UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

Petitioner,

v.

SHANGHAI MIRACOGEN INC.

Patent Owner.

Case IPR2025-00685

U.S. Patent No. 10,792,370

Title: Antibody-Drug Conjugate

PETITIONERS' RESPONSE TO PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL OF INSTITUTION

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I. INTRODUCTION

This is a straightforward case where discretionary denial should be declined and where Institution should be granted because the Petition relies on prior art that was never considered by the Office and the patent is facially obvious and was only allowed based on material error by the Examiner. It is largely undisputed that all Patent Owner did was take someone else's prior art antibody – BA03 – and attach this to a well-known linker-payload construct – vc-MMAE – which Patent Owner admittedly ***bought off the shelf.*** (*See* EX1001, 19:27-28 ("purchased from Haoyuan Chemical Technology Co.").) Patent Owner did not so much as *develop* this Antibody Drug Conjugate ("ADC"), but merely *copied* the prior art. Yet, despite its trivial effort, Patent Owner, inexplicably, now has expansive and exclusionary claims that cover any ADC containing an antibody with the same CDR sequences as the prior art antibody BA03 attached to any cleavable linker and any cytotoxic payload – coverage that blocks thousands of potential cancer therapies, including Petitioner's ADC candidate drug which has received three FDA fast track designations. (*See* EX1100, 1.)

As the Petition explains, the Examiner continuously rejected the pending claims for being obvious over the BA03 antibody (Liu) and Tikhomirov, which disclosed ADCs with the same vc-MMAE linker-payload construct as Patent Owner's working examples. Patent Owner advanced the same argument

throughout prosecution: that even though Tikhomirov disclosed ADCs with the same cleavable linker used by Patent Owner, Tikhomirov also disclosed that ADCs using cleavable linkers with certain anti-microtubule payloads could be potentially toxic to non-tumor cells. Patent Owner thus argued that its use of cleavable linkers was "unexpected" because Tikhomirov "taught away" from using them in ADCs.

None of the grounds of the Petition relies on Tikhomirov. While Patent Owner faults the Petition for relying on BA03 (Liu) as prior art, Petitioner would of course rely upon this antibody; after all, Patent Owner never tried to distinguish Liu during prosecution since it was undisputed that Patent Owner used this prior art antibody for its ADC.

Patent Owner's discretionary denial brief ("DDB") should be rejected because both Grounds 1 and 2 rely on Wei as their primary reference, and Wei was never considered by the Office during prosecution. Patent Owner tries to argue that Wei is cumulative to references that were before the Examiner, such as Tikhomirov, and Leanna, which was never discussed during prosecution but only listed on an IDS. But as demonstrated below, Wei is materially different from Leanna for several reasons – the most evident being that, unlike Leanna, Wei actually developed humanized cetuximab ADCs with cleavable linkers which are virtually identical to Patent Owner's preferred embodiment. Moreover, Wei actually contains experimental data of what Patent Owner argued was "missing"

from Tikhomirov during prosecution – cleavable linker ADCs which had low toxicity to non-tumor cells. By law, asserted art such as Wei, which was never considered by the Examiner, cannot be considered cumulative or substantially the same under the discretionary denial framework of *Advanced Bionics*, and therefore Patent Owner's requested relief must be denied.

Patent Owner's attempt to rely on certain factors identified in the Acting Director's March 26, 2025 Memorandum ("Director's Memo") fails considerably. For one thing, Patent Owner ignores any "settled expectations" of the parties, such as the length of time the claims have been in force. Here, because the '370 patent only issued on October 6, 2020 (less than 5 years from the date of the Petition), this clearly weighs against discretionary denial. As to the factors it does argue, Patent Owner identifies no purported weakness of the unpatentability challenge in the Petition but only improperly tries to incorporate a POPR that does not even exist yet. Patent Owner's purported "public health benefits" are also just as self-serving, especially since Patent Owner fails to recognize that it can still develop its pipeline product even if the '370 patent is invalidated. While Patent Owner touts FDA fast track approval of its product, Petitioner has this as well for its product, and this only magnifies the improper reach of the Challenged Claims. Finally, Patent Owner misconstrues the change in judicial precedent factor, which is tied to the parties' settled expectation, and which Patent Owner failed to even address.

II. LEGAL STANDARD FOR DISCRETIONARY DENIAL UNDER SECTION 325(D)

The Board considers whether the same or substantially the same prior art or arguments were previously before the Office during prosecution. 35 U.S.C. § 325(d); *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 at 7-8 (PTAB Feb. 13, 2020) (precedential). In making this consideration, the Board uses a two-part test: (1) whether the same or substantially the same art or arguments were previously presented to the Office; and, if the first part is met, (2) whether the petitioner has shown that the Office erred in a material way with respect to patentability. *Id*. at 8.

In applying this framework, the Board should consider the following factors:

(a) [T]he 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

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

Factors (a), (b), and (d) guide consideration of the first prong of *Advanced Bionics* and factors (c), (e), and (f) guide consideration of the second prong. *Oticon Med. AB v. Cochlear Ltd*., IPR2019-00975, Paper 15 (Oct. 16, 2019) (precedential).

