A macro complex** from a botulinum toxin-containing solution, the method comprising:

culturing *Clostridium botulinum* in an animal product-free medium to obtain a culture;

removing *Clostridium botulinum* 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.

Challenged claims 2-9 depend, directly or indirectly, from claim 1.

Claim 1 provides two alternative ion exchange purifications, labelled "(a)" and "(b)." Alternative (a) begins with flow-through AEX chromatography followed by CEX chromatography. The order is reversed in alternative (b), which

begins with CEX chromatography followed by flow-through AEX chromatography. The Petition focuses exclusively on alternative (a).

IV. CLAIM INTERPRETATION AND LEVEL OF SKILL IN THE ART

A. "Botulinum Toxin Type A Macro Complex" and "A pH Lower Than the Isoelectric Point (PI) of Botulinum Toxin"

For purposes of this preliminary response only, Medytox does not challenge Petitioner's proposed constructions of "botulinum toxin type A macro complex" or "a pH lower than the PI of botulinum toxin" (Petition, 17-18) because the Petition fails even under Petitioner's proposed constructions. Medytox reserves the right to dispute Petitioner's constructions of these terms in the future.

B. Level of Skill in the Art

For purposes of this preliminary response only, Medytox does not challenge Petitioner's proposed definition of a POSA (*id.*, 17) because the Petition fails even under Petitioner's definition. Medytox reserves the right to dispute Petitioner's definition of a POSA in the future.

V. PRIOR ART

A. Jung (EX1002)

Jung is directed to a safer method of culturing *Clostridium botulinum* that facilitates easy purification of BoNTA toxin while avoiding the "many labor and high investment costs and risk factors" that troubled prior art methods. EX1002, 2:38-55. Jung states that by using "a composition of plant-derived components"

for the culture medium, "a large amount of the *Clostridium botulinum* toxin was expressed outside the cell." *Id*., 2:46-49; *see also id.*, 3:10-13 Media containing plant-derived components are called animal protein-free (APF) media. *See* EX1003, 4:66-5:2.

Jung's improved upstream culture conditions simplified the downstream steps required to purify botulinum toxin: "the inventors of the present application found that *Clostridium botulinum* toxin could be easily and very simply purified from the culture from which the cell was removed." EX1002, 2:46-56.

Jung further taught that performing the culture and purification steps in "a closed system by using single use consumables" helped to avoid exposing "the outside of the container on which an operator works" to this toxin (*id*., 7:61-66), so that the "toxin can be produced safely" (*id*., 8:1), even though "[BoNTA] is the most lethal natural biological agent known to man" (*id*., 2:9-10).

Jung illustrates a working example in which *Clostridium botulinum* was cultured in an APF medium (*id*., 11:28-32) in a single-use fermentation bag (*id*., 8:56-9:32), and the culture medium was passed through a disposable filter to remove the cells and obtain a supernatant containing the toxin (*id*., 9:37-47, 10:11-18). The supernatant was acidified to precipitate the toxin, (*id*., 11:33-37), which was redissolved to obtain a solution (*id*., 11:51-53). The solution was filtered, (*id*., 11:65-66), and subjected to flow-through AEX chromatography and membrane

chromatography to obtain "*Clostridium botulinum* type A toxin having a purity of 95% or greater." *Id*., 12:4-26.

Jung does not disclose isolating the BoNTA macro complex. The specification is silent about whether the toxin isolated in the working example was the 150 kDa toxin or any of the complexes (i.e., 300, 500 and 900 kDa) in which BoNTA naturally occurs. *Id*., 1:43-51, 12:4-33. Moreover, the claims only recite a method of producing "*Clostridium botulinum* toxin" without specifying whether this toxin is obtained as a complex and, if so, of what size. *Id*., 12:49-14:21.

B. Ton (EX1003)

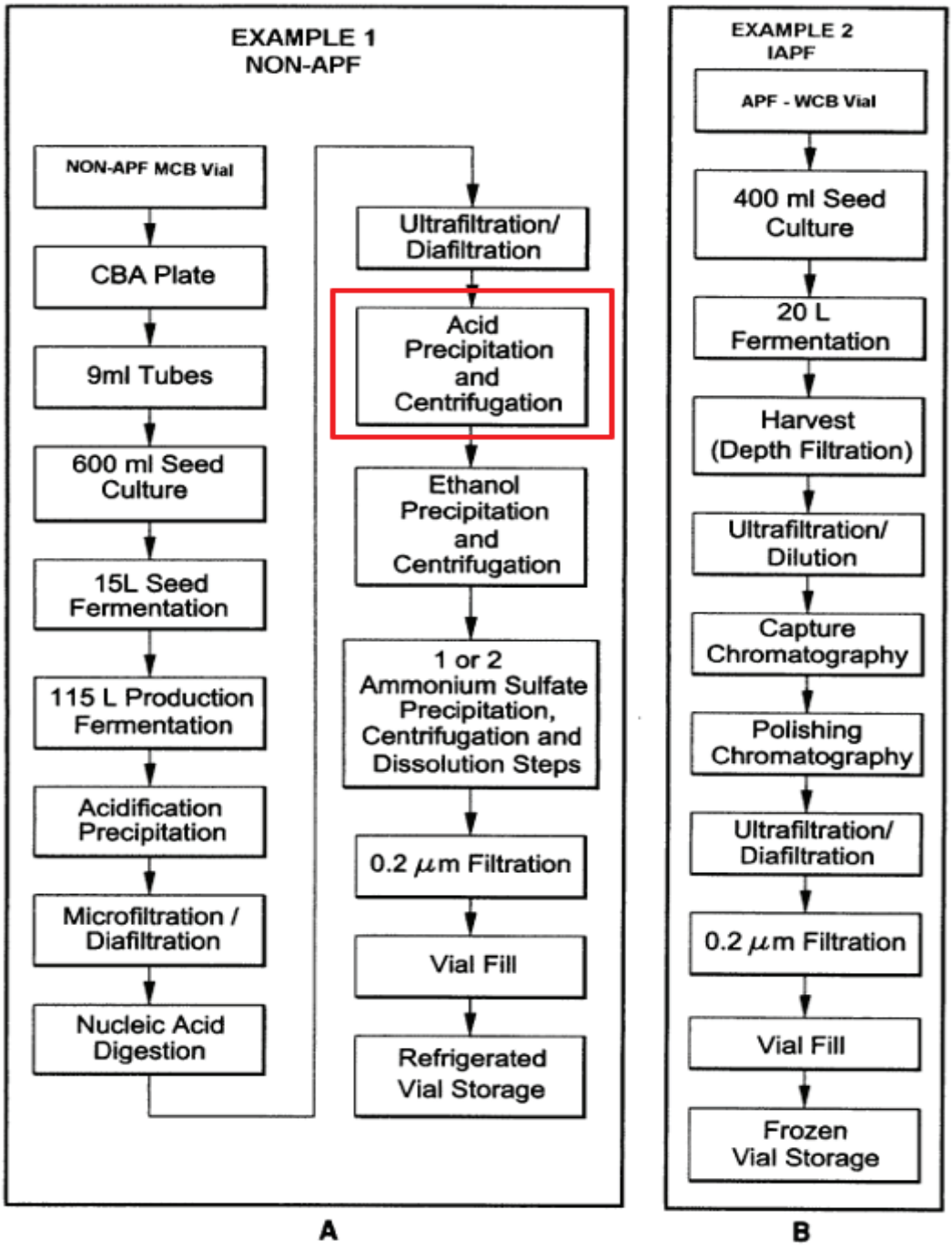
Ton discloses isolating the BoNTA macro complex by a process that (i) avoids acid precipitation, and (ii) uses **binding-mode** AEX chromatography, followed by binding-mode CEX chromatography.

Ton is directed to "a simple, fast and economical APF chromatographic system and process" for obtaining BoNT. EX1003, 24:8-12. The use of APF culture conditions – unlike the time-consuming non-APF "Schantz" process of the prior art that "takes about 3 weeks to complete," (*id*., 27:40-48) – is coupled with corresponding changes in the downstream purification steps to provide "a rapid APF, anion-cation chromatographic" process "for obtaining high yield, high purity botulinum neurotoxin" that "takes only 4-7 days, preferably about 4 to about 6 days" to complete. *Id*., 28:60-29:1.

Ton teaches **avoiding acid precipitation** prior to chromatography. Instead, Ton teaches "depth filtration to remove cell debris and nucleic acids, followed by ultrafiltration and dilution to prepare the fermentation medium for the next step in the process." *Id*., 30:63-66. Ton emphasizes: "This harvesting/cell debris clearing is **fundamentally different** from the [prior art] Schantz harvest process, which uses precipitation by acidification followed by microfiltration and diafiltration and exchange buffers in preparation for further processing." *Id*., 30:66-31:3. Ton identifies multiple problems with acid precipitation techniques: "low resolution, low productivity, difficulty of operation, difficulty to control and/or validate and/or difficulty to scale-up or scale-down." *Id.*, 6:37-41. Ton touts as one of its advantages "[r]eplacement of any precipitation steps with chromatographic steps to purify a bulk [BoNT] complex, which improves the specificity of the purification process." *Id.*, 44:58-59, 45:19-21.

