

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HUGEL, INC.,
Petitioner,

v.

MEDYTOX INC.
Patent Owner.

IPR2023-00604
Patent 11,331,598 B2

Before JO-ANNE M. KOKOSKI, KRISTINA M. KALAN, and
JEFFREY W. ABRAHAM, *Administrative Patent Judges*.

KOKOSKI, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Hugel, Inc. (“Petitioner”) filed a Petition to institute an *inter partes* review of claims 1–9 (the “challenged claims”) of U.S. Patent No. 11,331,598 B2 (“the ’598 patent,” Ex. 1001). Paper 2 (“Pet.”). Medytox Inc. (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

Institution of an *inter partes* review is authorized by statute when “the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314 (2018); *see also* 37 C.F.R. § 42.4 (2022). For the reasons discussed below, we deny the Petition and do not institute an *inter partes* review.

A. *Real Parties in Interest*

Each party identifies itself as the real party in interest. Pet. 4; Paper 10, 1 (Patent Owner’s First Updated Mandatory Notice).

B. *Related Matters*

Petitioner states that “[t]he ’598 patent is not currently the subject of any litigation or post-grant proceedings.” Pet. 4.

C. *The ’598 Patent*

The ’598 patent relates to methods of isolating botulinum toxin from a botulinum toxin-containing solution. Ex. 1001, 1:15–16. The ’598 patent explains that “[t]he genus *Clostridium* includes more than 127 species,” including *Clostridium botulinum*, “an anaerobic and Gram-positive bacterium which produces a strong polypeptide neurotoxin that causes a neuromuscular illness, known as botulism, in humans and animals.” *Id.* at 1:25–30. Botulinum toxin is divided into seven types, identified as types A–G, each of which “includes about 150 kDa of toxin protein, and naturally

is composed of a complex with a variety of non-toxic proteins bound thereto.” *Id.* at 1:35–39. According to the ’598 patent, “[a]n intermediate complex (300 kDa) is composed of a toxin protein and a non-toxic non-hemagglutinin (HA) protein, and a large complex (500 kDa) and a macro complex (900 kDa), each have a structure in which the intermediate complex is bound to hemagglutinin.” *Id.* at 1:39–43.

The ’598 patent explains that one problem previous methods of isolating botulinum toxin from a culture of *Clostridium botulinum* encountered was “that during purification of the botulinum toxin 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 botulinum toxin protein.” Ex. 1001, 2:40–45. The ’598 patent solves this problem by providing a method of isolating a botulinum toxin type A (“BoNTA”) macro complex from a botulinum toxin-containing solution that includes

contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than the isoelectric point (PI) of botulinum toxin; contacting the solution, which is not bound to the anion exchange chromatography medium, with a cation exchange chromatography medium at a pH lower than the PI of botulinum toxin; and separating the botulinum toxin type A macro complex from the cation exchange chromatography medium.

Id. at 2:57–67. Alternatively, the ’598 patent teaches first contacting the botulinum toxin-containing solution with the cation exchange (“CEX”) chromatography medium, separating the botulinum toxin from the cation exchange chromatography medium, and then contacting the solution containing the toxin separated from the cation exchange medium with the anion exchange (“AEX”) chromatography medium. *Id.* at 3:1–10.

D. Challenged Claims

Petitioner challenges claims 1–9 of the '598 patent. Pet. 1, 3–4. Claim 1, the only independent claim, is illustrative of the claimed subject matter and reproduced below.

1. 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.

Ex. 1001, 10:25–63.

E. Prior Art and Asserted Grounds

Petitioner asserts that claims 1–9 would have been unpatentable based on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–9	103 ¹	Jung, ² Ton ³
1–9	103	Kim '741, ⁴ Kim '565, ⁵ Jung

Pet. 3–4. Petitioner also relies on the Declaration of Ronald C. Bates, Ph.D. (“Bates Declaration,” Ex. 1021). *Id.* at 1.

II. ANALYSIS

A. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art (“POSA”) would have had “at least a graduate degree, such as a masters or Ph.D., in a relevant discipline such as biochemistry, process chemistry, protein chemistry, chemical engineering and/or biochemical engineering, among others, with at least four years of experience in those areas after receiving

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), revised 35 U.S.C. §§ 102 and 103 effective March 16, 2013. Petitioner argues, and Patent Owner does not contest, that the post-AIA statutory provisions apply. Pet. 19 n.6. Accordingly, we apply the post-AIA versions of §§ 102 and 103.

² Jung, US 8,993,268 B2, issued Mar. 31, 2015 (Ex. 1002).

³ Ton, US 8,932,827 B2, issued Jan. 13, 2015 (Ex. 1003).

⁴ Kim, US 2018/0251741 A1, published Sep. 6, 2018 (Ex. 1004).

⁵ Kim, WO 2016/175565 A1, published Nov. 3, 2016 (Ex. 1023).

the graduate degree.” Pet. 17 (citing Ex. 1021 ¶ 22). Patent Owner states that, for purposes of its Preliminary Response, it does not challenge Petitioner’s proposed definition of a POSA. Prelim. Resp. 20.

For purposes of this Decision, and based on the current record, we adopt the uncontested assessment offered by Petitioner.

