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Paper 19
Entered: December 10, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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BIOACTIVE LABORATORIES,
Petitioner,

v.

BTG INTERNATIONAL INC.,
Patent Owner.

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Case IPR2015-01305
Patent 8,048,414 B

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Before TONI R. SCHEINER, LORA M. GREEN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

## I. INTRODUCTION

Bioactive Laboratories ("Petitioner") filed a Petition (Paper 2, "Pet.") on May 29, 2015, requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,048,414 B1 (Ex. 1001, "the '414 patent"). BTG International Inc. ("Patent Owner") filed a Preliminary Response (Paper 12, "Prelim. Resp.") on September 11, 2015.[1] We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the information presented in the Petition and the Preliminary Response, we are not persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 1–22 of the '414 patent. Accordingly, we decline to institute an *inter partes* review of those claims.

### *A. Related Proceedings*

Petitioner represents that the '414 patent was involved in a prior *inter partes* review which was terminated prior to a decision on institution: *Laboratorios Silances, S.A. de C.V. v. BTG Int'l Inc.*, Case IPR2014-01269 (PTAB). In addition, Petitioner represents that the '414 patent was involved

[1] Patent Owner filed a Motion to Seal its Preliminary Response, as well as Exhibit 2033, submitted in support of the Preliminary Response. Paper 14. Patent Owner filed also a redacted version of the Preliminary Response. Paper 13.

in an investigation before the U.S. International Trade Commission: Certain Antivenom Compositions and Products Containing the Same (Inv. No. 337-TA-903). Petitioner was not a party to either matter. Pet. 1.

Patent Owner represents it is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in the proceeding. Paper 4.

*B. The Asserted Grounds of Unpatentability*

Petitioner asserts the challenged claims are unpatentable on the following grounds. Pet. 12–60.[2]

| **References** | **Basis** | **Claims Challenged** |
|---|---|---|
| the '352 patent[3] | § 102 | 1–7, 9–18, 21, and 22 |
| the '352 patent and the WHO Report[4] | § 103 | 8 and 19 |

[2] Petitioner supports its challenge with the Declaration of Anthony Kossiakoff, Ph.D., executed May 27, 2015, ("the Kossiakoff Declaration") (Ex. 1002), and the Declaration of Richard F. Clark, Jr., M.D., executed May 25, 2015 ("the Clark Declaration") (Ex. 1024).

[3] U.S. Patent No. 4,849,352, issued July 18, 1989 to Sullivan et al. ("the '352 patent") (Ex. 1004).

[4] WORLD HEALTH ORG., WHO OFFSET PUBLICATION NO. 58, 3–44, PROGRESS IN THE CHARACTERIZATION AND STANDARDIZATION OF ANTIVENOMS (1981) ("the WHO Report") (Ex. 1006).

| References | Basis | Claims Challenged |
|---|---|---|
| Chang[5] and the WHO Report | § 103 | 1–7, 9–18, and 20–22 |
| Chang, the WHO Report, and Smith[6] | § 103 | 8 and 19 |

*C. The '414 Patent (Ex. 1001)*

The '414 patent, titled "Antivenom Composition Containing Fab[7] Fragments," discloses "enzymoabsorbed affinity methods combined with reversible immunoabsorption chromatography procedures to produce and isolate F(ab) and $F(ab)_2$ fragments . . . to snake venoms as well as other venoms." Ex. 1001, 3:22–27. In addition, the '414 patent discloses an immunoabsorption procedure which produces "a highly refined IgG antibody from a bulk antibody source." *Id.* at 3:28–30.

According to the '414 patent, "[t]he F(ab) fragments, $F(ab)_2$ fragments and IgG thus produced are more highly purified, have greater antibody activities and are less likely to produce immunogenic reactions

[5] C.C. Chang & C.C. Yang, *Immunochemical Studies on Cobrotoxin*, 102 J. IMMUNOL. 1437–44 (1969) ("Chang") (Ex. 1005).

[6] T.W. Smith et al, *Immunogenicity and kinetics of distribution and elimination of sheep digoxin-specific IgG and Fab fragments in the rabbit and baboon*, 36 CLIN. EXP. IMMUNOL. 384–96 (1979) ("Smith") (Ex. 1007).