The differences between the prior-art non-APF process and Ton's improved APF process are illustrated below. The "Non-APF" process includes acid

precipitation (red box added) whereas the "I[mproved]APF" process advantageously eliminates it. Ton, Figures 1A-B.



Ton's process is likewise "fundamentally different" from the process disclosed in Jung, which includes acid precipitation, (EX1002, 11:33-36), and from the '598 Patent's claimed process, which requires "adding an acid to the [BoNT]-containing solution to precipitate the [BoNT] and obtain a precipitate…" (EX1001, 10:32-34).

Ton also states that "[a]n important aspect of our invention is the use of [AEX **binding-mode**][5] media chromatography followed by the use of [CEX] (polishing)[6] media chromatography…." EX1003, 24:33-38. Ton touts the benefit of AEX chromatography in binding mode as used in its invention:

> The [AEX] column **captures** the Clostridial neurotoxin (such as a [BoNT] complex) and reduces impurity levels. It was found that an [AEX] column provided an efficient **capture** of a [BoNT] complex

[5] Ton references "capture mode," which is synonymous with **binding mode**. *See* EX1030, 110 ("When ion exchange chromatography is applied in **capture**, the purpose will be to **adsorb** the protein of interest quickly from the crude feed stock….") (first emphasis in original).

[6] "Polishing" refers to a downstream purification step that is applied after most impurities have been removed. *See* EX1030, 111 ("In **polishing**…most impurities have already been removed except for trace amounts or closely related substances….") (emphasis in original).

> from harvested fermentation medium with retention of the biological activity of the [BoNT] complex, while also separating many impurities present with the [BoNT] in the fermentation medium.

Id., 25:48-55.

By underscoring the importance of AEX chromatography in ***binding mode***, Ton differs sharply from Example 3 of Jung and from the challenged claims, which use AEX chromatography in ***flow-through*** mode. EX1002, 12:12-16; EX1001, 10:43-47, 10:60-63.

C. Kim-741 (EX1004)

Kim-741 discloses (i) purifying BoNT macro complex by using flow-through AEX as the only chromatography step (EX1004, ¶¶[0102]-[0108]), and (ii) purifying the 150 kDa toxin by using AEX chromatography, followed by CEX chromatography. *Id*., ¶¶[0117]-[0139]. Each of these chromatography steps may be performed at a pH of 2-9, preferably 3-8. *Id*., ¶¶[0075], [0085], [0087].

Kim-741 provides "a more efficient and safe method for producing botulinum toxin, which can be performed under [APF] conditions." EX1004, ¶[0023]. Kim-741 describes a process that comprises (a) acid precipitation of BoNT from a culture of a botulinum toxin-producing bacterial strain (*id*., ¶[0026]); (b) adding a buffer to the precipitate and clarifying the resulting solution by filtration, membrane chromatography and/or centrifugation (*id*., ¶[0027]); (c) subjecting the clarified solution to additional upstream processing steps, (*id*.,

¶[0028]); and (d) subjecting the product to AEX chromatography to purify the BoNT. *Id*., ¶[0029]. The BoNT purified according to this aspect of Kim-741 "may have a form of 7S or 19S (molecular weight: 150 kDa-900 kDa)." *Id*., ¶[0046].

Kim-741 teaches that the product of this first AEX chromatography may be further processed by (e) adjusting the pH upwards (*id*., ¶[0078]); (f) subjecting the pH-adjusted material to a second AEX chromatography step (*id*., ¶[0079]); and (h) purifying the diluted BoNT from step (f) using CEX chromatography. *Id*., ¶[0080].

Kim-741's second AEX chromatography step and CEX chromatography step may be performed "at a pH of 2-9, preferably 3-8" and the second AEX chromatography step may be performed in flow-through or binding mode. *Id*., ¶[0085]. Kim-741 reports that the BoNT is recovered as a fraction that was "bound to the [CEX] chromatography resin." *Id*., ¶[0087].

Unlike the toxin recovered from the first AEX step, which may have a molecular weight of 150 kDa or 900 kDa, the [BoNT] obtained from Kim-741's subsequent CEX chromatography step "may have a form of 7S (molecular weight: 150 kDa.)." *Id*. In other words, **Kim-741 does not disclose a process that includes both AEX and CEX chromatography steps and isolates the BoNTA macro complex.**

This description is illustrated by four working examples. The first, Example 2-3-1, uses a single flow-through AEX chromatography step at pH 6.4-6.6. *Id*., ¶[0107]. This produced BoNTA of "about 900 kDa," *id*., ¶[0108], (*i.e.*, the macro complex) that was contaminated with "an impurity protein band of about 13 kDa," (*id*., ¶[0141]), or "an impurity protein band of about 37 kDa." *Id*., ¶[0142].

The other working examples (Examples 2-3-2, 2-3-3, and 2-3-4) removed these impurities by adding additional chromatography steps. *Id*., ¶¶[0109]-[0139]. But addition of second and third chromatography steps resulted in obtaining the 150 kDa form of BoNTA, not the 900 kDa macro complex. *Id*., ¶¶[0116], [0125], [0139].

D. Kim-565 (EX1023)

Kim-565 describes APF media suitable for producing cultures of *Clostridium botulinum* without risking infection with transmissible spongiform encephalopathy. EX1023, ¶37.

Petitioner relies on Kim-565 solely to satisfy the limitation: "culturing *Clostridium botulinum* in an animal product-free medium to obtain a culture." Petition, 43-44.

VI. THE PETITION MUST BE DENIED BECAUSE PETITIONER FAILED TO MEET ITS BURDEN TO DEMONSTRATE A REASONABLE LIKELIHOOD OF PREVAILING AS TO ANY CHALLENGED CLAIM

By statute, the Board may not institute an IPR unless "the information presented in the petition … shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged." 35 U.S.C. § 314(a). Petitioner fails to satisfy this burden for either Ground 1 or Ground 2.

A. Ground 1 (Jung and Ton) Fails for Three Independent Reasons

1. Introduction to Ground 1's Failures

Ground 1 of the Petition fails for three independent reasons detailed in §§ VI.A.2-4 below.

First, the challenged claims are directed to a method for isolating the BoNTA ***macro complex*** and option (a) – the only option Petitioner addresses – requires separating the BoNTA ***macro complex*** from the CEX chromatography medium. *See* § III.C *supra*. Jung fails to disclose isolating the BoNTA macro complex. The sections of Jung relied on by Petitioner describe collecting a BoNTA toxin of unspecified size. EX1002, 12:4-33. Jung does not identify which of the naturally-occurring molecular weight forms of the toxin were obtained (*i.e.*, 150 kDa, 300 kDa, 500 kDa or the 900 kDa macro complex). Ton cannot remedy this deficiency of Jung and the Petition never alleges otherwise. The Petition does

not contend, let alone prove, that adding Ton's CEX chromatography step after Jung's purification process could produce the macro complex if it is not present in the output of Jung's process. Thus, Jung's failure to disclose isolating the ***macro complex*** is fatal to Ground 1.

Second, Petitioner fails to establish a supportable non-hindsight reason why a POSA would have been motivated to add Ton's downstream CEX step to Jung. Ton uses binding-mode AEX chromatography, which removes ***positively-charged*** impurities and is thus complementary to Ton's next step (binding-mode CEX chromatography), which removes ***negatively-charged*** impurities. Ton, 24:33-35. But Jung's flow-through AEX chromatography step ***already removes negatively-charged impurities***. Petitioner alleges that the motivation for another chromatography step is to achieve greater purity (Petition, 31-32), but identifies no disclosure in Jung that its remaining impurities are negatively-charged and thus susceptible to removal by the additional CEX step Petitioner adds in hindsight. A POSA motivated by Ton to add another chromatography step to Jung would have added steps complementary to those already performed by Jung, which would fail to meet any challenged claim.

Third, Petitioner makes no showing that a POSA would have had a reasonable expectation of successfully obtaining the BoNTA macro complex by

adding a further purification step – CEX chromatography – after the process of Jung, which never discloses that it provides the macro complex in the first place.

2. Ground 1 Fails to Establish That Jung Discloses Isolating the BoNTA Macro Complex and Never Alleges That Ton Remedies That Deficiency

It was Petitioner's burden to establish that all claimed limitations are disclosed in the prior art. *Arendi. v. Apple*, 832 F.3d 1355, 1363 (Fed. Cir. 2016); 37 C.F.R. 42.104(b)(4) ("The petition must specify where each element of the claim is found in the prior art patents or printed publications relied upon.").

Claim 1 – and by dependency every challenged claim – is directed to "[a] method of isolating a [BoNTA] macro complex" (EX1001, 10:25-26) that culminates, in option (a), with "separating the [BoNTA] macro complex from the [CEX] chromatography medium…" *Id*., 10:48-49. The BoNTA macro complex has a molecular weight of 900 kDa. EX1001, 6:57-58. Petitioner failed to carry its burden to demonstrate that the Jung/Ton combination meets any challenged claim because Ground 1 relies entirely on Jung's alleged disclosure that its process isolates the BoNTA macro complex, but Jung provides no such teaching.