B. Claim Construction

We construe each claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b). Under this standard, claim terms are generally given their plain and ordinary meaning as would have been understood by a person of ordinary skill in the art at the time of the invention and in the context of the entire patent disclosure. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). Only those terms in controversy need to be construed, and only to the extent necessary to resolve the controversy. *Realtime Data LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019).

Petitioner proposes that the term “botulinum toxin type A macro complex” in claim 1 “should be construed to include a botulinum toxin type A of 900 kDa.” Pet. 17–18 (citing Ex. 1001, 6:56–60 (“botulinum toxin type A macro complex, *i.e.*, 900 kDa may be efficiently isolated from the botulinum toxin containing solution”); Ex. 1006,⁶ 626; Ex. 1021 ¶ 44) (emphases omitted). Petitioner also proposes that the term “at a pH lower than the PI of botulinum toxin” in claim 1 “should be construed to mean a pH lower than 6.06.” *Id.* at 18 (citing Ex. 1001, 4:16–23 (“An isoelectric

⁶ We refer to the page numbers added by Petitioner to the bottom left-hand corner of the page.

point of botulinum toxin A may be about 6.06.”); Ex. 1006, 626; Ex. 1021 ¶ 45) (emphases omitted). Patent Owner asserts that, for purposes of its Preliminary Response, it does not challenge Petitioner’s proposed constructions “because the Petition fails even under Petitioner’s proposed constructions.” Prelim. Resp. 20.

For purposes of this Decision, and based on the current record, we apply Petitioner’s proposed constructions of “botulinum toxin type A macro complex” and “a pH lower than the PI of botulinum toxin,” which are undisputed at this stage of the proceeding.

C. Asserted Obviousness over Jung and Ton

Petitioner contends that claims 1–9 would have been obvious over the combined teachings of Jung and Ton. Pet. 21–42.

1. Jung

Jung “relates to a method of producing *Clostridium botulinum* toxin using a media containing plant-derived components and a flexible closed container.” Ex. 1002, 1:23–25. Jung’s method includes “culturing *Clostridium botulinum* in a media containing plant-derived components to express *Clostridium botulinum* toxin outside a cell” and “removing the cell from the obtained culture to obtain a portion including *Clostridium botulinum* toxin expressed outside the cell and isolating the *Clostridium botulinum* toxin from the portion.” *Id.* at 2:66–3:6. Jung explains:

The expression “express *Clostridium botulinum* toxin outside the cell” indicates that after the cell produces the toxin therein, not only does the cell transport the toxin outside the cell spontaneously, but the cell containing the toxin expressed in the cell is also lysed whereby the toxin is exposed in a solution of the culture, not in the cell of the culture.

Id. at 3:13–19. Jung teaches the botulinum toxin can then be isolated “using a conventional method in which a toxin included in a solution is isolated,” such as by adding an acid to the obtained culture to precipitate *Clostridium botulinum* toxin, dissolving the isolated precipitate and ultra-filtering the resulting solution, and performing anion exchange chromatography on the ultra-filtered solution. Ex. 1002, 4:33–48. According to Jung, because the *Clostridium botulinum* toxin is expressed outside the cell, “*Clostridium botulinum* toxin can be purified and produced easily and very simply.” *Id.* at 7:54–57.

2. Ton

Ton “relates to a rapid, animal protein free, chromatographic process and system for obtaining a high potency, high purity, and high yield biologically active botulinum neurotoxin.” Ex. 1003, 1:19–23. Ton teaches that such a highly potent botulinum neurotoxin, which is “most preferably a botulinum neurotoxin type A complex of about 900 kDa or the 150 kDa neurotoxic component therefrom,” can be used for research purposes and/or to make pharmaceutical compositions. *Id.* at 6:52–7:3.

Ton teaches “a substantially animal product free (APF) chromatographic system for obtaining a biologically active botulinum neurotoxin” that comprises “a substantially APF fermentation medium, *Clostridium botulinum* bacteria for fermenting in the fermentation medium, an anion exchange chromatography medium for recovering biologically active botulinum neurotoxin from the fermentation medium, and a cation exchange chromatography medium for recovering further biologically active botulinum neurotoxin from an eluent” of the anion exchange chromatography medium. Ex. 1003, 11:18–30. Ton explains that, although it was previously thought that anion exchange chromatography had a

detrimental effect on botulinum neurotoxin purification, “[w]e found that use of an anion exchange followed by use of a cation exchange chromatography media provides an effective and rapid method for obtaining high purity, high yield botulinum neurotoxin.” *Id.* at 24:38–46.

Ton describes an example wherein the material harvested from the APF fermentation medium is loaded onto an anion exchange column, and the botulinum neurotoxin complex binds to the anion exchange material. Ex. 1003, 39:56–64. After a washing step, an elution buffer is pumped onto the anion exchange column, and the collected eluate pool is then prepared for addition onto the cation exchange column. *Id.* at 39:64–40:20. The eluate pool is then passed through the cation exchange column, the cation exchange column is washed two times, and an elution buffer is pumped onto the cation exchange column for elution of bulk botulinum neurotoxin complex. *Id.* at 40:29–56.