In the Director's Memo, the PTAB outlined a non-exhaustive list of relevant considerations for discretionary denial including:

1. Whether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims;

2. Whether there have been changes in the law or new judicial precedent issued since issuance of the claims that may affect patentability;

3. The strength of the unpatentability challenge;

4. The extent of the petition's reliance on expert testimony;

5. Settled expectations of the parties, such as the length of time the claims have been in force;

6. Compelling economic, public health, or national security interests; and

7. Any other considerations bearing on the Director's discretion.

III. ARGUMENT

A. Petitioner's Prior Art References And Arguments Are Materially Different From Those Considered By The Examiner And Therefore The Board Should Decline Discretionary Denial.

Petitioner relies on Wei as its primary reference for Grounds 1 and 2 of the Petition, and Wei was neither cited nor discussed anywhere during prosecution. This alone proves fatal to Patent Owner's request for discretionary denial. For the reasons discussed below, Wei is not cumulative to Leanna or the issues discussed during prosecution regarding Tikhomirov. Moreover, to the extent Leanna was considered by the Examiner because it was listed on an IDS, it was material error for the Examiner to allow the claims without recognizing Leanna, which also compels denial of Patent Owner's request for discretionary relief.

1. Wei is not cumulative to Leanna because of substantial differences

Rather than make a serious attempt at analyzing the differences between Wei and Leanna, Patent Owner instead resorts to attorney argument by alleging that Petitioner "implicitly admits" that these references are cumulative based on statements within the Petition. (DDB at 5-6). But Patent Owner's perfunctory argument cannot withstand scrutiny. As Patent Owner should know, any grounds for Petition need to prove that prior art references meet certain elements of the claims and are distinguished from references and arguments raised during prosecution. This is exactly what Petitioner did when it stated, for example, that

Wei and Leanna, both disclosed certain claimed elements (*i.e.,* Pet. at 34 ("disclose anti-EGFR ADCs with cleavable linkers without any toxicity concerns associated with cleavable linkers")) and did not suffer from the same criticisms that Patent Owner leveled against Tikhomirov during prosecution (*i.e.,* Pet. at 44 ("do not focus exclusively on non-cleavable linkers but have working examples of ADCs using cleavable linkers;" "nothing in Wei and Leanna would indicate to a POSA that cleavable linkers used in anti-EGFR ADCs are disfavored;")). However, just because both references qualify as grounds for challenging the patentability of Patent Owner's claims, this does not mean that they are cumulative. *See Juniper Networks, Inc. v. Swarm Tech. LLC*, IPR2021-01445, Paper 15 at 16 (PTAB March 2, 2022) ("The issue is not just whether the same elements can be found in each of the references, but whether the elements function the same way. That is, even though Leong and Bates have the same elements, that does not mean that the elements interact with each other the same way or perform the same functions as recited in the claims."); *PLR Worldwide Sales Ltd. v. Flip Phone Games Inc.*, IPR2024-00200, Paper 9 at 16 (PTAB May 10, 2024) ("Such high-levels of similarity are to be expected as all of the references involve [subject matter of the claims]. But such high-level similarity is not sufficient. Instead, Patent Owner must demonstrate that the references relied on in the Petition are substantially the same in all material respects to the prior art the Examiner actually relied on.");

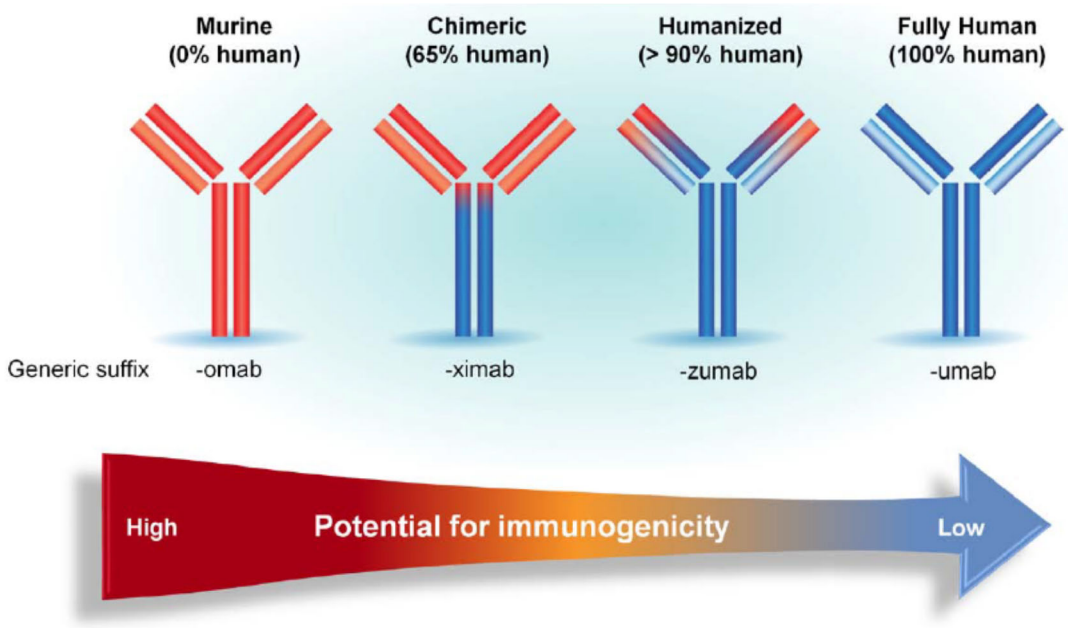
Geneoscopy Inc. v. Exact Scis. Corp., IPR2024-00459, Paper 9 at 28 (PTAB July 26, 2024) ("Patent Owner states that, like Vilkin, Levi describes an automated iFOBT that was more efficient than gFOBTs. [internal citation omitted] We are not persuaded. The mere fact that Levi and Vilkin generally describe the same work by the same group does not mean their disclosures are the same.").