Given this failure of proof as to an element of the challenged claims, Ground 1 fails.

a. Petitioner Failed to Establish That Jung Discloses Isolating the BoNTA Macro Complex

i. The Petition Fails to Identify This Element in Jung

The Petition must show "[h]ow the construed claim is unpatentable." 37 CFR § 42.104 (b)(4). The Petition alleges that "the term 'botulinum toxin type A macro complex' should be construed to include **a botulinum toxin type A of 900 kDa**." Petition, 17-18 (emphasis original). Thus, to meet the challenged claims under its own construction, Petitioner needed to show that Jung discloses isolating "a botulinum toxin type A of 900 kDa."

Ground 1 alleges that "Jung discloses '[a] method of isolating a [BoNTA] macro complex from a botulinum toxin-containing solution.'" Petition, 22. But the cited evidence does not support this assertion.

The only portion of Jung cited by Petitioner that mentions the macro complex is Jung's background section, which discusses several forms in which BoNT naturally occurs. Petition, 21-22 (citing EX1002, 1:43-49). This section of Jung discloses that each BoNT type has "about 150 kDa of toxin protein, and **naturally comprises** a complex with a variety of non-toxic proteins bound thereto" and that these complexes can take the form of "[a]n intermediate complex (300 kDa)[,] …a large complex (500 kDa) and a macro complex (900 kDa) …."

EX1002, 1:43-51. This section of Jung says nothing about what form of BoNTA is isolated by Jung's method.

With respect to what Jung ***isolates***, the Petition cites Jung's disclosure that "the toxin existing in the culture [of Clostridium *botulinum*] … is isolated." Petition, 22 (quoting EX1002, 4:37-38). From this, the Petition states the naked conclusion: "Therefore, Jung discloses '[a] method of isolating a [BoNTA] ***macro complex*** from a botulinum toxin-containing solution." *Id*. But Jung never says that it isolates the macro complex – nothing in Jung supports Petitioner's conclusory assertion.

As discussed above, Jung notes that BoNTA can exist as a 150 kDa toxin protein, a 300 kDa intermediate complex, or a 500 kDa large complex as well as the 900 kDa macro complex. EX1002, 1:44-49. The Jung statement identified in the Petition discloses isolating "the toxin existing in the culture" – it does not disclose doing so while avoiding the "problem" of "dissociat[ion] and remov[al]" of toxin components, (EX1001, 2:40-45) so as to isolate the ***macro complex***, as the challenged claims require.

The Petition offered no evidence or argument explaining how or why Jung's disclosure of isolating "the toxin" is a disclosure of isolating the macro complex. That is a fatal failure – institution should be denied. *Kartri Sales v. Zahner Design Group*, IPR2016-01327, Paper 10, at 13 (PTAB Jan. 3, 2017) (denying institution:

"Petitioner fails to show how the portion of the [prior art element] it relies upon satisfies the [claim limitation]…."). The regulations that define the showing required for institution specify that the "petition … ***must*** include … [a] full statement of the reasons for the relief requested, including a ***detailed explanation of the significance of the evidence***." 37 CFR § 42.22(a)(2). The Petition offered ***no*** explanation of the "significance" of the cited evidence – Jung's disclosure of isolating "the toxin" – let alone the required "detailed explanation." *Id*.

A petition "may be considered only if" the grounds are identified "with particularity" and Ground 1 facially is not. 35 U.S.C. § 312(a)(3). Petitioner cannot meet its burden by implication as it needs to state the grounds "with particularity" and to provide a "detailed explanation." *Id*.; 37 CFR § 42.22(a)(2); *Harmonic v. Avid Tech.*., 815 F.3d 1356, 1363 (Fed. Cir. 2016) (affirming final written decision of nonobviousness because prior art contained "no express teaching of [a claim] limitation" and petitioner's "unsupported and inferential theories" about what the prior art discloses were insufficient).

Ground 1 fails on its face because the Petition never explains how or why Jung discloses isolating the ***macro complex*** when Jung says no such thing.

ii. Petitioner's Expert Declaration Cannot Save Ground 1

Petitioner supports its conclusory assertion that Jung discloses isolating the macro complex by citing a single paragraph from its expert's declaration. Petition,

22 (citing EX1021, ¶64). But this paragraph merely parrots the Petition's flawed arguments (discussed above) without citing additional evidence or providing any meaningful explanation of how or why Jung allegedly discloses isolating the macro complex. *Compare* Petition, 21-22 *with* EX1021, ¶64. Thus, the expert's conclusory testimony is entitled to no weight. *Xerox Corp. v. Bytemark*, IPR2022-00624, Paper 9, at 15 (PTAB Aug. 24, 2022) (***precedential***) (denying institution where petitioner attempted to satisfy a claim limitation by relying on expert testimony that "merely repeats, *verbatim*, the conclusory assertion for which it is offered to support."); *Harmonic*,815 F.3d at 1363 ("[Petitioner's] expert testimony in support of this theory is equally unavailing, adding nothing beyond the conclusory statements in [the] petition.").

Other than noting Jung's background disclosure of various forms in which BoNT naturally occurs and Jung's disclosure that "the toxin" is isolated, the expert notes that "'the culture from which the cells are removed' in Jung is 'a botulinum toxin-containing solution' according to the '598 patent." EX1021, ¶64. But that adds nothing to Jung's disclosure of what is ***isolated*** from that solution. In this respect, Petitioner's expert – like the Petition – relies entirely on Jung's statement that "the toxin" is isolated, but provides no evidence or analysis explaining how or why this discloses isolating the macro complex.

b. Petitioner Does Not Rely on Ton to Change the Toxin Isolated by Jung

Ground 1 adds Ton's additional CEX chromatography step to Jung to "improve the purity and yield of ***the collected botulinum neurotoxin in Jung***." Petition, 32. Petitioner does not contend, let alone demonstrate, that adding Ton's additional CEX chromatography step to Jung's process could provide the macro complex unless it is present in the "collected botulinum neurotoxin in Jung." Petition, 32.

Petitioner's failure to establish that the "collected botulinum neurotoxin in Jung" is the macro complex (*see* § VI.A.2.a above) is fatal to Ground 1.

3. Petitioner Established No Non-Hindsight Reason Why a POSA Would Have Combined Jung and Ton in the Manner Alleged

Petitioner uses the '598 Patent as a template to reconstruct the claims in hindsight by combining disparate disclosures from Jung and Ton in a manner that is totally unsupported. As detailed below, Petitioner provides no evidence that the purified BoNTA provided by Jung needs further purification. In addition, Petitioner provides no evidence of what residual contaminants are in the BoNTA provided by Jung, or that they would be expected to be removed by adding Ton's binding-mode CEX chromatography. Even worse, Petitioner provides no evidence or explanation as to why a POSA would combine Ton's CEX chromatography step

with upstream acid precipitation (as required by the challenged claims) when Ton discourages using acid precipitation.

a. Petitioner Fails to Show That a POSA Would Have Deemed the Botulinum Toxin Purified by Jung as Needing Further Purification

Petitioner fails to support its contention that a POSA would have considered the BoNTA provided by Jung as requiring further purification. Petitioner relies on Ton's disclosure of providing "high purity, high yield botulinum neurotoxin" (Petition, 32, quoting EX1003, 24:38-41 and 24:47-49), and improperly relies in hindsight on the disclosure of the '598 Patent. (Petition, 32 n.15 (quoting EX1001, 10:20-22 (disclosing "Industrial Applicability" of purification method of isolating "with high purity" a "macro complex of [BoNTA] which is not dissociated")); *see also Vanguard Products Group v. InVue Security Products*, IPR2020-00014, Paper 8, at 19 (PTAB Apr. 1, 2020) (denying institution because petition was "based on impermissible hindsight reconstruction" that used challenged patent's improvement "as a guide to combine the teachings" of two prior art references). Petitioner's expert parrots this argument, (EX1021, ¶75), and asserts that it is "generally accepted" that a binding step is needed downstream of a flow-through chromatographic step, (*id*., ¶76) without identifying any need for further purifying the BoNTA provided by Jung.

But Jung discloses that its disclosed process already achieves "[BoNT] with high purity" (EX1002, 8:4), so that no additional steps are needed to achieve the "high purity" purportedly achieved by Ton. (*See South-Tek Sys v. Engineered Corrosion Sols*, 748 F. App'x 1003, 1007 (Fed. Cir. 2018) (affirming final written decision finding no motivation to combine because proposed combination would produce "redundant functions").) Moreover, adding an additional purification step contradicts Jung's goal of avoiding "multi-step chromatography" with its "labor and high investment costs, and the high risk" (*id*., 2:35-38) of manipulating "the most lethal natural biological agent known to man." *Id*., 2:9-10. Adding a redundant chromatography step also disserves Ton's goal of achieving "rapid" purification of BoNT, (EX1003, 6:52), in which unnecessary steps "have been eliminated" to "reduc[e] production time." *Id*., 45:51-46:3.

b. Petitioner Fails to Show That a POSA Would Have Added the Binding-Mode CEX Step of Ton Even If Further Purification Were Needed

Even if a POSA were motivated to further purify the BoNTA of Jung, Petitioner fails to support its contention that a POSA would have turned to the binding-mode CEX chromatography step of Ton to do so.