3. Discussion

Petitioner contends that Jung teaches or suggests all the limitations of claim 1 except “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,” which Petitioner contends Ton discloses. Pet. 21–38. Patent Owner responds that Petitioner does not establish that the proposed combination discloses “isolating a botulinum type A macro complex” as required by claim 1, and also does not establish a sufficient reason to combine Jung and Ton as proposed. Prelim. Resp. 31–45. We focus our

discussion on the “isolating a botulinum type A macro complex” limitation of claim 1, as it is dispositive for purposes of this Decision.

Claim 1⁷ recites “[a] method of isolating a botulinum type A macro complex from a botulinum toxin-containing solution” and “separating the botulinum toxin type A macro complex from the cation exchange chromatography medium.” Ex. 1001, 10:25–27, 10:48–49. As set forth above, for purposes of this Decision, we construe “botulinum type A macro complex” as used in claim 1 to include “a botulinum toxin type A of 900 kDa.” *See* Section II.B *supra*. Thus, Petitioner must show that the combined teachings of Jung and Ton disclose a method of isolating a botulinum toxin type A of 900 kDa that includes the step of separating a botulinum toxin type A of 900 kDa from the cation exchange chromatography medium to meet the “method of isolating a botulinum type A macro complex from a botulinum toxin-containing solution” and “separating the botulinum toxin type A macro complex from the cation exchange chromatography medium” limitations of claim 1. We are not persuaded, based on the current record, that Petitioner has carried its burden of doing so.

⁷ Claim 1 recites two alternatives: alternative (a), in which anion exchange chromatography is performed prior to cation exchange chromatography, and alternative (b), in which the order is reversed. Ex. 1001, 10:39–63. Petitioner focuses its arguments on alternative (a), and we do the same. *See* Pet. 26 n.12; *see also Fresenius USA, Inc. v. Baxter Int’l, Inc.*, 582 F.3d 1288, 1298 (Fed. Cir. 2009) (“Element (a) is written in Markush form, such that the entire element is disclosed by the prior art if one alternative in the Markush group is in the prior art.”).

With respect to the “method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution” limitation⁸ of claim 1, Petitioner first contends that “Jung discloses a method of producing *Clostridium botulinum* toxin by using a media containing plant-derived components.” Pet. 21 (citing Ex. 1002, code (57)). Petitioner then points to Jung’s statement that *Clostridium botulinum* toxin is preferably botulinum toxin type A, and “[e]ach toxin has about 150 kDa of toxin protein, and naturally comprises a complex with a variety of non-toxic proteins bound thereto. An intermediate complex (300 kDa) comprises toxin protein and non-toxic non-hemagglutinin protein, and a large complex (500 kDa) and a macro complex (900 kDa).” *Id.* at 21–22 (citing Ex. 1002, 1:43–49, 6:36–38). After asserting that the ’598 patent teaches that the botulinum toxin solution can be a culture of *Clostridium botulinum*, Petitioner contends that “Jung discloses that the toxin existing in the culture from which the cell is removed is isolated.” *Id.* at 22 (citing Ex. 1002, 4:37–38). Based on these cited disclosures, Petitioner concludes that Jung discloses “[a] method of isolating a botulinum toxin type A macro complex from a botulinum toxin-containing solution.” *Id.* (citing Ex. 1021 ¶ 64).

Petitioner, however, does not adequately explain how Jung’s disclosure of isolating “a toxin existing in the culture from which the cell is

⁸ Because this preamble language provides antecedent basis for “the botulinum toxin type A macro complex” recited in the body of the claim, we determine, based on the current record, that the preamble is limiting. *See Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (“In general, a [claim] preamble limits the invention if it recites essential structure or steps, or if it is ‘necessary to give life, meaning, and vitality’ to the claim.”); *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1358 (Fed. Cir. 2012) (“a preamble phrase that provides antecedent basis for a claim limitation generally limits the scope of the claim”).

removed” meets claim 1’s requirement of isolating a botulinum toxin type A *macro complex*. Although Jung’s background section teaches that botulinum toxins comprise intermediate, large, and macro complexes, Petitioner does not point us to anything in Jung that indicates that the macro complex is isolated by Jung’s method. *See* Pet. 21–22. Instead, the Jung disclosures on which Petitioner relies only indicate that Jung’s method can isolate botulinum toxin type A, and that each botulinum toxin has about 150 kDa of toxic protein and naturally comprises an intermediate complex (300 kDa), a large complex (500 kDa), and a macro complex (900 kDa). Ex. 1002, code (57), 1:44–49, 6:36–38. The fact that one form in which botulinum toxin type A can exist is a macro complex is not sufficient, on its own, to establish that Jung teaches a method of isolating a botulinum toxin type A macro complex, particularly in light of other prior art that shows isolation of forms of botulinum toxin type A other than the macro complex. *See, e.g.*, Ex. 1004 ¶¶ 87, 116, 125 (purified botulinum toxin with molecular weight of 150 kDa).