As discussed in the Petition, there are material differences between Wei and Leanna, which Patent Owner glaringly ignores in its DDB, and thus, cannot be considered cumulative or substantially the same for purposes of satisfying the first prong of *Advanced Bionics*. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 15 (holding that prior art is substantially the same if "Petitioner relies on [the new art] in substantially the same manner as the Examiner cited [the previous art] during prosecution such that [the new art] discloses substantially the same information as [the previous art] in relevant part.").

First, unlike Leanna, Wei is directed to modified cetuximab antibodies and ADCs using these modified antibodies. This is a critical difference because the preferred embodiment of the '370 patent uses the prior art BA03 antibody (Liu) to describe its claimed ADCs, and BA03 is also a modified cetuximab antibody. In fact, the '370 patent describes that the whole purpose of its alleged invention was trying to make ADCs by modifying existing commercialized anti-EGFR antibodies, such as cetuximab. (*See* EX1001, 1:57-60 ("At present, there are two

anti-epidermal growth factor receptor antibodies in the market, one is human-mouse chimeric antibody C225 antibody (Erbitux or Cetuximab…").) Thus, the fact that Wei disclosed ADCs using modified cetuximab antibodies would have provided the POSA with even more motivation to combine this with the prior art BA03 modified cetuximab antibody of Liu. *See* Pet. at 2 ("the motivation to combine the prior-art BA03 antibody with vc-MMAE in an ADC was also known because, among other things, Liu discloses that the BA03 antibody has several advantages over the prior art."); (EX1002, 275.)

Second, not only does Wei disclose ADCs with modified cetuximab antibodies, Wei also disclosed that these cetuximab antibodies used for the ADCs were ***humanized***, just as the prior art BA03 antibody is a humanized cetuximab antibody. Leanna does not disclose ADCs using humanized cetuximab antibodies. As explained in the Petition, the progression from murine to chimeric to humanized antibodies was certainly a known driver in antibody and ADC development because this led to lower immunogenicity in patients.



(EX1034, 4.)

Thus, this provided even more motivation to combine the humanized cetuximab ADCs of Wei with the humanized cetuximab BA03 antibody of Liu to arrive at the Challenged Claims, which is another critical factor distinguishing Wei from Leanna. *See e.g.*, Pet. at 39-40 (in discussing motivation to combine, "both Wei and Liu disclose and characterize humanized anti-EGFR antibodies, which a POSA would recognize as having lower immunogenicity than murine and chimeric antibodies."); *id.* at 42 ("it was this well-known progression of antibody engineering, from murine to chimeric to humanized antibodies, that compelled the Office to conclude that ADCs using the antibody of claim 1 were obvious over the prior art.").

In fact, because Wei's ADCs employed modified and humanized cetuximab antibodies along with the same cytotoxic payload and linker as the preferred embodiment of the Challenged Claims, Petitioner's expert – Dr. Bournazos – concluded in his supporting declaration that the ADCs disclosed in Wei are virtually identical to those covered by claim 1 of the '370 patent. (*See* EX1002, ¶188 ("In fact, Wei discloses a humanized version of its cetuximab variant ADC – huY104D-MMAE – which is substantially identical to the humanized cetuximab – vc-MMAE (MYK-3) disclosed as preferred embodiments in the '370 patent and claimed by the Challenged Claims.").)

Third, as discussed in the Petition, Patent Owner misled the Office by apparently convincing the Office to allow the claims because the prior art reference on record – Tikhomirov – allegedly taught away from having a POSA use cleavable linkers to arrive at the anti-EFGR ADCs of the Challenged Claims. Tikhomirov states that an ADC using a cleavable linker "potentiates its toxicity" against both normal cells and cancer cells," and Patent Owner latched onto this statement which resulted in a number of material errors committed by the Examiner regarding Tikhomirov. Pet. at 45–48.