Jung and Ton use very different purification techniques. Jung uses acid precipitation and AEX in **flow-through** mode, whereas Ton disparages the use of

acid precipitation and identifies **binding-mode** AEX as an important aspect of its invention.

Ton uses binding-mode AEX chromatography, which removes ***positively***-charged impurities, and binding-mode CEX chromatography, which removes ***negatively***-charged impurities. Conversely, Jung uses flow-through AEX chromatography to remove ***negatively-charged*** impurities. Petitioner fails to explain why a POSA motivated to further purify Jung's output would not have added a chromatography technique to remove ***positively***-charged impurities to complement the chromatography technique Jung already uses, and would not have found Ton's CEX chromatography technique cumulative of that in Jung.

Petitioner provides no evidence of the identity of any contaminants in Jung's BoNTA, still less that Jung's purified preparation contains negatively-charged contaminants that would be removed by binding-mode CEX chromatography. Petitioner also fails to identify any instance in which the prior art purified BoNTA by using flow-through AEX chromatography at a pH below the pI of BoNTA, followed by CEX chromatography.

While Petitioner admits "Ton's failure to disclose [AEX] chromatography in flow-through mode" (Petition, 33), it disregards Ton's teaching that "[a]n important aspect" of its improved purification process "is the use of [binding-mode AEX] chromatography followed by the use of [CEX] (polishing) media

chromatography to purify botulinum neurotoxin ….” *Id*., 24:33-38. And yet Petitioner quotes the immediately following sentence, which states: “We found that use of [AEX] followed by use of [CEX] chromatography media provides an effective and rapid method for obtaining high purity, high yield botulinum neurotoxin.” *See* Petition, 32 (quoting EX1003, 24:38-41).

But Petitioner fails to explain why a POSA would have disregarded the teaching of Ton that ***binding-mode*** AEX chromatography is “an important aspect” of the disclosed process (EX1003, 24:33-35) and substituted in its place Jung’s ***flow-through*** AEX chromatography step. Indeed, after considering Ton-409, the Examiner withdrew the rejection (*id*., 497), finding persuasive Medytox’s arguments that: (i) Ton does not teach or suggest using “a pH lower than the PI of [BoNT]” and (ii) a POSA “would not have a reason to modify ‘… eluting the captured botulinum neurotoxin from the [AEX] medium to obtain a first eluate’ of Ton into ‘contacting a flow-through portion of the [BoNT]-containing solution, which is not bound to the [AEX] medium, with a [CEX] medium’ of claim 1(a).” *Id*., 486-487 (emphasis original).

c. Petitioner Ignores Teachings in Ton That Show a POSA Would Not Have Combined the CEX Step of Ton with an Upstream Acid Precipitation Step from Jung

In *Gilead Sciences v. Regents of the University of Minnesota*, the Board denied institution because the petitioner “fail[ed] to consider that the prior art as a

whole, including references Petitioner relie[d] on," taught that the proposed substitution would have undesirable consequences. IPR2017-01753, Paper 42, at 23 (PTAB Apr. 22, 2020). Here, Petitioner commits the same error by selectively citing portions of its references and failing to address the other portions that show a POSA would not have made the asserted combination. In doing so, Petitioner's proposed Ground 1 combination disregards teachings of Ton that would lead a POSA away from its combination with Jung.

Ton discourages the use of acid precipitation prior to chromatography – a step that is required by the challenged claims. Ton instead teaches using "depth filtration, followed by ultrafiltration and dilution" to remove cell debris and nucleic acids prior to chromatography, describing this technique as "fundamentally different" from prior art processes that "use[] precipitation by acidification…." EX1003, 30:63-31:3. Ton explains that "[t]he use of chromatography instead of precipitation and the reduced processing time resulted in ***a significantly improved, consistent downstream process***, as herein disclosed." *Id*., 33:55-58.

Ton identifies numerous problems caused by precipitation: "Unfortunately, previous precipitation techniques for purifying [BoNT] have the drawbacks of low resolution, low productivity, difficulty of operation, difficulty to control and/or validate and/or difficulty to scale-up or scale-down." *Id.*, 6:37-41. Ton touts "[r]eplacement of any precipitation steps with chromatographic steps to purify a

bulk [BoNT] complex, which improves the specificity of the purification process" as an advantage of its invention. *Id.*, 44:58-59; 45:19-21.

Neither Petitioner nor its expert acknowledge this aspect of Ton, let alone offer any explanation why a POSA would disregard those teachings by combining the CEX chromatography step of Ton with an acid precipitation step from Jung. This omission is even more remarkable given that Petitioner's expert is a named inventor of Ton.

Petitioner's failure to address the full scope of its own cited references undermines its argument that it would have been obvious to combine Jung with Ton as proposed. "[T]he prior art must be considered for all its teachings, not selectively." *Henny Penny v. Frymaster*, 938 F.3d 1324, 1332 (Fed. Cir. 2019) (affirming Board's finding of no motivation to combine because proposed combination would have added "complexity" and "decreased efficiency"). Institution should be denied for this additional reason. *Gilead*, IPR2017-01753, Paper 42, at 23.

d. Petitioner Relies on Hindsight, Using the '598 Patent as a Roadmap to Select and Combine Particular Steps from Jung and Ton in a Way That Disregards Ton's Teachings

Petitioner selected Jung not because it discloses isolating the BoNTA macro complex – it does not – but based on the text of the challenged claims and the

inventors' disclosure in the '598 Patent (but not in the prior art) that the claimed process yields the BoNTA macro complex.

Petitioner then selected Ton based on the recitation of binding-mode CEX chromatography in the challenged claims. Petitioner offers no explanation why, when combining Ton's downstream CEX step with Jung's upstream processing steps, a POSA would have ignored Ton's teaching that eliminating acid precipitation was fundamentally different from prior art processes that included this step. Nor does Petitioner explain why a POSA, combining Ton with Jung, would have disregarded Ton's teaching that an important aspect of its invention was the use of AEX in **binding** mode.

Petitioner's transparent use of the challenged claims as a blueprint for Ground 1 impermissibly relies on hindsight and *ex post facto* reasoning. The Supreme Court has "warn[ed] against a 'temptation to read into the prior art the teachings of the invention in issue' and instruct[ed] courts to 'guard against slipping into use of hindsight.'" *KSR Int'l v. Teleflex*, 550 U.S. 398, 421 (2007) (quoting *Graham v. John Deere*, 383 U.S. 1, 36 (1966)); *Metalcraft of Mayville v. The Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017) ("[W]e cannot allow hindsight bias to be the thread that stitches together prior art patches into something that is the claimed invention.").

Ground 1 fails for this reason alone.

4. Ground 1 Fails to Establish That the Proposed Jung/Ton Combination Would Reasonably Have Been Expected to Isolate the BoNTA Macro Complex

Not only does Petitioner fail to explain why a POSA would have disregarded Ton's express teachings to arrive at the proposed combination with Jung, but it also fails to establish that a POSA would reasonably have expected the proposed combination to isolate the BoNTA macro complex.

To establish obviousness, the Petition must demonstrate that a POSA would have had a reasonable expectation of successfully arriving at the challenged claims based on the cited references. *Procter & Gamble v. Teva Pharms.*, 566 F.3d 989, 996-997 (Fed. Cir. 2009). But Petitioner failed to show a reasonable expectation that the proposed combination of Jung and Ton would succeed in isolating the BoNTA macro complex.

As discussed in § VI.A.2 above, Petitioner makes no showing that Jung discloses isolating the macro complex, as distinct from a smaller form of BoNTA. Because a POSA would not have understood Jung to provide the macro complex, they would not have had a reasonable expectation of successfully obtaining it by adding a further purification step – binding-mode CEX chromatography as taught by Ton – after the process disclosed in Jung.

Petitioner's expert opines that "[a] POSA would have had a reasonable expectation of success in making [a combination of flow-through AEX

chromatography followed by binding-mode CEX chromatography]" and that such a combination provides an "effective and rapid method for obtaining **high purity, high yield botulinum neurotoxin**." EX1021, ¶77 (emphasis in original). But motivation to provide BoNTA in high purity and yield are inapposite absent a reasonable expectation of isolating the macro complex. Petitioner makes no showing that, if the process of Jung does not provide the macro complex but only a smaller form of BoNTA, a POSA would have had a reasonable expectation that adding a CEX chromatography step would provide the macro complex.

Accordingly, Petitioner fails to explain why a POSA would have had a reasonable expectation of isolating the BoNTA macro complex by adding the CEX chromatography step of Ton after the process of Jung.