That Petitioner relies on Ton as disclosing the “separating the botulinum toxin type A macro complex from the cation exchange chromatography medium” limitation of claim 1 does not cure this deficiency. Pet. 34 (citing Ex. 1003, 27:25–27, 40:45–46; Ex. 1021 ¶ 79). Ton’s cation exchange chromatography will only produce “high purity, high yield” botulinum toxin type A macro complex when the material entering the cation exchange column includes botulinum toxin type A macro complex. *See* Ex. 1003, 13:14–16 (“*In particular embodiments*, the biologically active botulinum neurotoxin obtained by the process and systems herein disclosed has a molecular weight of about 900 kDa.”) (emphasis added), 27:27–33 (“Systems and method disclosed herein for

purifying a botulinum toxin type A complex with a molecular weight of about 900 kDa, have ready applicability to the purification of about 150 kDa, about 300 kDa, about 500 kDa as well as other molecular weight toxins, complexes, botulinum toxin serotypes and botulinum toxin neurotoxic component.”). And, as discussed above, Petitioner does not sufficiently establish that Jung’s method produces the botulinum toxin type A macro complex. Petitioner does not rely on Ton for any limitations of claim 1 other than those directed to cation exchange chromatography. *See id.* at 21–34.

Petitioner also directs us to the Bates Declaration to support its contentions that Jung discloses isolating a botulinum toxin type A macro complex. Pet. 21–22 (citing Ex. 1021 ¶ 64). Dr. Bates’s testimony, however, does not add to or expound on the evidence presented in the Petition. Ex. 1021 ¶ 64.

Petitioner “has the burden from the outset to show with particularity why the patent it challenges is unpatentable.” *Harmonic, Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also SAS Inst., Inc. v. Iancu*, 138 S.Ct. 1348, 1355 (2018) (“in an inter partes review, the petitioner is the master of its complaint”). A petition for *inter partes* review must identify how the challenged claims are unpatentable, and must specify where each element of the claim is found in the relied-upon prior art. 37 C.F.R. § 42.104(b); *see also* 35 U.S.C. § 312(a)(3) (a petition must identify, “with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim”). A petition must also include “a detailed explanation of the significance of the evidence including material facts, and the governing laws, rules, and precedent.” 37 C.F.R. § 42.22(a)(2). What is

missing from both the Petition and the supporting testimony is an adequate explanation of how or why a POSA would have understood that Jung teaches the isolation of a botulinum toxin type A macro complex in particular, when Jung is silent as to the form of the toxin being produced. In this case, it is not enough to simply cite evidence; an explanation of the significance of that evidence is necessary.

Based on our review of the record, we find that there is insufficient explanation and insufficient supporting evidence that Jung teaches isolating a botulinum toxin type A macro complex. Petitioner's statements, and Dr. Bates's testimony, that Jung teaches isolating a botulinum toxin, and that botulinum toxins "naturally comprise[] a complex with a variety of non-toxic proteins bound thereto" that can be intermediate, large, or macro in size, are conclusory because they do not explain why the form of toxin ultimately isolated in Jung is a macro complex. Therefore, Petitioner does not sufficiently show that the combination of Jung and Ton discloses "[a] method of isolating a botulinum toxin type A macro complex from a botulinum containing solution" or "separating the botulinum toxin type A macro complex from the cation exchange chromatography medium" as required by claim 1 of the '598 patent.

Accordingly, on the record before us,⁹ the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing that claim 1,

⁹ With our authorization, Petitioner filed a Motion for Leave to File a Reply to Patent Owner's Preliminary Response (Paper 7), and Patent Owner filed an Opposition (Paper 8). We denied Petitioner's Motion. Paper 9. The issues addressed in this Decision (whether Petitioner has met its burden) are unrelated to the arguments to which Petitioner sought a reply (Patent Owner's positions regarding Jung's disclosures). *See* Paper 7; Ex. 1032.

and claims 2–9 that depend, directly or indirectly, therefrom, would have been obvious over the combined teachings of Jung and Ton.

D. Asserted Obviousness over Kim ’741, Kim ’565, and Jung

Petitioner contends that claims 1–9 would have been obvious over the combined teachings of Kim ’741, Kim ’565, and Jung. Pet. 42–63.

1. Kim ’741

Kim ’741 “relates to a method for producing a botulinum toxin by an animal product-free (APF) process.” Ex. 1004 ¶ 1. In particular, Kim ’741 describes a method comprising the steps of: (1) treating a culture of a botulinum toxin-producing strain with acid to form a botulinum toxin-containing precipitate; (2) adding a buffer to the botulinum toxin-containing precipitate, and then clarifying using one or more of depth, micro-, ultra-, and sterile filtration, membrane chromatography, and centrifugation; (3) subjecting the resulting botulinum toxin-containing solution to diafiltration or precipitation and diluting or dissolving the result in a buffer; and (4) subjecting the resulting solution to anion exchange chromatography (AEX) to purify the botulinum toxin. *Id.* Kim ’741 teaches that the anion exchange chromatography step “may be performed at a pH of 2–9, preferably 3–8,” and the purified botulinum toxin “may be collected as a botulinum toxin-containing fraction (flow-through mode) of a flow-through (FT) fraction eluted from anion-exchange chromatography or as a fraction containing the botulinum toxin bound to anion exchange chromatography resin.” *Id.* ¶ 72.

2. Kim ’565

Kim ’565 relates “to a medium composition for culture of strains of *Clostridium* capable of producing botulinum toxin” that “comprises at least one plant-derived peptone selected from the group consisting of a garden pea

hydrolysate, a cotton seed hydrolysate and wheat gluten hydrolysate.”