While both Leanna and Wei disclose none of these toxicity concerns regarding cleavable linkers, Wei goes even further than Leanna in affirmatively refuting Patent Owner's arguments during prosecution that ADCs using cleavable

linkers have the potential of being toxic to normal, non-tumor cells. As explained in the Petition, the humanized cetuximab variant ADCs of Wei exhibited reduced growth inhibition of ***non-tumor*** cells compared to the chimeric antibody at physiological pH (pH of the human body). Wei states:

> Therefore, these results show that ADC conjugates of the humanized forms of the Y104D- and Y104E-anti- EGFR variants exhibit greater pH-dependent activity than the chimeric Y104D-MMAE conjugate. For example, while each are as effective as the chimeric Y104D-MMAE for inhibiting tumor cell growth at pH 6.8, each exhibit reduced growth inhibition of non-tumor kératinocytes at pH 7.4 compared to the chimeric Y104D-MMAE.

(EX1005, [1139].).

Therefore, the Petition concludes that "[t]his would have provided even more motivation to create the humanized ADCs of claim 1 because humanized cetuximab variant ADCs were more selective in targeting tumor cells than chimeric ADCs." Pet. at 41; (*see also* EX1002 at ¶188 ("Notably, Wei teaches that its humanized cetuximab variant ADCs exhibited more selective killing of tumor cells by reducing growth inhibition of non-tumor cells compared to the chimeric antibody at physiological pH. (EX1005 at ¶ [1139].) Thus, Wei provides further motivation for a POSA to create ADCs with a humanized anti-EGFR antibody, such as BA03.").) Again, these explicit scientific results and conclusions within

Wei, which wholly reject Patent Owner's arguments regarding toxicity of cleavable linker ADCs in Tikhomirov, is yet another compelling difference between Wei and Leanna which precludes Patent Owner's request for discretionary denial.

Fourth, the Background of the '370 patent makes clear that Patent Owner's intended contribution over the prior art was **not** the overly broad ADC genus claims of several of the Challenged Claims, but was instead the development of ADCs which were more effective in treating patients who had particular genetic mutations, such as the KRAS mutation. Because existing therapies, such as cetuximab, did not seem to inhibit tumor growth in patients with this mutation, Patent Owner purported to develop ADCs that allegedly solved this problem by attempting to treat patients who were afflicted with this unique genetic mutation. (*See* EX1001, 2:50-55 ("Therefore, it is in need in the art to have humanized anti-epidermal growth factor receptor antibody drugs with biological activity, especially antibody drugs, such as antibody-drug conjugates, with curative effects to KRAS mutants, so as to improve therapeutic efficacy and reduce side effects.").) Patent Owner prosecuted ADC claims specifically directed to treating patients with this KRAS mutation, along with another mutation – BRAF, and these claims eventually matured into claims 20 – 23. (*See id*., *e.g.*, claim 20 ("The method according to claim 17, wherein the tumor is a tumor with KRAS gene mutation.");

claim 21 ("The method according to claim 17, wherein the tumor is a tumor with BRAF gene mutation.").)

Critically, Wei specifically discloses humanized cetuximab ADCs which inhibit tumor activity in tumors which have both these KRAS and BRAF gene mutations. For example, the Petition states that:

> Wei discloses that the Y104D-MMAE and huY104D-MMAE were tested in breast cancer xenograft models (MDA MB 231M TNBC) of KRAS-mutated tumors, and that these ADCs "exhibit a strong anti-tumor response in KRAS mutated, EGFR+ tumor model" and that "[t]he anti-tumor response of each of the tested antibodies achieves tumor growth regression." (*Id.*, [1116]-[1127].)

Pet. at 63.

> As discussed above, Wei discloses that the Y104D-MMAE and huY104DMMAE ADCs were tested in breast cancer xenograft models (MDA MB 231M TNBC) and exhibited a strong anti-tumor response and achieved tumor growth regression. As of the earliest possible effective filing date of the Challenged Claims, it was known that the MDA MB 231M TNBC tumors tested with Wei's ADCs are BRAF-mutated tumors. (EX1018, 939, 942 ("MDA-MB-231 (KRASG13D and BRAF-G464V mutations)").)

Id. at 64.

As a result, the Petition, along with Dr. Bournazos' supporting declaration, conclude that claims 20–23 are obvious over Wei and Liu. *See id.* at 63 – 65.

The Petition relies only upon Wei, and specifically not Leanna, to disclose these crucial findings regarding ADCs that treated tumors with these KRAS and BRAF mutations. Thus, this too significantly distinguishes Wei from Leanna, which further provides support for the Office to decline exercising its discretion to deny the Petition based on Patent Owner's erroneous arguments of cumulativeness between Wei and Leanna. *See Jumio Corp. v. FaceTec, Inc.*, IPR2025-00108, Paper 17 at 9-13 (PTAB June 9, 2025) (in declining discretionary denial, "Although both Todorki and Tanii teach image distortion, the types of distortion the references are cited for are materially different… These specific disclosures relied upon by Petitioner from Tanii demonstrate that Petitioner does not rely on Tanii in the same manner as the Examiner relied on Todoroki for during prosecution.); *Dr. Squatch, LLC v. The Proctor & Gamble Co.*, IPR2024-01498, Paper 9 at 33 (PTAB April 11, 2025) (in declining discretionary denial, "We do not discern that any of Lesniak, Phinney, Bianchi '254, Native, and Sturgis to disclose that use of magnesium hydroxide and therefore Easy Homemade is not cumulative to any of Lesniak, Phinney, Bianchi '254, Native, and Sturgis."); *Amazon.com, Inc. v. NL Giken Inc.*, IPR2024-01161, Paper No. 11 at 44 (PTAB February 26, 2025) (in declining discretionary denial, "Although certain aspects of

Cooper and Kutsuna are similar, there exist material differences between their disclosures with respect to key features.")