B. Ground 2 (Kim-741, Kim-565 and Jung) Also Fails

1. Ground 2 Should Be Discretionarily Denied under 35 U.S.C. § 325(d)

The Board has discretion to deny institution. 37 C.F.R. § 42.108(b); *Harmonic*, 815 F.3d at 1367 ("the PTO is permitted, but never compelled, to institute an IPR proceeding.").

In determining whether to institute an *inter partes* review, "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the

Office." 35 U.S.C. § 325(d). In exercising this discretion, the Board uses a two-part framework:

> (1) whether the same or substantially the same art previously was presented to the Office **or** whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the claims.

Advanced Bionics v. MED-EL Elektromedizinische Geräte, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

With respect to Ground 2, the Board should discretionarily deny institution because the asserted combination relies on Kim-741 to teach a critical aspect of the challenged claims – performing AEX chromatography at a pH below the pI of BoNT – based on an argument that Kim-741's disclosure of a broad pH range extending above and below that pI is an "overlapping range" that rendered the claimed pH range presumptively obvious. Petition, 48-49. As explained in § I.B above, this Ground 2 argument parrots the Examiner's initial rejection and seeks to relitigate the issue addressed during prosecution of whether Kim-741 renders this claim limitation obvious.

But the Examiner withdrew his initial finding that Kim-741 renders obvious performing AEX chromatography at a pH below the pI of BoNT because Medytox

submitted evidence – a sworn declaration and data – that the Examiner found demonstrated the criticality of using the claimed pH range for efficiency of purification. *Supra* § III.B. Petitioner did no testing to rebut Medytox's experimental data and Petitioner's expert never disputes the criticality of using a pH below the pI of BoNT for efficiently achieving a high level of purification.

Instead, Petitioner and its expert obfuscate by alleging that using a pH below the pI of botulinum toxin was expected to cause the toxin to flow through an AEX column. Petition, 50-51, 65; EX1021, ¶¶113-114. That is simply irrelevant to the unexpected result of higher purification efficiency that the Examiner found rendered the claims unobvious. EX1006, 627.

As detailed in § III.B above, Kim-741 was cited, considered, extensively discussed in three Office Actions, overcome in prosecution, and appears on the face of the patent. *See* EX1006, 499-501 (applying Kim-741 to reject the claims); *id.*, 546-549 (discussing and applying Kim-741 to reject the claims); *id*., 586-590 (same); *id*., 626-627 (withdrawing rejections over Kim-741 in view of experimental evidence of criticality for efficiency of BoNT recovery).

Although Kim-565 and Jung were not of record, the Examiner's Reasons for Allowance do not identify as relevant to patentability the claim limitations that Petitioner contends are disclosed by Kim-565 and Jung. EX1006, 626-627. The Board has found that "substantially the same art was previously presented to the

Office" even where, as here, a petitioner's grounds included references not of record because the petitioner relied "primarily on" a reference that was also the primary reference during prosecution. *Lower Drug Prices for Consumers v. Forest Labs. Holdings*, IPR2016-00379, Paper 14 at 9 (PTAB July 1, 2016) (denying institution under § 325(d) where "[p]etitioner's obviousness challenge is based on (i) the same primary reference addressed during prosecution … and (ii) the same arguments regarding that primary reference and how it allegedly would have been modified.").

In addition, the disclosures for which Petitioner relies on Kim-565 and Jung in Ground 2 are cumulative of prior art considered and applied during prosecution. Petitioner relies on Kim-565 solely to satisfy the claim limitation of "culturing *Clostridium botulinum* in an [APF] medium to obtain a culture." Petition, 43-45. Ton-409, which was applied and overcome during prosecution, (EX1006, 329-330, 497), provides the same teaching. (EX2002, 9:36-38 (teaching "(a) providing a substantially APF fermentation medium; [and] (b) fermenting *Clostridium botulinum* bacteria in the fermentation medium").)

In Ground 2, Petitioner relies on Jung to satisfy the allegedly "trivial" step of "removing the cells from the culture prior to adding an acid to precipitate the toxin." Petition, 45. Ton-409 provides the same teaching. EX2002, 28:13-20 ("A filtrate of the culture medium can be prepared using a single layer depth filter **to**

remove gross impurities (*i.e.*, **whole and ruptured cells**) thereby obtaining a clear solution referred to as a clarified culture. Collection of botulinum neurotoxin **from clarified culture** was accomplished by lowering the pH of the clarified culture to pH 3.5 with 3M sulfuric acid to precipitate the raw toxin at 20°C (acidification precipitation).").

Thus, the art presented to the Office – and applied during prosecution – is substantially the same as the art Petitioner asserts in Ground 2.

Petitioner's failure to provide any evidence to rebut Medytox's experimental data showing superior efficiency in recovery of BoNTA macro complex at the recited pH range further supports discretionary denial. *See Apotex v. Celgene*, IPR2018-00685, Paper 8 at 25-26 (PTAB Sept. 27, 2018) (denying institution of certain grounds under 325(d) where petitioner relied on same primary reference overcome during prosecution with unexpected results evidence where petitioner's new secondary reference was "no more informative as to expected results than the references the Examiner relied on").

Because Petitioner's Ground 2 merely rehashes the same issue overcome by Medytox's data during prosecution without presenting any countervailing evidence, the Board should exercise its discretion and deny institution of Ground 2.

2. Ground 2 Fails Even If Considered on Its Merits

If the Board considers Ground 2 on its merits, it fails for each of the independently fatal reasons detailed in §§ (a)-(e) below.

First, Medytox's unexpected results evidence that the Examiner credited demonstrate nonobviousness over Petitioner's Ground 2 combination. Medytox's experimental data demonstrated that AEX chromatography at a pH below the pI of BoNTA (rather than the higher pH exemplified by Kim-741) provided unexpectedly superior "efficiency of botulinum toxin recovery." EX1006, 567. Petitioner does not attempt to rebut those data. Instead, Petitioner mischaracterizes the prosecution history to misrepresent what Medytox and the Examiner identified as the unexpected result.

Second, Petitioner fails to show that Kim-741 discloses "adding an acid to the botulinum-toxin containing solution" as required by the challenged claims.

Third, the portions of Kim-741 that Petitioner relies on fail to disclose "separating the [BoNTA] ***macro complex*** from the [CEX] chromatography medium." Kim-741 only obtained a smaller form of BoNTA (the 150 kDa toxin) from the CEX step, not the macro complex as required by the challenged claims.

Fourth, Petitioner's reliance on overlapping ranges as a motivation to modify Kim-741's pH range is unavailing because Petitioner fails to demonstrate

that pH was recognized as a result-effective variable for efficiency of BoNTA recovery.

Finally, Petitioner makes no showing that a POSA would reasonably have expected Petitioner's proposed modification of Kim-741's pH range to successfully isolate the BoNTA macro complex as claimed.

a. Petitioner Fails to Rebut Experimental Evidence of Unexpected Results, and Resorts to Mischaracterizing the Prosecution History

Petitioner relies on the same prior art reference (Kim-741) that the Examiner applied during prosecution and Medytox overcame with experimental evidence of unexpected results, as detailed in § III.B above. Petitioner submits no contrary data and never substantively addresses Medytox's data. Instead, Petitioner mischaracterizes the nature of the unexpected result that Medytox established, and which the Examiner accepted.

Specifically, Petitioner alleges – falsely – that Medytox identified the unexpected result as "that [AEX] 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 …." Petition, 51. Petitioner contends it was known that at a pH lower than the pI of BoNT, an AEX column operates in flow-through mode, not binding mode, and that this result was "entirely expected." *Id.* Medytox agrees. *See* § II *supra* (explaining flow-through versus binding mode). But that does not aid

Petitioner because it has nothing to do with the unexpected result that the Examiner found Medytox had established.

Medytox never alleged that the inventors discovered that BoNTA flows through (rather than binding to) an AEX column at a pH below its pI. This was well-known by the priority date, as the Examiner recognized in stating that "one of ordinary skill in the art of chromatography would find it obvious to perform [flow-through AEX] at a lower pH range to maximize the flow-through of [BoNTA] macro complex through the AEX resin." EX1006, 587. Rather, the "showing of criticality" that the Examiner found "persuasive" to overcome the rejection over Kim-741 was made by "comparing the relative ***efficiency of [BoNT] recovery*** from an [AEX] process between using a pH lower than the pI of [BoNT] and a pH higher than the pI of [BoNT]." EX1006, 627. The superior efficiency of the claimed AEX process was shown by the simplicity of the purification and the high purity of the macro complex in the output. EX1016, 568.

Unable to confront the **actual** unexpected results that Medytox's data established, Petitioner obfuscates by building up and knocking down a strawman. Petitioner's failure to address or refute Medytox's unexpected results is fatal to Ground 2.

i. Petitioner Mischaracterizes the Nature of Medytox's Unexpected Results – Efficiency of BoNTA Purification, Not Whether BoNTA Flows Through AEX Media

As discussed in § III.B above, the Examiner acknowledged the non-obviousness of the claims over Kim-741 and its disclosure of a pH range for an AEX process. The Examiner previously rejected the claims as obvious based on same disclosure in Kim-741 relied on by Petitioner. *Compare* EX1006, 546 (citing Kim-741, ¶[0085]) *with* Pet, 48-49 (citing Kim-741, ¶[0085]). The Examiner relied on the same rationale Petitioner now advances. *Compare* EX1006, 546 (Examiner asserting that "the taught pH ranges of 3-8 during AEX and CEX chromatography steps f and h [of Kim-741] overlap with the claimed ranges … and therefore, establishes cases of *prima facie* obviousness") *with* Petition, 49 (same).