[7] The acronym "Fab" (which stands for "fragment antigen-binding") is used interchangeably with "F(ab)" in the '414 patent, the briefings, and this decision.

than their counterpart antibodies produced by processes utilizing [prior art] precipitation procedures." *Id.* at 3:32–37. Further according to the '414 patent, "lethality-neutralizing . . . tests clearly established that the F(ab) fragment antibodies and IgG produced by the processes of this invention afford better protection against venom-induced pathophysiology than the [prior art] commercial antivenin on a milligram per milligram basis." *Id.* at 4:43–48. In addition, the '414 patent teaches that $F(ab)_2$ fragments produced according to the invention "should also afford greater protection against venom-induced pathophysiology than the commercial antivenin . . . [and] produce less acute hypersensitivity reactions than those produced by the commercial antivenin." *Id.* at 4:54–58.

Finally, the '414 patent teaches that "IgG, F(ab) fragments and $F(ab)_2$ fragments often have separate utilities" and "F(ab) and $F(ab)_2$ fragments may sometimes be used together." *Id.* at 2:1–3. According to the '414 patent, Fab fragments and $F(ab)_2$ fragments will have the same antibody specificity as the antibody they are cleaved from, but their differing molecular weights affect a number of functions, including distribution in the body (e.g., whether or not they can cross the blood/brain barrier), the ability to be excreted by kidney functions, etc. *Id.* at 1:42–2:50.

> If, for example a sought after antigen molecule is already a large molecule, the use of F(ab) fragments is limited. Even though the F(ab) fragments can be used to neutralize large antigen molecules, the kidneys still will not be able to excrete them. In such cases it may be better to use a whole IgG

> molecule to find the large antigen molecule so that the entire molecule assembly is phagocytized.

*Id.* at 2:18–24.

### *D. Illustrative Claims*

Petitioner challenges claims 1–22 of the '907 patent. Claims 1, 19, and 20 are independent. Claims 1 and 20, reproduced below, are illustrative.

> 1. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus.
>
> 20. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said Fab fragments neutralize the lethality of the venom of a snake of the *Crotalus* genus in the absence of IgG and $F(ab)_2$.

Ex. 1001, 13:16–23, 14:35–42.

## II. ANALYSIS

### *A. Claim Construction*

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b);

Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275–79 (Fed. Cir. 2015). Under that standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Petitioner and Patent Owner proffer proposed constructions of several claim terms (Pet. 11–18; Prelim. Resp. 17–22), but we determine that none of these claims terms requires construction beyond our discussion below of the claim term "said [or the] antivenom pharmaceutical composition neutralizes the lethality of the venom of the snake of the *Crotalus* genus."

### *B. Claims 1–7, 9–18, 21, and 22—Asserted Anticipation by the '352 Patent*

#### *1. The '352 Patent (Ex. 1004)*

The '352 patent, titled "Antibody Purification Process," matured from application No. 06/659,629 ("the '629 application"), and was filed on October 9, 1984.

The '414 patent was filed on March 15, 1995, as a

> Continuation of application No. 08/277,288, filed on Jul. 22, 1994, now abandoned, which is a continuation of application No. 08/124,438, filed on Sep. 22, 1993, now abandoned, which is a continuation of application No. 07/5 93,271, filed on Oct. 1, 1990, now abandoned, which is a division of application No. 07/ 378,925, filed on Jul. 12, 1989, now abandoned, which is a division of application No. 06/659,629, filed on Oct. 9, 1984, now Pat. No. 4,849,352.

Ex. 1001, [22], [60].

Petitioner and Patent Owner agree that the disclosures of the ’352 patent and the ’414 patent are identical. Ex. 1001; Ex. 1004; Pet. 29; Prelim. Resp. 23.

*2. Analysis*

Petitioner contends that claims 1–7, 9–18, 21, and 22 of the ’414 patent “are not entitled to the benefit of *any* earlier-filed application identified in the [’414] patent’s priority claim” (Pet. 20), because no earlier-filed application “discloses and enables the invention claimed in the later filed application sufficient to satisfy the requirements of § 112” with respect to these claims (*id.*). Accordingly, Petitioner contends that the ’352 patent, which was filed on October 9, 1984, and issued on July 18, 1989, “is prior art to the ’414 patent under 35 U.S.C. § 102(b).” *Id.* at 29.