2. Wei is not being used in the Petition for substantially the same arguments that Patent Owner used to overcome Tikhomirov during prosecution.

Patent Owner tries to distort the discretionary denial analysis of *Advanced Bionics* by arguing that Petitioner is using Wei "for substantially the same teachings and arguments as the Examiner used Tikhomirov for during prosecution." (DDB at 7.) As discussed in the Petition, the pending claims were rejected numerous times over the span of several years based on the Examiner's understanding that Tikhomirov disclosed an anti-EGFR antibody using the same cleavable linker and cytotoxic payload as the preferred embodiment of the '370 patent, and therefore, its combination with the prior art BA03 antibody of Liu rendered the claims obvious. Despite these numerous rejections, Patent Owner only had one response – that Tikhomirov disclosed that cleavable linkers could potentially be toxic to normal cells and therefore constituted a "teaching away" from the Challenged Claims. *See supra* at III.A.1 (Third point). While the Examiner provided no reasons for allowing the claims, given that Patent Owner essentially recycled the same response regarding Tikhomirov throughout prosecution, it is more than likely that the claims were allowed because the Examiner was led into error by concluding that a POSA would understand that

ADCs with cleavable linkers (as opposed to non-cleavable linkers) are toxic to non-tumor normal cells.

However, as discussed above, Wei taught just the opposite. Not only was Wei devoid of Tikhomirov's concerns that ADCs with cleavable linkers could potentially cause toxicity to normal cells, the humanized cetuximab ADCs with cleavable linkers of Wei exhibited reduced growth inhibition of ***non-tumor*** cells and therefore were not toxic to these normal cells. Therefore, Wei cannot be cumulative to the prosecution issues regarding Tikhomirov since Wei actually discloses what the Office concluded was lacking in the prior art in allowing the claims – namely, that anti-EGFR ADCs with cleavable linkers are not toxic to non-tumor cells. Under these circumstances, where the art cited in the Petition specifically addresses what the Examiner understood was ***missing*** from the prior art in allowing the claims, the Board has consistently held that Petitioner's art is not cumulative, and therefore, discretionary denial is not appropriate. *See BMW of N. Am., LLC v. Foras Techs. Ltd.*, IPR2024-01346, Paper 7 at 20 (PTAB March 7, 2025) (in declining discretionary denial because the references were not cumulative, "Petitioner relies on the additional references Arai and Landry for teachings that the applicants asserted were missing from Safford and Fox during prosecution."); *Axion Biosystems, Inc. v. Agilent Techs., Inc.*, IPR2024-01467, Paper 9 at 28-29 (PTAB March 13, 2025) (in declining discretionary denial, Board

ruled that "Oka [prosecution art] is not cumulative to Jones [petition's art] because Jones "clearly teaches" features applicant argued were lacking in overcoming the "Examiner's rejections based on Oka".); *Dish Network LLC v. Digit. Broad. Sols.*, IPR2023-00976, Paper 8 at 30-31 (PTAB December 11, 2023) (in declining discretionary denial, the Board found that the art asserted in the petition was not cumulative because it taught "displaying the entire video program during a first time period 'regardless of a playback state of said DVR'" which Patent Owner stated that the prosecution art "failed to disclose."); *PLR Worldwide Sales Ltd. v. Flip Phone Games Inc.*, IPR2024-00200, Paper 9 at 16-17 (PTAB May 10, 2024) (in declining discretionary denial, the Board found "substantial differences between the prior art [sic] relied on by Petitioner and the prior art cited by the Examiner" because petitioner's art teaches "limitation 1(d)" and "the Examiner allowed the claims based on the cited prior art not including limitation 1(d).").

Moreover, Wei is not cumulative to Tikhomirov because Wei is directed to ***humanized*** cetuximab ADCs; the cetuximab antibody used in the ADCs of Tikhomirov were not humanized but were chimeric. (*See* EX1009, 12.) As discussed above, the humanized cetuximab ADCs of Wei would have provided even more motivation to a POSA to combine this reference with the BA03 humanized cetuximab of Liu since both references disclose humanized antibodies,

which had advantages over chimeric antibodies because of their reduced immunogenicity profile. *See supra* at III.A.1 (Second point).