In response, Medytox submitted a declaration by co-inventor Song comparing AEX at pH 5.5 (below the pI of botulinum toxin) with AEX at pH 6.5 (above that pI) "to compare **the relative efficiency of botulinum toxin recovery**." EX1006, 567; *id*., 570, ¶4. The data showed that at pH 5.5 the BoNTA macro complex was obtained "immediately after loading the sample," indicating that it was "contained in the flow through solution with a purity of 91.98%." *Id*., 567-68. By contrast, a pH of 6.5 resulted in a purity of "about 30% to 88%," with the macro complex "not purified but distributed to … all the fractions [of the eluted material]." *Id*., 568. Based on these results, Medytox argued that "**when pH 5.5 is**

used, [the macro complex] can be simply purified from the flow through solution with high purity and there is no need to add an additional eluting step. **This is an unexpected benefit of the claimed invention**." EX1006, 568. Thus, the unexpected result was a simple purification process that achieves high purity, enabling the macro complex to be "efficiently isolated from the botulinum toxin-containing solution." EX1001, 6:59-60; *see* EX1003, 6:52-56 (identifying need for "rapid" processes that provide "high purity" botulinum toxin).

In allowing the claims over Kim-741, the Examiner stated:

> Applicant has also provided a declaration by co-inventor SONG (22 July 2021) comparing **the relative efficiency of [BoNT] recovery** from an [AEX] process using a pH lower than the pI of [BoNT] and a pH higher than the pI of [BoNT], thereby showing the criticality of such a claimed limitation. This showing of criticality was persuasive to overcome the [§ 103] rejection of Claim 1 as being unpatentable over [Kim-741].

EX1006, 627 (Reasons for Allowance).

Having no evidence to rebut this conclusion by the Examiner, Petitioner falsely portrays Medytox as representing during prosecution that it was unexpected that "'a pH lower than the pI of botulinum toxin' (e.g., a pH of 5.5) results in the toxin flowing through the matrix …." Petition, 51; *see also id*., 65 ("That the botulinum toxin flowed through the anion exchange chromatography column at pH 5.5 would have been entirely expected."). Petitioner's selective quote from

Medytox's Office Action Response misleadingly changes the meaning of what was argued. Petitioner mischaracterizes the nature of the "unexpected result" by cropping Medytox's statement ***to ellipsis out the key unexpected advantage*** provided by the claimed method. The full quote cropped by Petitioner (Petition, 50) is shown below, with the portion selectively quoted in underline:

> The Declaration states that "[a]s shown in Table I, the ***purity*** of [BoNT] fraction no. 3, i.e., the flow through solution was 91.98%, which ***is significantly higher*** than the control sample purity, 74.09%." The Declaration also states that "[a]s shown in Table 2, the ***purity*** of [BoNT] fraction no. 1, 3, 5, and 7, i.e., the eluted solution was about 30% to 88%. Even in the eluted solution, [macro complex] is not purified but distributed to the all the fractions." These results from using pH 5.5 and pH 6.5 show that [macro complex] can be purified from the flow through solution when pH 5.5 is used but at pH 6.5, [macro complex] was not present in the flow through solution but was present in the eluted solution, distributed in a wide retention time. In this regard, ***when pH 5.5 is used, [macro complex] can be simply purified from the flow through solution with high purity and there is no need to add an additional eluting step***. ***This*** is an unexpected benefit of the claimed invention.

EX1006, 568 (7-22-2021 Response, 10).

Worse yet, Petitioner relies on its mischaracterization of Medytox's evidence to contend (1) Mr. Song was "highly disingenuous" (Petition, 50) and

(2) the Examiner "erred in a manner that was material to patentability." *Id*., 66. Petitioner mischaracterizes the record.

The prosecution history refutes Petitioner's assertion that the Examiner found it unexpected that BoNTA flows through AEX media at a pH below its pI. In initially responding to the Song Declaration, the Examiner stated this basic principle of ion exchange chromatography:

> **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 [CEX] resin **and will not bind to the positively charged functional groups of an [AEX] resin**.

EX1006, 586-87.

Moreover, Medytox never argued it was unexpected "[t]hat the [BoNT] flowed through the [AEX] chromatography column at pH 5.5" as Petitioner falsely contends. Petition, 65; *see also id.*, 50-51.

The Examiner allowed the claims because he found the Song Declaration established that using the lower pH for AEX unexpectedly improved the "efficiency of [BoNT] recovery" (EX1016, 627) by providing the macro complex with high purity from a single flow-through fraction, whereas the higher pH provided the macro complex at lower purity in the eluted solution, distributed amongst multiple fractions. *Id*., 568. The Examiner specifically identified "relative efficiency of [BoNT] recovery" in finding that Medytox's evidence

"show[ed] the criticality of such a claimed [pH] limitation." EX1006, 627 (Reasons for Allowance). Petitioner never attempts to refute that ***this*** result was unexpected.

ii. Petitioner Cannot Show the Absence of Unexpected Results by Ignoring the Evidence and Attacking a Strawman

Petitioner instead focuses on its mischaracterization of Medytox's unexpected results, arguing that "the claimed pH range cannot be critical to practicing the claimed method if flow-through [AEX] chromatography can be achieved with a pH higher than the pI of botulinum toxin." Petition, 53. As detailed above, the Examiner found unexpected the superior efficiency of BoNT recovery at a pH less than the pI, not (as Petitioner contends) "[t]hat the [BoNT] flowed through the [AEX] chromatography column at pH 5.5." Petition, 65.

Thus, Petitioner's argument that Example 2-3-1 in "Kim-741 successfully conducted [AEX] chromatography in flow-through mode at a pH higher than the pI of botulinum toxin" (Petition, 52-53) is irrelevant. Kim-741 does not report any quantitative recovery data in Example 2-3-1 (EX1004, ¶¶[0102]-[0108]), much less compare the "relative efficiency" of BoNTA macro complex recovery at pHs above and below its pI.

Petitioner's focus on a strawman (*i.e.*, ensuring flow-through of BoNTA) warps its interpretation of Kim-741 and *Hospira v. Genentech,* IPR2016-01837,

Paper 40 at 24 (PTAB Mar. 6, 2018). Petitioner observes that Kim-741 "successfully conducted [AEX] chromatography in flow-through mode at a pH higher than the pI of botulinum toxin" (Petition, 52-53), *i.e.*, 6.4-6.6, and cites *Hospira* to support its conclusion that the claimed pH cannot be critical "if flow-through [AEX] chromatography can be achieved with a pH higher than the pI of botulinum toxin. " (Petition, 53). But in *Hospira*, the claimed range was found not to be "critical to practicing the alleged invention" because "the sole alleged benefit is also achieved below the range." IPR2016-01837, Paper 40 at 24. Unlike *Hospira*, here there is no evidence that Kim-741's AEX chromatography at a pH of 6.4-6.6 achieved the key and unexpected benefit of improving the efficiency of BoNTA recovery. Petitioner's focus on the fact that Kim-741 allegedly achieved flow-through at a pH above BoNTA's pI is legally irrelevant to the obviousness inquiry because it is not the unexpected result demonstrated during prosecution and accepted by the Examiner.

Federal Circuit cases cited by Petitioner are inapposite because there the patent owners failed to demonstrate unexpected results. Petition, 54 (citing *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341-42 (Fed. Cir. 2020) and *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012)). In *Genentech*, the patent owner did not dispute that it had "failed to establish criticality for the claimed temperature range." 946 F.3d at 1341. In *Applied Materials*, the patent

owner did not offer any evidence of unexpected results. 692 F.3d at 1297. Here, by contrast, the Examiner allowed the claims based on Medytox's evidence of unexpected results, finding that they demonstrated criticality. EX1006, 627.

"Objective indicia can be the most probative evidence of nonobviousness in the record, and … are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (reversing obviousness determination where Board disregarded test data). Petitioner never confronted the unexpected result the Examiner relied on and offered no contrary evidence of its own.

iii. The Board Routinely Denies Institution Where – As Here – The Petition Fails to Persuasively Address Objective Evidence of Nonobviousness Relied on by the Examiner

Petitioner never substantively addresses Medytox's evidence of unexpected results regarding "the relative efficiency of [BoNT] recovery" at a pH less than the pI of BoNTA, leaving these objective indicia unrebutted. EX1006, 627. In similar circumstances, the Board routinely denies institution because a petitioner cannot carry its burden at institution to demonstrate a reasonable likelihood of prevailing when it fails to persuasively address objective evidence of non-obviousness relied on by the Examiner.