Ex. 1023 ¶ 1. Kim ’565 explains that the medium generally used to culture *Clostridium botulinum* contains animal components, which could contain “an animal abnormal prion known as an agent that causes transmissible spongiform encephalopathy” due to contamination. *Id.* ¶ 11. Kim ’565 further teaches that “a potential risk may exist of acquiring a prion mediated disease, such as Creutzfeldt-Jacob disease, from the administration of a pharmaceutical composition which contains a biologic, such as a botulinum toxin, obtained using animal-derived components.” *Id.* ¶ 15. Kim ’565 teaches that “when a medium comprising transmissible spongiform encephalopathy(TSE)-free plant-derived peptone and mineral components is used for culture of *Clostridium botulinum* in order to prevent the risk of developing” a prion-mediated disease, “the risk of development of the prion-mediated disease that can occur in a medium that” contains animal-derived components “can be excluded, and the growth rate of *Clostridium botulinum* in the medium can be increased compared to that in the medium” that contains animal-derived components. *Id.* ¶ 16.

3. 35 U.S.C. § 325(d)

Patent Owner argues that we should exercise our discretion under 35 U.S.C. § 325(d) to deny institution of this asserted ground because Kim ’741 was raised during prosecution of the ’598 patent, and the Office previously considered the question of whether Kim ’741’s disclosure of a range of pH values for performing anion exchange chromatography renders the claimed pH below the PI of botulinum toxin obvious. Prelim. Resp. 45–49.

Section 325(d) provides that, 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.” The Board uses a two-part framework for evaluating arguments under § 325(d):

- (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 challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”). In applying this framework, we consider the *Becton, Dickinson*¹⁰ factors that address discretion to deny institution when a petition presents the same or substantially the same prior art or arguments previously presented to the Office, including:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and

¹⁰ *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”).

(f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, Paper 8 at 17–18. Factors (a), (b), and (d), relate to whether the same or substantially the same art or arguments were previously presented to the Office, and factors (c), (e), and (f) relate to whether the petitioner demonstrates that the Office erred in a manner material to the patentability of the claims. *Advanced Bionics*, Paper 6 at 9–11. Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether the petitioner has demonstrated a material error by the Office. *Id.*

a) *Relevant Prosecution History*

During prosecution of the '598 patent, the Examiner rejected then-pending claim 1 as obvious over Kim '741. Ex. 1006, 499. In particular, the Examiner found that Kim '741 teaches a method of isolating a botulinum toxin type A macro complex that includes anion exchange (AEX) and cation exchange (CEX) chromatography steps performed at a pH of 3–8, which “overlap with the claimed ranges of ‘a pH lower than the pI of botulinum toxin’ and therefore, establishes cases of *prima facie* obviousness.” *Id.* at 499–500. In response, the applicant argued, *inter alia*, that in the examples in Kim '741, “the actual pH during the anion and cation exchange chromatographies was higher than the PI of botulinum toxin,” and “the final purified botulinum toxin is a form of 7S (molecular weight: about 150 kDa), not 19S (molecular weight: about 900 kDa).” *Id.* at 533–534. The Examiner maintained the rejection, and stated that “[a]bsent showings of significance or criticality to the claimed ‘a pH lower than the pI of botulinum toxin,’ the

disclosure of [Kim '741] would render the claimed invention obvious to one of ordinary skill in the art.” *Id.* at 546.

To overcome the rejection, the applicant submitted a Declaration from co-inventor Jung Hyun Song (“the Song Declaration,” Ex. 1006, 570–577). Ex. 1006, 567–569. The applicant stated that the Song Declaration describes experiments designed “to compare the relative efficiency of botulinum toxin recovery between an AEX using a pH lower than the pI of botulinum toxin and an AEX using pH higher than the pI of botulinum toxin.” *Id.* at 567. The applicant argued that the results reported in the Song Declaration “show that 19S can be purified from the flow through solution when pH 5.5 is used but at pH 6.5, 19S was not present in the flow through solution but present in the eluted solution, distributed in a wide retention time.” *Id.* at 568. According to the applicant, “when pH 5.5 is used, 19S can be simply purified from the flow through solution with high purity and there is no need to add an additional eluting step. This is an unexpected benefit of the claimed invention.” *Id.*

In the Final Office Action that followed, the Examiner maintained the rejection over Kim '741, stating that the applicant “has only provided comparisons of botulinum toxin recovery between pH lower than the pI and pH higher than the pI for only AEX chromatography, i.e., no nexus has been shown between the provided data and the claimed inventive method.” Ex. 1006, 587. The applicant responded by amending the claims to require upstream culture and processing steps before the downstream chromatography steps, and reiterating its arguments regarding the differences between the Kim '741's method and the claimed method. *Id.* at 608–620.

Following the response, the Examiner allowed the claims. Ex. 1006, 626–628. In the Notice of Allowability, the Examiner stated:

While the most relevant prior art of record, [Kim ’741], discloses a method for producing and purifying botulinum toxin, including the desired type A macro complex, using anion exchange and cation exchange chromatography, [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. As argued by Applicant . . . , one of ordinary skill in the art would not have been motivated to select a pH lower than the pI of botulinum from the pH range of 3–8 disclosed by [Kim ’741] because [Kim ’741] does not disclose or provide any reason that the anion exchange or cation exchange processes can be performed at such a lower pH level. Applicant has also provided a declaration by co-inventor Song . . . comparing the relative efficiency of botulinum toxin recovery from an anion exchange process between using a pH lower than the pI of botulinum toxin and a pH higher than the pI of botulinum toxin, thereby showing the criticality of such a claimed limitation. This showing of criticality was persuasive to overcome the 35 USC 103 rejection of Claim 1 as being unpatentable over [Kim ’741].