Claim 1 is directed, in relevant part, to an antivenom pharmaceutical composition comprising Fab fragments which bind specifically to a venom of a snake of the *Crotalus* genus, wherein “said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus” (the “neutralizes the lethality” limitation).

Petitioner acknowledges that “technological knowledge describe[s] antivenom compositions comprising antibody fragments that are the active components.” *Id.* at 22. Petitioner, however, contends that the challenged claims “are broader than the supporting disclosure because they encompass an antivenom pharmaceutical composition containing Fab fragments that do

not necessarily have to neutralize the lethality of the venom" (*id.*), thus, the claims "encompass nearly unlimited compositions that are defined almost exclusively by their function" (*id.*). Petitioner contends that "[n]one of the priority applications describe[s] any components other than antibodies or antibody fragments that could function to neutralize the lethality of the venom of a *Crotalus* snake." *Id.* (citing Ex. 1002 ¶ 53). Petitioner contends, therefore, that the claims "lack written description support in the alleged priority applications, because those applications do not adequately describe what the claimed compositions *are*." *Id.*

Additionally, Petitioner contends that "none of the priority applications enable the full scope of the claims" (*id.* at 24 (citing Ex. 1002 ¶¶ 53–55)), because "direction . . . for making and using Fab fragment-based antivenom pharmaceutical compositions where the Fab fragments do not, themselves, neutralize lethality" is lacking in the priority applications and in the prior art (*id.* at 24–25 (citing Ex. 1002 ¶¶ 56–58)).

Petitioner's broad construction of the "neutralizes the lethality" limitation to include compositions in which Fab fragments or a combination of Fab and $F(ab)_2$ fragments do not neutralize the lethality of *Crotalus* venom, forms the basis of its contention that the '352 patent "is prior art to the '414 patent under 35 U.S.C. § 102(b), given the March 15, 1995 effective filing date of claims [1–7, 9–18], 21, and 22." *Id.* at 29. Petitioner contends that "the '352 patent specification—which is identical to the '414 patent specification—[nevertheless] does disclose at least one specific or

subgeneric embodiment that anticipates each and every element of the broadly construed claims 1–7, 9–18, 21, and 22." *Id.* at 29.

As discussed above, however, in an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. The specification of the '352 patent (which matured from the '629 application), like the specification of the '414 patent, discloses that "lethality-neutralizing . . . tests clearly established that the F(ab) fragment antibodies and IgG produced by the processes of this invention afford . . . protection against venom-induced pathophysiology" (Ex. 1004, 4:53–57), and that "$F(ab)_2$ fragments [produced according to the invention] should also afford . . . protection against venom-induced pathophysiology" (*id.* at 4:66–67). In addition, the specification of the '352 patent, like the specification of the '414 patent, discloses that "IgG, F(ab) fragments and $F(ab)_2$ fragments often have separate utilities" and "F(ab) and $F(ab)_2$ fragments may sometimes be used together." *Id.* at 1:61–63.

We are not persuaded that Petitioner has shown that the '629 priority application (or the '352 patent) fails to provide proper written descriptive support or enablement for claim 1. In a nutshell, we agree with Patent Owner that "construing the limitation to include compositions in which the Fab or Fab/$F(ab)_2$ fragments do not neutralize the lethality of *Crotalus* venom is not reasonable in light of the specification." Prelim. Resp. 25. That is, we agree that "[p]roperly construed, the claims cover a composition

in which Fab fragments neutralize venom, either alone or in combination with $F(ab)_2$ fragments." *Id.*

Moreover, to the extent Petitioner argues that the general statement in the background section of the specification of the '352 patent that "Fab and $F(ab)_2$ fragments may sometimes be used together" (Ex. 1004, 1:62–63) is inadequate to describe or enable compositions containing both Fab and $F(ab)_2$ fragments wherein the composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus (Pet. 25–26 (citing Ex. 1002 ¶¶ 59–61)), we are not persuaded. We note that the Examiner considered this very issue during prosecution of the '414 patent. That is, the Examiner acknowledged that "[t]he specification sets forth the concept of antivenoms comprised of Fabs and $F(ab)_2$" (Ex. 1016, 1209), but was concerned initially that the specification "does not provide any description of how such components would be effective . . . [because] Fabs and $F(ab)_2$s would be expected to compete for binding to the same sites and could thus reasonably be expected to interfere with each other's activity" (*id.* at 1209–10). As explained in the Examiner's Answer, following a series of interviews, and consideration of several declarations of record, the Examiner concluded "based on the evidence of record, that this competition would likely be minimized because of the differences in the various antibody fragment pharmacokinetics." *See id.* at 1538.