In *Gilead Sciences, Inc. v. United States of America*, IPR2019-01454, Paper 15 at 36 (PTAB Feb. 20, 2020), the Board denied institution where the Petition failed to address evidence of unexpected results the Examiner relied on because "Petitioner's failure to persuasively address the results in its Petition means Petitioner falls short of its burden to establish a reasonable likelihood of success in prevailing on its challenge."

Similarly, in *CFAD* the Board denied institution because there were "unrebutted objective indicia of nonobviousness presented in the prosecution history of the [challenged] patent" that were "relied upon by the Examiner" and not meaningfully addressed in the Petition. IPR2015-01792, Paper 14 at 18 (Petitioner "should have addressed the evidence of unexpected results as part of Petitioner's showing of a reasonable likelihood of success on the merits.").

Because Petitioner "failed to grapple persuasively with well-developed evidence of unexpected results presented during the prosecution of the [challenged] patent," it failed to meet its burden for Ground 2 of demonstrating a reasonable likelihood of prevailing. *Gilead*, IPR2019-01454, Paper 15 at 32; *see also CFAD*, IPR2015-01792, Paper 14 at 18. Ground 2 fails for this reason alone.

b. Petitioner Fails to Establish That Kim-741 Discloses Adding an Acid to the Botulinum Toxin-Containing Solution

Petitioner fails to establish that Kim-741 discloses "adding an acid to the botulinum-toxin containing solution" as required by the challenged claims.

Petitioner relies on Kim-741's disclosure of "treating **a culture** of botulinum toxin-producing strain with acid to form a botulinum toxin-containing precipitate". Petition, 46 (citing EX1008, ¶[42]). Petitioner contends that the "solution" may be a "culture of Clostridium botulinum **or** a solution derived therefrom." Petition, 46 (quoting EX1001, 3:27-30). Petitioner's expert parrots the same argument without citing additional evidence or providing additional analysis. EX1021, ¶106. This conclusory testimony is entitled to no weight. *Xerox Corp.*, IPR2022-00624, Paper 9, at 15; *Harmonic*,815 F.3d at 1363.

Although the '598 Patent specification describes two alternatives for the acid precipitation, the claims require adding acid to **a solution obtained by removing bacterial cells from a culture**, as the claim language clearly specifies:

> [a] removing *Clostridium botulinum* cells from the culture **to obtain a botulinum toxin-containing solution**;
>
> [b] adding an acid to ***the*** **botulinum toxin-containing solution** to precipitate the botulinum toxin and obtain a precipitate; ….

EX1001, 10:30-34. Kim-741 fails to meet limitation [b] because it discloses adding an acid to "a culture of [*Clostridium botulinum*]," (EX1008, ¶[42]), not

adding acid to a solution obtained by removing the bacterial cells. This is fatal to Ground 2.

Tacitly acknowledging this deficiency, Petitioner asserts in a footnote that "[this limitation] is disclosed in Jung." Petition, 47 n.22. The footnote cannot fill this gap. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1383 (Fed. Cir. 2015) ("Arguments raised only in footnotes ... are waived."). Even if the footnote is considered, merely identifying this limitation in Jung is unavailing. It is a claim "as a whole" that must be proven obvious, not a single limitation. *Gillette v. S.C. Johnson & Son*, 919 F.2d 720, 723-24 (Fed. Cir. 1990) ("Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.").]

c. The Portions of Kim-741 That Ground 2 Relies on Do Not Disclose the Claimed Step of "Separating" the BoNTA Macro Complex

Ground 2 relies on Kim-741, ¶¶[0087], [0117]-[0122] to satisfy the claim limitation of "separating the [BoNTA] macro complex from the [CEX] chromatography medium." Petition, 57. But the cited portions of Kim-741 include no such disclosure.

Under its own construction of "botulinum toxin type A macro complex," Petitioner needed to show that Kim-741 discloses separating "a botulinum toxin type

A of 900 kDa." Petition, 17-18. But Ground 2 makes no such showing. Indeed, Kim-741 is explicit that the passages relied upon by Petitioner describe separating a smaller form of BoNT – "molecular weight: 150 kDa" – from the CEX medium. Kim-741, ¶¶[0087], [0125]. That is fatal to Ground 2.

i. Kim-741, ¶[0087] Does Not Disclose Separating the Macro Complex

The language Petitioner quotes from Kim-741, ¶[0087] only refers to "collec[ting] a fraction containing the **botulinum toxin** bound to the [CEX] chromatography resin." Petition, 57 (quoting EX1004, ¶[0087]) (original emphasis deleted). As discussed in § VI.A.2.a.i above, BoNT occurs in numerous forms other than the macro complex, so a generic disclosure of collecting BoNT does not disclose collecting the macro complex.

Worse yet, Kim-741, ¶[0087] reveals that macro complex was not recovered from the CEX column, but only the smaller 150 kDa BoNTA protein. Petitioner attempts to hide the ball by misleadingly truncating a sentence from this passage. Petition, 57. The complete sentence (with removed text in bold) reads:

> In the [CEX] chromatography of step (h), the botulinum toxin may be collected as a fraction containing the botulinum toxin bound to the [CEX] chromatography resin**, and the finally purified botulinum toxin may have a form of 7S (molecular weight: 150 kDa)**.

EX1004, ¶[0087].

ii. Kim-741, ¶¶[0117]-]0122] Relate to Collecting the Smaller 150 kDa Toxin, Not the Macro Complex

Petitioner also relies on Kim-741, ¶¶[0117]-[0122] to satisfy the claim limitation of "separating the [BoNTA] macro complex from the [CEX] chromatography medium." Petition, 57. These paragraphs partially describe Example 2-3-3, the results of which are presented in a paragraph – not cited by Petitioner – that states:

> As a result, it was shown that the botulinum toxin could be produced with high purity and that **the final botulinum toxin had a form of 7S (molecular weight: 150 kDa**).

Id., ¶[0125].

"***The petition*** must specify where each element of the claim is found in the prior art patents or printed publications relied upon." 37 C.F.R. § 42.104(b)(4). The Petition alleges that Kim-741 discloses separating the macro complex but its citations to Kim-741 nowhere support that assertion. Indeed, Kim-741 demonstrates that it includes no such disclosure. "Petitioner fails, accordingly, to meet its burden for instituting *inter partes* review on the basis of" Kim-741. *NanoCellect Biomedical, Inc. v. Cytonome/ST, LLC*, IPR2020-00548, Paper 15 at 22 (PTAB Sept. 1, 2020) (denying institution because petition's obviousness-based grounds failed to establish prior art disclosed claimed limitation). Ground 2 fails for this additional independent reason.

iii. Citation to Petitioner's Expert Declaration Cannot Save Ground 2

Petitioner also cites ¶122 of its expert's declaration to support the disclosure of this limitation in Kim-741. Petition, 57 (citing EX1021, ¶122). But this paragraph cites the same portions of Kim-741 as the Petition and suffers the same fatal flaw.

In a footnote to EX1021, ¶122 that is nowhere referenced in the Petition, Petitioner's expert makes an additional confusing argument. This argument cannot be incorporated by reference into the Petition so it should not be considered. 37 C.F.R. § 42.6(a)(3); *Cisco Sys. v. C-Cation Techs.*, IPR2014-00454, Paper 12 at 10 (PTAB Aug. 29, 2014) ("It is improper to incorporate by reference arguments from one document into another document. 37 C.F.R. § 42.6(a)(3) .... [W]e will not consider arguments that are not made in the Petition, but are instead incorporated by reference to the cited paragraphs… of [the expert's] Declaration.").

Even if considered, the argument found only in the expert declaration fails. Petitioner's expert argues (without citing any evidence) that "[a] POSA would understand that at a pH of 6.9-7.1, the toxin complex breaks down into the individual components … [b]ut at a pH below the pI of [BoNT] … a POSA would have expected [BoNTA] to be present as a complex, e.g., 900 kDa." EX1021, ¶122 n.12. Because this testimony states a naked conclusion without any supporting evidence it is entitled to no weight. 37 C.F.R. § 42.65(a) ("Expert

testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *Cradlepoint, Inc. v. Sisvel International SA*, IPR2020-01069, Paper 11 at 19 (PTAB Jan. 12, 2021) (denying institution and giving "little to no weight" to expert testimony regarding a POSA's understanding of prior art because unsupported by evidence).

Even if Petitioner's expert had cited evidence to establish that the macro complex would have been present at a lower pH, this footnote argument still fails. The expert alleges that "this knowledge would be yet an additional motivation for the POSA to conduct anion and cation exchange chromatography at a lower pH, e.g., below the pI of botulinum toxin." EX1021, ¶122 n.12. Thus, the expert nakedly alleges that a POSA would have been motivated to use a lower pH so that the macro complex would be present, but fails to identify (let alone establish) any reason ***why*** a POSA would have sought to ensure that the macro complex was present in the first place. The only rationale for this "motivation" was an improper attempt to reconstruct the claims in hindsight. *Catalent Pharma Solutions, Inc. v. Patheon Softgels Inc.*, IPR2018-00421, Paper 9 at 12-15 (PTAB Aug. 13, 2018) (denying institution where petitioner failed to explain ***why*** a POSA "would modify the teachings of [the prior art] to produce the claimed invention": "Given the unexplained 'picking-and-choosing' activity in Petitioner's analysis, we are

persuaded that Petitioner and its expert have impermissibly relied on hindsight ….").