Id. at 627.

b) Petitioner’s Arguments

Petitioner contends that Kim ’741 teaches all of the limitations of claim 1, except for “culturing *Clostridium botulinum* in an animal product-free medium to obtain a culture,” which Petitioner contends Kim ’565 discloses, and “removing *Clostridium botulinum* cells from the culture to obtain a botulinum toxin-containing solution,” which Petitioner contends Jung discloses. Pet. 42–59. With respect to the “contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than an isoelectric point (PI) of botulinum toxin” limitation of claim 1, Petitioner contends that “Kim ’741 discloses subjecting the botulinum toxin solution to anion exchange chromatography at a pH of 2–9,

preferably 3–8.” *Id.* at 48 (citing Ex. 1004 ¶ 72) (emphases omitted). Therefore, according to Petitioner, “Kim ’741 discloses performing anion exchange chromatography at a pH range that overlaps with ‘a pH lower than an isoelectric point (PI) of botulinum toxin,’ *i.e.*, a pH of 6.06 or lower, as this term is properly construed.” *Id.* at 49 (citing Ex. 1021 ¶¶ 109–110) (emphasis omitted). Petitioner further contends that “[i]n cases involving overlapping ranges, courts have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.” *Id.* (citing *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003)).

With respect to the “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 the botulinum toxin” limitation of claim 1, Petitioner similarly argues that “Kim ’741 discloses that a further ‘cation exchange chromatography in step (h) may be performed at a pH of 2–9, preferably 3–8.’” Pet. 56 (citing Ex. 1004 ¶ 87). Petitioner also argues that the overlap between Kim ’741’s pH range and the claimed pH lower than the PI of botulinum toxin “creates a presumption of obviousness.” *Id.* at 56–57.

Petitioner further argues that Patent Owner did not rebut the presumption of obviousness during prosecution of the ’598 patent. Pet. 49–55.

c) Part One of the Advanced Bionics Framework

We first consider whether Petitioner asserts the same or substantially the same prior art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8. We conclude that Petitioner asserts not only the same prior art, but also the same arguments that previously were

presented to the Office.¹¹ Petitioner asserts Kim '741, Kim '565, and Jung against the challenged claims of the '598 patent. Petitioner concedes that the Examiner considered Kim '741 during prosecution. Pet. 65. Thus, Kim '741 previously was presented to the Office.¹²

Further, as explained above, the Examiner rejected the claims during prosecution after finding that Kim '741 teaches a method of isolating a botulinum toxin type A macro complex that includes anion exchange and cation exchange chromatography steps performed at a pH of 3–8, which overlaps with the claimed pH lower than the PI of botulinum toxin. *See* Ex. 1006, 499–500, 546–547, 586–587. Here, Petitioner relies on Kim '741 as allegedly teaching all limitations of claim 1 but two, and argues that Kim '741 discloses performing anion exchange and cation exchange chromatography at a pH range “that overlaps with ‘a pH lower than an isoelectric point (PI) of botulinum toxin,’ *i.e.*, a pH of 6.06 or lower, as this term is properly construed.” Pet. 49, 56–57. Thus, although Petitioner relies on two additional references that were not presented to the Examiner, the vast majority of Petitioner’s analysis makes the same arguments the Office previously considered regarding Kim '741.

Accordingly, we are persuaded that Patent Owner has satisfied part one of the *Advanced Bionics* framework.

¹¹ Under *Advanced Bionics*, either the same or substantially the same prior art previously must have been presented to the Office, or the same or substantially the same arguments previously must have been presented to the Office, to reach the second part of the framework, *i.e.*, a showing of error material to patentability. *Advanced Bionics*, Paper 6 at 8.

¹² Kim '565 and Jung were not considered during prosecution. Nevertheless, part one of the framework is written in the alternative, and here we discuss both.

d) Part Two of the Advanced Bionics Framework

Petitioner argues that “the Examiner erred in crediting the purported evidence of criticality presented by Patent Owner during prosecution,” which was “the sole reason the Examiner allowed the claims.” Pet. 65 (citing Ex. 1006, 627). In particular, Petitioner argues that “[a]ccording to Patent Owner, results showing that ‘19S can be purified from the flow through solution when pH 5.5 is used but at pH 6.5, 19S was not present in the flow through solution . . . is an unexpected benefit of the claimed invention,” despite there being “nothing unexpected about that observation.” *Id.* at 50 (citing Ex. 1006, 568, 620) (alteration in original, emphases omitted). Petitioner notes that Jung discloses performing anion exchange chromatography at pH 5.5, which resulted in botulinum toxin type A in the flow through portion. *Id.* (citing Ex. 1002, 11:20–12:16). Petitioner also points to the Bates Declaration, which explains that it was known that “[a] protein at a pH below its pI will carry a net positive charge and is less likely to interact with a positively charged separation matrix (anion exchanger)” and “is more likely to flow through the matrix.” *Id.* at 51; *see also id.* (“This is how ion exchangers work, as everyone in the industry knew from well before the ’598 patent.”). Petitioner also argues that in Example 2–3–1, “Kim ’741 successfully conducted anion exchange chromatography in flow-through mode at a pH higher than the pI of botulinum toxin (e.g., about 6.06).” *Id.* at 53 (citing Ex. 1021 ¶ 115) (emphasis omitted). Therefore, according to Petitioner, “the claimed pH range cannot be critical to practicing the claimed method if flow-through anion exchange chromatography can be achieved with a pH higher than the pI of botulinum toxin.” *Id.* (citing Ex. 1021 ¶ 115) (emphasis omitted).