In summary, we are not persuaded that Petitioner has shown that the '352 patent is prior art to claim 1 of the '414 patent. Moreover, we are not

persuaded that Petitioner has shown that the ’629 application (or the ’352 patent) fails to provide written description support and enablement for the additional limitations of claims 2–7, 9–18, 21, and 22. Therefore, we are not persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing in its challenge to claims 1–7, 9–18, 21, and 22 on the basis of anticipation by the ’352 patent.

### *C. Claims 8 and 19—Asserted Obviousness over the ’352 Patent and the WHO Report*

Claim 8 is directed to “[t]he antivenom pharmaceutical composition of claim 1, further comprising $F(ab)_2$ fragments.” Claim 19 is an independent claim—like claim 8, claim 19 is directed to an antivenom pharmaceutical composition that comprises both Fab and $F(ab)_2$ fragments, “wherein the antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus.”

For the reasons discussed above, we are not persuaded that the ’352 patent lacks written description support and enablement for an antivenom pharmaceutical composition comprising Fab fragments and $F(ab)_2$ fragments “wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the *Crotalus* genus.” Thus, this challenge, based on the ’352 patent, suffers from the same infirmity as that discussed above, in that Petitioner has not established that the ’629 priority application fails to provide proper written descriptive support or enablement for claims 8 and 19.

Therefore, we are not persuaded that Petitioner has shown that the '352 patent is prior art to claims 8 and 19. Consequently, we are not persuaded that Petitioner has demonstrated a reasonable likelihood of prevailing in its challenge to claims 8 and 19 on the basis of obviousness over the '352 patent and the WHO Report.

### *D. Claims 1–7, 9–18, and 20–22—Asserted Obviousness over Chang and the WHO Report*

#### *1. Chang (1005)*

Chang describes a study conducted in 1968 in which the crystalline toxic protein, cobrotoxin, isolated from Formosan cobra venom, was used as an antigen to produce antiserum. Ex. 1005, 1. "The immunologic activities of the antisera and of the specific antibody purified were investigated" (*id.*), as was the activity of "univalent [Fab] fragments" obtained by papain digestion of the purified antibody (*id.*). The results indicated that "cobrotoxin is immunochemically homogeneous and is the main toxic protein in Formosan cobra venom." *Id.* at 7. The univalent Fab fragments were used to determine that cobrotoxin has three antibody combining sites per molecule. *Id.*

In addition, the neutralizing capacity of the various antibody preparations was tested by pre-incubating the antibody preparations with cobra venom and cobrotoxin, removing precipitates, and injecting the supernatants intraperitoneally into mice. *Id.* at 2, 3, Table II. "The specific neutralizing capacity of F I [the fraction containing Fab fragments] was even

higher than that of the purified antibody" (*id.* at 4, Table II (compare purified antibody with papain digest FI)), and "[t]he neutralizing capacity of all antibody preparations was of the same order for both cobra venom and cobrotoxin, indicating that cobrotoxin is the main toxic protein in cobra venom" (*id.* at 3).

According to Chang, "[t]he univalent [Fab] fragments together with the purified antibody may provide valuable tools for an immunochemical approach to the elucidation of the toxic nature of snake venom." Ex. 1005, 7. Further according to Chang, "[s]ince the neutralizing capacity of the purified antibody was 17.5 times greater than that of the antisera, . . . this may also contribute to the therapy of snake bites." *Id.*

*2. The WHO Report (Ex. 1006)*

The WHO Report, titled "Progress in the Characterization of Venoms and Standardization of Antivenoms," was published in 1981, and includes a "Table of Poisonous Animals and Available Antivenoms" (Ex. 1006, 1, 26–36) that lists several antivenoms effective against various species of *Crotalus* (*id.* at 26).