The footnote in Petitioner's expert declaration also fails to explain how or why "Kim-741 discloses 'separating the [BoNTA] macro complex from the [CEX] chromatography medium'" as asserted by Petitioner and the cited paragraph of its expert's declaration. *See* Petition, 57; EX1021, ¶122. Neither the Petition nor the cited expert testimony identifies any disclosure in Kim-741 of separating the BoNTA macro complex from the CEX medium – indeed, there is none.

d. Petitioner's Reliance on Overlapping Ranges Fails Because It Did Not Show that pH Was Recognized as a Result-Effective Variable That Affects BoNTA Recovery

Petitioner relies on Kim-741's disclosure of a pH range for the AEX step that overlaps with the range recited in the claims, stating that "overlapping ranges create a presumption of obviousness." Petition, 49 (citing *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018)).

As *Dupont* explains, a presumption of obviousness arising from overlapping ranges can be rebutted in at least two ways relevant to Petitioner's challenge. First, nonobviousness is demonstrated if the patentee shows the claimed range is "critical" in that it produces a new and unexpected result. *Dupont*, 904 F.3d at 1006. Medytox satisfied this test with the Song Declaration, as discussed in §§ III.B and VI.B.2.a above. Second, an overlapping range will not render claims

obvious "if the parameter was not recognized as result-effective." *Id*. Here, Petitioner has failed to make any showing as to this second issue.

In particular, to prevail on a theory of obviousness based on overlapping pH ranges, Petitioner must show that pH was recognized as a variable that affects ***the property relevant to the unexpected result*** demonstrated by Medytox: ***BoNTA recovery***. *Id.*, 904 F.3d at 1009 ("[I]f the prior art does recognize that the variable affects ***the relevant property or result***, then the variable is result-effective."). Given the absence of any such showing, Petitioner's reliance on overlapping ranges fails.

As discussed in § VI.B.2.a above, Petitioner's obviousness argument focuses on the wrong result – "ensur[ing] that the toxin flowed through the matrix." Petition, 54. That was not the unexpected result demonstrated by Medytox, and was not the reason the Examiner allowed the application. The relevant result is efficiency of BoNTA macro complex recovery. Petitioner does not contend – and provides absolutely no evidence to prove – that pH was known to affect efficiency of BoNTA macro complex recovery from an AEX medium. Its obviousness theory therefore cannot succeed.

The Board applied *DuPont* to similar facts in *Ex Parte Blak*, and vacated the Examiner's obviousness rejection of claims directed to methods of culturing stem cells at a particular osmolality range to differentiate them into progenitor cells.

Appeal No. 2019-006661, 2020 WL 4200052, at *7 (PTAB July 14, 2020). There, the Examiner contended that the claims were obvious because the prior art taught "an osmolality range that encompasses the claimed range," and "provided reasons to optimize osmolality for ***cell growth***." *Id*. But the applicant's evidence showed that the claimed osmolality range was critical to a different result – "a dramatic increase [in differentiation] as compared to higher osmolalities" – and that osmolality was not known to affect differentiation. *Id*., at *6. Applying *DuPont*, the Board vacated the rejection because the Examiner failed to prove that the prior art "recognize[d] that osmolality (the claimed parameter) affects ***differentiation*** (the claimed result)." *Id*., at *7 (citing *DuPont*).

Here, as in *Blak*, Petitioner relies on evidence that the variable (pH) was known to affect a different result (whether toxin flows through a matrix) but offers no proof that pH was known to affect the relevant unexpected result: efficiency of BoNTA recovery. For this reason alone, Petitioner's reliance on overlapping ranges fails.

e. Petitioner Fails to Address the Full Scope of Kim-741's Teachings, Which Prevent it from Demonstrating a Reasonable Expectation of Isolating the BoNTA Macro Complex

Petitioner's argument that Kim-741's disclosure of "pH ranges that overlap with the claimed pH range" establishes a reasonable expectation of success (Petition, 54) in isolating the macro complex using AEX and CEX chromatography

fails because it is unsupported by Kim-741 and ignores Kim-741's teachings to the contrary. This is fatal to Ground 2. *Gilead*, IPR2017-01753, Paper 42 at 23 (denying institution where Petitioner "fails to consider … the prior art as a whole").

Kim-741's four working examples show that it never isolated the BoNTA macro complex using AEX chromatography followed by CEX chromatography. As Kim-741 explains, use of AEX chromatography alone provided the 900 kDa macro complex contaminated by "an impurity protein band of about 13 kDa" (*id*., ¶[0141]) or "about 37 kDa." *Id*., ¶[0142]. To remove these impurities, Kim-741 added further chromatography steps that resulted in highly purified BoNT "**after dissociation of toxin complex** for purification of **the low-molecular-weight [BoNT**]." *Id*., ¶[0143]. Kim-741 accordingly discloses that an AEX step followed by additional chromatography steps failed to produce the macro complex as required by the challenged claims.

This is demonstrated in the table below, which shows that only the first working example – Example 2-3-1: AEX in flow-through (FT) mode – produced the macro complex, and this example only removed "most major impurities." EX1004, ¶[0108]. Kim-741 included additional chromatography steps after the AEX column to improve purity, but those other examples (Examples 2-3-2, 2-3-3,

and 2-3-4) only obtained the 150 kDa toxin protein – ***not*** the 900 kDa macro complex.

Kim-741 Example	**Chromatography Steps**			**BoNTA form**
	First ("TQ")	**Second ("HQ")**	**Third ("XS")**	
Ex. 2-3-1 ¶¶[0102]-[0108]	AEX FT (pH 6.4-6.6)			900 kDa
Ex. 2-3-2 ¶¶[0110]-[0116]	AEX FT (pH 6.4-6.6)	AEX binding (pH 7.7-7.9)		150 kDa
Ex. 2-3-3 ¶¶[0117]-[0125]	AEX FT (pH 6.4-6.6)	AEX binding (pH 7.7-7.9)	CEX binding (pH 6.9-7.1)	150 kDa
Ex. 2-3-4 ¶¶[0126]-[0139]	AEX FT (pH 6.4-6.6)	AEX FT (pH 7.7-7.9)	CEX binding (pH 6.9-7.1)	150 kDa

But Petitioner ignores Kim-741's teachings about either obtaining the BoNTA macro form (with contaminants) or obtaining highly-purified BoNTA (but as a smaller form) after successive AEX and CEX chromatography. Nor does it even attempt to explain why a POSA would have been motivated to reduce Kim-741's disclosed pH range of 3-8 to the claimed range (*i.e.*, a pH of 6.06 or lower) or why they would have had a reasonable expectation of successfully obtaining the macro complex by doing so.

Petitioner also ignores Kim-741's teaching that the macro complex was isolated at a pH of above 6.06: Example 2-3-1 purportedly achieved that at a pH of 6.4-6.6. EX1004, ¶¶[0102]-[0108]. Thus, Kim-741 does not teach that a pH below 6.06 is needed to isolate the macro complex, but precisely the opposite. Instead, Kim-741 teaches that it was only able to isolate the macro complex using a single

AEX chromatography step, because every example in Kim-741 that included additional chromatography steps failed to isolate the macro complex. Nothing in Kim-741 suggests that lowering the pH over the course of multiple chromatography steps would reasonably have been expected to isolate the macro complex. The Petition wholly failed to establish a reasonable expectation of success for its Ground 2 combination, which fails for this additional independent reason.

VII. CONCLUSION

For the foregoing reasons, Petitioner has failed to establish a reasonable likelihood of prevailing in demonstrating any claim of the '598 Patent unpatentable. Medytox respectfully requests that the Board deny institution.

Respectfully submitted,
Medytox Inc.

Date: May 30, 2023

/Jonathan Ben-Ur Roses/
Jonathan B. Roses, Reg. No. 61,115
WOLF, GREENFIELD & SACKS, P.C.

11448354

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the foregoing **PATENT OWNER'S PRELIMINARY RESPONSE** contains 13,984 words excluding; a table of contents, a table of authorities, Mandatory Notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing. Patent Owner has relied on the word count feature of the word processing system used to create this paper in making this certification.

Date: May 30, 2023

/Jenni Hibbard/
Jenni Hibbard
Paralegal
WOLF, GREENFIELD & SACKS, P.C.

CERTIFICATE OF SERVICE UNDER 37 C.F.R. § 42.6 (e)(4)

I certify that on May 30, 2023, I will cause a copy of the foregoing document, including any exhibits filed therewith, to be served via electronic mail, as previously consented to by Petitioner, upon the following:

Dion M. Bregman	Dion.bregman@morganlewis.com
Guylaine Hache	Guylaine.hache@morganlewis.com
Charles H. Rexer Jr.	Charles.rexer@morganlewis.com

Date: May 30, 2023

/Jenni Hibbard/
Jenni Hibbard
Paralegal
WOLF, GREENFIELD & SACKS, P.C.