In addition, Wei is not cumulative to other prior art references raised during prosecution and briefed in Patent Owner's DDB as being related to arguments concerning Tikhomirov. Specifically, while the Examiner rejected the pending claims in part because Doronina showed greater potency of ADCs using cleavable linkers over those using non-cleavable linkers, as Patent Owner argued during prosecution, Doronina's ADC utilized an anti-CD30 antibody, not the anti-EGFR antibody of the instant claims, and certainly not the humanized cetuximab antibody of the preferred example. (EX1004, 247; EX1029, 1.) Patent Owner explained:

> First, D5 [Doronina] relates to enhanced activity of monomethylauristatin F through monoclonal antibody delivery and analysis of linker technology on efficacy and toxicity. The antibody used in D5 is an anti-CD30 antibody, cACl0. Because the target to which an ADC binds influences the efficacy of the ADC, and because the target of the ADC of D5 is different from the target of the claimed ADC of the present application, EGFR, D5 fails to provide a sufficient motivation for one of ordinary skill to use a cleavable linker to link an anti-EGFR antibody and MMAE together…Thus, one skilled in the art would not have been motivated to use a cleavable linker with MMAE in an ADC with a target

> different from CD30 simply because D5 uses a cleavable linker and MMAE combination in an anti-CD30 ADC.

(EX1004, 299.)

Here, Wei's ADCs are not directed to the anti-CD30 antibody of Doronina, but employ an anti-EGFR humanized cetuximab antibody which makes Wei's ADCs substantially identical to the Challenged Claims. (EX1002, 188.) Thus, Wei is materially different from Doronina for the very same reasons that Patent Owner distinguished Doronina from the claims during prosecution, and thus Wei again fills the gap that Patent Owner argued was missing from the prior art. *See BMW of N. Am.,* IPR2024-01346, Paper 7 at 20.

Finally, as discussed above, Wei is also relied upon in the Petition for disclosing the claimed methods of treating tumors with the KRAS and BRAF gene mutations. *See supra* at III.A.1 (Fourth point). Because Tikhomirov was never relied upon by the Examiner for disclosing these treatment methods, this is yet another reason why Wei is not cumulative to Patent Owner's arguments regarding Tikhomirov during prosecution and why the Board should therefore decline discretionary denial.

Thus, under Part One of the *Advanced Bionics* analysis, the *Becton Dickinson* factors (a), (b), and (d) in this case demonstrate that Wei (or art substantially the same as Wei) ***was not*** presented to the Office and that the same or

substantially the same arguments concerning Wei ***were not*** previously presented to the Office. As discussed above, there are material differences between Wei and Leanna which prevent them from being considered cumulative (*Becton Dickinson* factors (a) and (b)). Moreover, there is no overlap between the arguments made during examination regarding Tikhomirov and the manner in which Petition relies on Wei. (*Becton Dickinson* factor (d)).

Since Wei is part of a new combination of references for Grounds 1 and 2 of the Petition that was never considered by the Examiner, the PTAB should decline discretionary denial because Patent Owner has not satisfied the first prong of *Advanced Bionics. See Advanced Bionics,* IPR2019-01469, Paper 6 at 8-9; *Thorne Rsch. v. Trs. of Dartmouth Coll.,* IPR2021-00491, Paper 18 at 8-9 (PTAB Aug. 12, 2021) ("we find that the same or substantially the same art or arguments were not previously presented to the Office during prosecution" because of new prior art combinations never considered by the Office); *Halliburton Energy Servs., Inc. v. U.S. Well Servs., LLC*, IPR2021-01036, Paper 12 at 20 (PTAB Jan. 19, 2022) (the first part of the *Advanced Bionics* framework was not satisfied where the Petition set forth obviousness grounds based on combinations involving a reference previously considered by the Examiner with other references that had not been considered); *K/S HIMPP v. Bragi GmbH,* IPR2023-01205, Paper 8 at 20 (PTAB Mar. 19, 2024) ("[A]lthough one reference, Shaffer, was previously presented to

the Office, in each asserted ground, Petitioner relies on either Hain or Hain in combination with Sørensen. Because neither of those references was before the office, Patent Owner has not satisfied the first prong of the *Advanced Bionics* test."); *ResMed Inc. v. New York Univ.*, IPR2022-00990, Paper 16 at 15-16 (PTAB Dec. 6, 2022) (first prong of the *Advanced Bionics* framework is not satisfied because "there are no rejections based on the combination of references asserted here.").

B. Discretionary Denial Should Also Be Declined Because The Office Committed Material Error Which Affected The Patentability Of The Challenged Claims

The Board should decline discretionary denial because even if the Board determines that Leanna was considered by the Examiner, the Examiner committed material error in allowing the claims for failing to recognize that Leanna in combination with Liu and Wei (Ground 2) render the Challenged Claims obvious. As discussed below, the Examiner erroneously disregarded the significance of Leanna and was misled into allowing the claims based on Patent Owner's defective unexpected results arguments.

1. Even if Leanna was considered by the Examiner, it was never discussed during prosecution which demonstrates material error by the Examiner for failing to recognize Leanna's significance.

Even if the Board determines that Leanna was considered by the Examiner because it was cited on an IDS, the Board should still deny Patent Owner's request

for discretionary denial because the Office erred in a manner material to the patentability of the Challenged Claims. As discussed above, Patent Owner advanced a single line of argument throughout prosecution in order to eventually overcome the numerous Office Action rejections: that the Office was wrong to rely upon Tikhomirov because rather than teach that anti-EGFR ADCs could be effective with cleavable linkers, Tikhomirov actually "taught away" from this because it stated that an ADC using a cleavable linker "potentiates its toxicity" against both normal cells and cancer cells.