The WHO Report notes that "[a] survey of the immunochemical purity of commercially available antivenoms has disclosed a wide variety of composition" (Ex. 1006, 15), and that "[o]nly a few are nearly pure $F(ab)_2$ immunoglobulins and some are even crude unpurified hyperimmune horse serum." *Id.* Petitioner does not point to, and we do not find, any mention of antivenoms containing Fab fragments. Moreover, the WHO Report states

that "proposed international standard antivenoms," including one effective against *Crotalus adamanteus*, "should be an almost pure $F(ab)_2$ plasma fraction." Ex. 1006, 37.

*2. Analysis*

With respect to claim 1, Petitioner, relying on Dr. Kossiakoff's testimony, contends that:

> [A person of ordinary skill in the art] would have had a reason to combine the teachings of Chang and the WHO report to arrive at the subject matter recited by independent claims 1 and 20, and . . . would have had a reasonable expectation of success in doing so. Chang teaches an antivenom composition comprising Fab fragments that bind cobrotoxin and are capable of neutralizing both cobrotoxin and cobra venom, and the WHO report discloses *Crotalus* genus antivenoms. Ex. 1002, ¶83. A [person of ordinary skill in the art] would have been motivated to combine the teachings of the two references to generate an antivenom having the *in vivo* activity of the Fab fragment-containing antivenoms (as in Chang), applied to *Crotalus* (as in WHO), which would not cause serum sickness to take advantage of Fab fragment *in vivo* characteristics. *See* Ex. 1002, ¶¶95-96. The resulting antivenom composition would comprise Fab fragments (as in Chang) against *Crotalus* snake venom (as in WHO). *Id.* Because of Chang's effectiveness in neutralizing cobra snake venom, a [person of ordinary skill in the art] would have had a reasonable expectation of success because the [person of skill in the art] would only be applying the teachings to a different species of snake. *Crotalus* venom would also have . . . reasonably been expected to behave similarly to cobra venom *in vivo*.

Pet. 39–40.

As Dr. Kossiakoff explains, "the WHO report discloses that whole antibody based antivenom . . . [against Crotalidae] causes unwanted immune reactions" and "[a]s of October 9, 1984, Fab fragments were known to be less prone to have immune reactions than whole antibody antivenoms." Ex. 1002 ¶ 96. "As such, a [person of ordinary skill in the art] reading Chang would also have had a reason to extend Chang's Fab fragments to fragments against *Crotalus* venom because Fab fragments would cause less unwanted immune reaction." *Id.*

In addition, with respect to independent claim 20, which requires that the Fab fragments neutralize the lethality of *Crotalus* venom in the absence of IgG and $F(ab)_2$, Petitioner contends that one of ordinary skill in the art, "would have had a reason to keep the advantages of Fab fragments by including a sufficient quantity of the Fab fragments such that they neutralize the lethality of *Crotalus* venom, regardless whether IgG or F(ab)2 fragments are present." *Id.* at 44.

Patent Owner contends, at least in part, that "Chang teaches that antibody [Fab] fragments can be useful as a **research tool** for studies on cobrotoxin" (Prelim. Resp. 32), but "the only statement in Chang that suggests a potential therapeutic application focuses on whole [purified] antibodies" (*id.* at 33).

We agree with Patent Owner on this point—Chang explicitly characterizes both the Fab fragments and the purified antibody as "valuable tools for an immunochemical approach to the elucidation of the toxic nature

of snake venom" (Ex. 1005, 7), but only the purified antibody is mentioned in connection with "the therapy of snake bites" (*id.*), despite Chang's observation that "[t]he specific neutralizing capacity of F I [the fraction containing Fab fragments] was even higher than that of the purified antibody" (*id.* at 4, Table II).

Moreover, Patent Owner contends that Petitioner's argument "is based on the assumption that [a person of ordinary skill in the art] would have believed that experimental results obtained using cobrotoxin, the single dominant toxin of the [Formosan] cobra venom, could easily be extrapolated to complex venoms such as venom of the *Crotalus* genus." Prelim. Resp. 35–36.

Patent Owner contends that it is not the case that one of ordinary skill in the art would have "extrapolat[ed] the teachings of Chang to such venoms." *Id.* at 36.