Patent Owner responds that “Petitioner mischaracterizes the nature of the unexpected results that Medytox established, and which the Examiner accepted.” Prelim. Resp. 51. In that regard, Patent Owner argues that it “never alleged that the inventors discovered that BoNTA flows through (rather than binding to) an AEX column at a pH below its pI” because “[t]his 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.’” *Id.* at 52 (citing Ex. 1006, 587) (alteration in original). Instead, Patent Owner argues that “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].’” *Id.* (citing Ex. 1006, 627) (alterations in original, emphases omitted).

We agree with Patent Owner that Petitioner mischaracterizes the nature of the data in the Song Declaration, and also mischaracterizes the Examiner’s determination of its criticality. Looking first at the experiments using pH 5.5 (lower than the pI of botulinum toxin), the Song Declaration explains that a botulinum toxin containing sample was loaded to the anion exchange chromatography column “by flowing the sample through the column,” then “the column was eluted.” Ex. 1006, 573. The Song Declaration presents a chromatogram for the flow through solution and the eluted solution, and explains that “the botulinum toxin containing sample was detected immediately upon loading the sample” but “no significant . . . peaks appeared in the eluted solution,” indicating “that the botulinum toxin is contained in the flow through solution.” *Id.* at 574. The Song Declaration

then presents a chromatogram of the flow through sample, and reports that the purity of the botulinum toxin in “the flow through solution was 91.98%, which is significantly higher than the control sample purity, 74.09%.” *Id.* at 574–575.

The same process was followed using a pH of 6.5 (higher than the pI of botulinum toxin). Ex. 1006, 575–576. The Song Declaration reports that the chromatogram of the flow through solution and the eluted solution shows that “the botulinum toxin was detected at about 50 ml retention time and after starting the elution with buffer B after loading the sample,” indicating “that the botulinum toxin is not contained in the flow through solution, but contained in the eluted solution with buffer B.” *Id.* at 576. The Song Declaration then presents a chromatogram of four different fractions from the eluted solution, and explains that the purity of the botulinum toxin “in the eluted solution was about 30% to 88%,” and “19S is not purified but distributed to all the fractions.” *Id.*

The applicant explained the significance of the data to the Examiner:

These results from using pH 5.5 and pH 6.5 show that 19S can be purified from the flow through solution when pH 5.5 is used but at pH 6.5, 19S was not present in the flow through solution but present in the eluted solution, distributed in a wide retention time. In this regard, when pH 5.5 is used, 19S can be simply purified from the flow through solution with high purity and there is no need to add an additional eluting step. This is an unexpected benefit of the claimed invention.

Ex. 1006, 568. In other words, the “unexpected benefit” of using a pH lower than the pI of botulinum toxin is that botulinum toxin type A macro complex could be purified directly from the flow through solution, which is more efficient than using a pH higher than the pI of botulinum toxin, which requires an additional step of eluting the anion exchange chromatography

column to purify botulinum toxin type A. This is the “showing of criticality” that the Examiner found “persuasive to overcome” the rejection of claim 1 over Kim ’741. *Id.* at 627 (explaining that the Song Declaration “compar[es] the relative efficiency of botulinum toxin recovery from an anion exchange process between using a pH lower than the pI of botulinum toxin and pH higher than the pI of botulinum toxin, thereby showing the criticality of such claimed limitation”).

Accordingly, Petitioner’s argument that “there is nothing special, critical, or unexpected about the pH range claimed by the ’598 patent” because “[t]hat botulinum toxin flowed through the anion exchange chromatography column at pH 5.5 would have been entirely expected” attacks an argument that the applicant did make, and on which the Examiner did not rely. Pet. 65. And Petitioner does not address or attempt to explain how the Examiner erred in finding that the Song Declaration’s data regarding the *relative efficiencies* of botulinum toxin recovery at a pH higher than the pI of botulinum toxin and a pH lower than the pI of botulinum toxin shows the criticality of the claimed pH.

Petitioner also argues that “the claimed pH range cannot be critical to practicing the claimed method if flow-through anion exchange chromatography can be achieved with a pH higher than the pI of botulinum toxin.” Pet. 53 (emphasis omitted). Petitioner points to Kim ’741’s Example 2-3-1, in which “anion exchange chromatography was performed at a pH of 6.4–6.6, and ‘it was shown that the botulinum toxin was not adsorbed onto the TQ resin, and most major impurities were removed by adsorption, and thus a botulinum toxin could be produced with high purity.’” *Id.* at 52–53 (citing Ex. 1004 ¶¶ 102–108) (emphases omitted). Because the resulting botulinum toxin was form 19S (molecular weight: about 900 kDa),

Petitioner argues that “Kim ’741 successfully conducted anion exchange chromatography in flow-through mode at a pH higher than the pI of botulinum toxin (e.g., about 6.06).” *Id.* at 53 (citing Ex. 1004 ¶ 108; Ex. 1021 ¶ 115).