However, Leanna does not express any of Tikhomirov's toxicity concerns regarding the use of cleavable linkers with anti-EGFR ADCs. As explained in the Petition, Patent Owner made the following arguments regarding Tikhomirov to overcome the obviousness rejections:

> (a) the only reference cited in the office Action that discloses a linker used in forming an anti-EGFR ADC, D1 [Tikhomirov], focuses almost exclusively on noncleavable linkers *(see especially* Abstract, the first sentence in the Summary of the Invention section on page 3),
> (b) D1 provides extensive disclosures and numerous examples of non-cleavable linkers *(see* pages 6, 13, and 14),
> (c) all the ADCs disclosed with experimental data in D1 uses a non-cleavable linker, SMCC, except that

> Cetux2C9-MMAE uses a cleavable linker, valine citrulline *(see* Examples I to 4),
> (d) Example 4 of D1 shows that the cleavable linker, Cetux2C9-MMAE, is not favorable compared to a noncleavable linker because this ADC with the cleavable linker had potentiated toxicity against normal cells *(see* Figure 13 and its description at the end of page 9), and
> (e) D1 states that "a safe anti-EGFR ADC **should** incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a **non-cleavable linker**" *(see* the last sentence of the first paragraph on page 30) (emphasis added).

(EX1004, 200 (emphasis in original).)

But as the Petition further explains, none of these points apply to Leanna because (a) rather than focus on exclusively non-cleavable linkers, Leanna has actual working examples of ADCs using cleavable linkers (EX1006, Examples 1, 4); (b) while Leanna does disclose ADCs with non-cleavable linkers, it also extensively discusses and teaches ADCs with cleavable linkers, including the specific vc cleavable linker disclosed as a preferred embodiment and claimed in the '370 patent (EX1001, 5:25-6:65; EX1006, 8.); (c) substantial amounts of the experimental data in Leanna are directed to anti-EGFR ADCs using cleavable linkers (EX1006, Examples 1-3, 6); (d) nothing in Leanna would indicate to a POSA that cleavable linkers used in anti-EGFR ADCs are disfavored; and (e)

Leanna teaches that a safe anti-EGFR ADC can incorporate a strongly antagonistic anti-EGFR antibody linked to an antimicrotubule payload by a ***cleavable linker***, especially since Leanna discloses and claims pharmaceutical compositions and methods of treatment using these cleavable linker ADCs (EX1006, 15, 34-51).

For example, Leanna describes a "pharmaceutical composition" as a specific embodiment and "methods of treating cancer" by administering the cleavable linker ADCs. (*Id.*, 8, 36 ("In one aspect of the invention, there is provided a ***method for treating a subject comprising administering a therapeutically effective amount of an anti-EGFR ADC*** in any of the compositions as described herein, wherein the subject has a disorder requiring treatment with the anti-EGFR antibody in the composition *(e.g.* a tumor, a cancerous condition, a precancerous condition, and any condition related to or resulting from hyperproliferative cell growth") (emphasis added).)

Leanna states further that:

> Also included in the invention are methods of treating cancer in a subject comprising administering a composition described herein to the subject such that cancer is treated. In one embodiment, the cancer is selected from the group consisting of squamous tumors (including, squamous tumors of the lung, head and neck, cervical, etc.), glioblastoma, glioma, non-small cell lung cancer, lung cancer, colon cancer, head and neck cancer,

> breast cancer, squamous cell tumors, anal cancer, skin cancer, and vulvar cancer.
>
> In one embodiment, the compositions of the invention are used to treat glioblastoma multiforme.
>
> In one embodiment, the compositions of the invention are used to treat a solid tumor having overexpression of EGFR. In one embodiment, the compositions of the invention are used to treat a subject having an advanced solid tumor likely to overexpress EGFR.
>
> In one embodiment, the compositions of the invention are administered intravenously.

(*Id.*, 8; *see also id*., 35 ("The unique specificity of the compositions comprising anti-EGFR ADCs ***provides diagnostic and therapeutic uses*** to identify, characterize, target and treat, reduce or eliminate a number of tumorigenic cell types and tumor types") (emphasis added); *id.*, 37 (describing pharmaceutical compositions and various excipients and carriers); *id*., 38 (describing co-administration of the anti-EGFR cleavable linker ADCs "with one or more ***additional therapeutic agents to treat cancer.***") (emphasis added); *id*., 49 (describing that the anti-EGFR cleavable linker ADCs can be provided as a "pharmaceutical kit" comprising a "lyophilized" form of the ADC and a diluent for injection); claim 49 ("A ***pharmaceutical composition*** comprising the composition of any one of claims 38-48 and a pharmaceutically acceptable carrier) (emphasis

added); claim 50 ("A ***method of treating cancer*** in a subject comprising administering the ***pharmaceutical composition*** of claim 49 to the subject, such that cancer is treated.") (emphasis added).)