> [C]obrotoxins, as disclosed in Chang, are relatively small, low molecular weight proteins. Ex. 2016 ¶ 87; Ex. 2015 ¶ 260. A POSA [person of ordinary skill in the art] may have considered such low molecular weight antibody fragments, such as Fab fragments, to have useful pharmacokinetic characteristics for neutralizing **small toxins**. Ex. 2016 ¶ 87. However, *Crotalus* toxins are significantly larger than cobrotoxins. Ex. 2016 ¶ 88. Due to both their low molecular weight, and their monovalent (single antigen-binding) nature, which could render them unable to cross-link to larger molecules, a [person of ordinary skill in the art] would have been concerned that Fab fragments would not be effective against these **larger molecules**. *Id*. Thus, a [person of ordinary skill in the art] would not have

> applied the teaching in Chang of compositions comprising Fab fragments to the pursuit of antivenom for the *Crotalus* genus.

Prelim. Resp. 37 (citing Ex. 2016 (Rebuttal Report of Dr. Richard C. Dart); Ex. 2015 (Rebuttal Report of Professor Stephen MacKessy)).

Petitioner does not address the similarities and/or differences between cobrotoxin, the dominant, relatively small toxin in cobra venom, and the toxins in *Crotalus* toxin. Moreover, Petitioner has not explained adequately why Chang's disclosure would have given one of ordinary skill in the art a reason, at the time of the invention, to develop an Fab fragment-based antivenom pharmaceutical composition against *Crotalus* venom in the first place, particularly in light of the WHO Report, which teaches explicitly that "international standard antivenoms . . . should be an almost pure $F(ab)_2$ plasma fraction." Ex. 1006, 37.

Having considered the arguments and evidence presented with the Petition, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge to claims 1–7, 9–18, and 20–22 on the basis of obviousness over Chang and the WHO Report.

### *E. Claims 8 and 19—Asserted Obviousness over Chang, the WHO Report, and Smith*

#### *1. Smith (Ex. 1007)*

Smith discusses the immunogenicity and kinetics of distribution and elimination of digoxin-specific IgG and Fab fragments, and teaches that "digoxin-specific Fab fragments undergo more rapid and extensive distribution to the extracellular compartment and also more rapid renal

excretion than IgG" and "are significantly less immunogenic than the parent IgG population." Ex. 1007, 1. Smith teaches that "[r]elatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance." *Id.* at 10.

*2. Analysis*

Petitioner contends that a person of ordinary skill in the art "would have recognized that Fab fragments are particularly suited for treating snake bite victims because they act quickly on toxins and are effective at neutralizing snake venoms." Pet. 48 (citing Ex. 1002 ¶ 134). Petitioner contends "because of the rapid clearance of Fab fragments, to obtain continued control of the toxic effect from snake venoms," a person of ordinary skill in the art "would have been motivated to make and administer a composition comprising Fab and $F(ab)_2$ fragments." *Id.* (citing Ex. 1002 ¶¶ 135–139. Dr. Kossiakoff asserts that a person of skill in the art "would have understood that the pharmacokinetic properties of Fab and IgG or $F(ab)_2$ would complement each other." Ex. 1002 ¶ 139.

To the extent this challenge is based on Chang and the WHO Report, it suffers from the same infirmity as that discussed above. Further, as in the ground discussed above, Petitioner does not address the similarities and/or differences between digoxin and the toxins in *Crotalus* toxin, even though the Smith reference was asserted in a rejection against the claims during prosecution of the '414 patent, a similar issue was raised, and the rejection was ultimately withdrawn. *See, e.g.*, Ex. 1016, 1194–95, 1538–39. Thus,

Petitioner has not explained adequately how Smith cures the infirmity in Petitioner's proposed combination of Chang and the WHO Report

Having considered the evidence and arguments presented in the Petition, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge to claim 8 and 19 on the basis of obviousness over Chang, the WHO Report, and Smith.

*F. Motion to Seal*

Patent Owner's Preliminary Response (Paper 12) was accompanied by a Motion to Seal its Preliminary Response and Exhibit 2033, an associated exhibit (Paper 14, "Motion to Seal"), and a redacted version of the Preliminary Response (Paper 13).

As we did not rely on the material Patent Owner sought to seal, we decline to address the merits of the Motion to Seal. Patent Owner is authorized to file a motion to expunge any material that it seeks to keep confidential within thirty (30) days of the date of this decision, or within thirty (30) days of a decision on rehearing, if rehearing is requested.

## III. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–22 of the '414 patent are unpatentable under 35 U.S.C. § 103(a).

## IV. ORDER

Accordingly, it is

ORDERED that the Petition is denied and no *inter partes* review is instituted.

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