This argument is also based on a mischaracterization of the results reported in the Song Declaration and on the Examiner’s reliance thereon in finding criticality. The Examiner stated that the Song Declaration compared “the *relative efficiencies* of botulinum toxin recovery from an anion exchange process between using a pH lower than the pI of botulinum toxin and pH higher than the pI of botulinum toxin, *thereby showing the criticality of such a claimed limitation.*” Ex. 1006, 627 (emphases added). Thus, as discussed above, the unexpected result that overcame the Examiner’s rejection based on Kim ’741 was that botulinum toxin recovery is *more efficient* using a pH lower than the pI of botulinum toxin than using a pH higher than the pI of botulinum toxin. Petitioner does not point us to, and we do not discern, anything in Kim ’741’s Example 2-3-1 that undermines the Examiner’s determination of criticality based on the relative efficiencies of the process.

Becton, Dickinson also advises that we should consider “the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments” when determining whether to exercise our discretion under § 325(d) when the same or substantially the same prior art or arguments were previously presented to the Office. *Becton, Dickinson*, Paper 8, 17–18. Petitioner contends, in a footnote to its argument with respect to the “contacting the botulinum toxin-containing solution with an anion exchange chromatography medium at a pH lower than the PI of botulinum toxin” limitation of claim 1, that “[t]o the extent

Patent Owner argues Kim '741 does not disclose or otherwise render this claim limitation obvious, it is disclosed in Jung.” *Id.* at 55 n.25. Petitioner supports this contention by referring back to the argument it made regarding the same limitation in its challenge based on Jung and Ton. *Id.* (citing § XI.B.1.g (Pet. 26–29). It is not clear, however, if Petitioner is contending that a POSA would replace Kim '741’s anion exchange chromatography step with Jung’s anion exchange chromatography step, or would modify Kim '741’s anion exchange chromatography step based on Jung’s anion exchange chromatography step.

Either way, Petitioner does not meet its burden of establishing why a POSA would have been motivated to make the proposed combination or modification with respect to the anion exchange chromatography limitation of claim 1. Petitioner’s only argument with respect to the proposed combination of Kim '741 and Jung is directed to the “removing *Clostridium botulinum* cells from the culture to obtain a botulinum toxin-containing solution” limitation of claim 1. *See* Pet. 46, 58–59. With respect to the anion and cation exchange chromatography limitations, Petitioner argues that “it would have been obvious to try pHs at all points in Kim '741’s disclosed range, to ensure that the toxin flowed through the matrix (as taught by Kim '741),” and that the existence of the overlapping ranges provides sufficient motivation to optimize the range. *Id.* at 53–54; *see also id.* at 59 (“[I]t would have been obvious to try pHs within the range disclosed in Kim '741, and observe whether varying the pH affecting the binding of the toxin to the matrix.”). Notably, the Petition is silent as to the combination of Kim '741 and Jung with respect to the anion exchange chromatography limitation of claim 1. *See id.* at 48–55, 57–59.

To support a conclusion of obviousness when combining the teachings of multiple references, an articulated reason with some rational underpinning to combine the known elements in the fashion claimed must be provided. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007); *see also In re Magnum Oil Tools, Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (It is the petitioner's "burden to demonstrate both that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention[s], and that the skilled artisan would have had a reasonable expectation of success in doing so." (citation and internal quotation marks omitted)). Here, the Petition lacks an adequate explanation as to why a POSA reading Kim '741 would have looked to Jung for its teachings regarding anion exchange chromatography, and how a POSA would have combined the teachings of Kim '741 and Jung in the manner claimed.

Because we are not persuaded that Petitioner sufficiently establishes a motivation to combine Kim '741 and Jung with respect to the anion exchange chromatography limitation of claim 1, we are not persuaded that Petitioner's alternative assertion of Jung for this limitation warrants reconsideration of the prior art and arguments previously considered by the Office. Accordingly, we find that the Examiner's failure to consider Jung in combination with Kim '741 with respect to the anion exchange chromatography limitation of claim 1 is not an error that weighs in favor of institution.

For these reasons, we are not persuaded that Petitioner sufficiently establishes that the Examiner erred in a manner material to the patentability of the challenged claims in finding that the Song Declaration shows the criticality of the claimed pH.

e) Conclusion

The Petition relies on Kim '741 and presents arguments regarding Kim '741 that are the same as those the Examiner considered and the applicant overcame during the prosecution of the '598 patent. Petitioner does not demonstrate that the Examiner materially erred in considering such arguments. Accordingly, in light of the circumstances of this case, we determine that, with respect to Petitioner's Ground 2, it is appropriate to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

III. CONCLUSION

Based on the arguments in the Petition and the Preliminary Response, and the evidence of record, and for the reasons set forth above, with respect to Ground 1, we determine that Petitioner does not establish a reasonable likelihood of prevailing with respect to at least one challenged claim of the '598 patent. We also determine, with respect to Ground 2, that the Petition presents the same art and arguments as those presented to the Examiner during prosecution of the '598 patent, and Petitioner does not establish that the Examiner erred in a manner material to patentability.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* and no trial is instituted.

IPR2023-00604
Patent 11,331,598 B2

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