Indeed, in explaining the rationale for the therapeutic effectiveness and safety of its anti-EGFR cleavable linker ADCs, Leanna specifically describes how these ADCs target the "toxic" cytotoxic payload to the specific site of the disease and that cleavage of the cytotoxic payload at the cancer site reduces the risk of toxicity to the patient's non-tumor cells. Leanna states:

> In one embodiment, the anti-EGFR antibody of the invention is conjugated to at least one MMAE (mono-methyl auristatin E). Monomethyl auristatin E (MMAE, vedotin) inhibits cell division by blocking the polymerisation of tubulin. ***Because of its super toxicity, it also cannot be used as a drug itself.*** In recent cancer therapy developments, it is linked to a monoclonal antibody (mAb) that recognizes a specific marker expression in cancer cells and directs MMAE to the cancer cells. In one embodiment, the linker linking MMAE to the anti-EGFR antibody is stable in extracellular fluid (i.e., the medium or environment that is external to cells***), but is cleaved by cathepsin once the ADC has bound to the specific cancer cell antigen and entered the cancer cell, thus releasing the toxic MMAE***

> ***and activating the potent anti-mitotic mechanism***. The structure of MMAE is provided in Figure 1.

(*Id.*, 31 (emphasis added).)

Thus, the POSA, reviewing this disclosure of Leanna, would not have any of the concerns expressed by Tikhomirov and advanced by Patent Owner during prosecution regarding the potential toxicity to normal cells based on ADCs with cleavable linkers. If anything, Leanna's explanation of specifically targeting cancer cells with an otherwise "super toxic" payload such that this payload can be cleaved at the cancer site, in addition to its repeated objectives or creating safe and effective methods of treating cancer with therapeutic amounts of the cleavable linker ADCs, would have alleviated any concerns that the POSA might have regarding toxicity issues with cleavable linker ADCs to normal cells. Indeed, as pointed out in the Petition, as of the filing of the Challenged Claims, there were only two FDA-approved ADCs—Mylotarg® (anti-CD33) and Adcetris® (anti-CD30)—for use in cancer treatments; **both** used cleavable linkers. (*See* EX1010, 3; Pet. at 50.) Hence, the Examiner's failure to recognize that Leanna nullifies Patent Owner's "teaching away" arguments regarding Tikhomirov was material error.

Under the second prong of *Advanced Bionics*, the Board considers "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics*, IPR2019-01469, Paper 6 at 8. "An example of a material error may include misapprehending or overlooking

specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Id*. The Board evaluates *Becton, Dickinson* factors (c), (e), and (f) in order to determine whether the Office committed material error.

Applied here, factor (c) – "the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection" – clearly supports a finding of material error, since Leana was never even discussed by Patent Owner or the Office during prosecution. Moreover, factor (e) – "whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art" – also weighs in favor of finding material error by the Office, since as explained above, Petitioner has clearly shown that Leanna contradicts Patent Owner's argument that Tikhomirov would have taught away from using cleavable linkers in ADCs because of toxicity concerns. Rather than being toxic, Leanna discloses that the cleavable linker mechanism of its ADCs prevents toxicity to the patient because the ADCs selectively release their cytotoxic payload at the cancer site and thus provides the basis of therapeutically effective and safe methods of treating cancer. Finally, factor (f) – "the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments" – is not applicable here. As discussed above, because Leanna was never even evaluated or argued during prosecution, there is no need to

rely upon additional facts or evidence to warrant reconsidering something that was never even addressed. Indeed, as the Board has recognized, "if the record of the Office's previous consideration of the art is not well developed or ***silent***, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f)." *Id.* (emphasis added).[1]

Here, the utter lack of any discussion of Leanna by Patent Owner and the Examiner during prosecution is a deafening silence that justifies a finding of material error by the Examiner, which precludes Patent Owner's request for discretionary denial. *See Klein Tools, Inc. v. Milwaukee Elec. Tool Corp*., IPR2024-01400, Paper 17 at 25-26 (PTAB April 8, 2025) (finding material error

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[1] In a transparent attempt to equate the Petition with the prosecution file history, Patent Owner erroneously frames the material error analysis of *Advanced Bionics* as requiring Petitioner to "show error in the Examiner's consideration of the argument [during prosecution] that a POSA would not have been motivated to combine Tikhomirov with Liu." (DDB at 13-16.) Not so. As discussed above and in the Petition, prong two's determination of Examiner error requires an examination of the asserted art in the Petition, which in this case is Leanna, not Tikhomirov, and whether the Examiner erred in this examination. *See Becton Dickinson* factors (c) and (e); *Advanced Bionics*, IPR2019-01469, Paper 6 at 8.

where despite patent owner's argument that the Examiner clearly understood the art, "***[g]iven the prosecution history's silence*** on Burchia and Metabowerke, however, we do not view the alleged understanding as in any way 'clear[]'") (emphasis added); *Amazon.com Inc. v. Nokia Tech*., IPR2024-01140, Paper 9 at 16 (PTAB February 12, 2025) (finding material error where the prosecution was "***silent***" as to the key prior art reference and "***there was no discussion or analysis of [this art] apart from its inclusion on the IDS***.") (emphasis added).

2. To the extent Patent Owner's unexpected results argument rebutted the prima facie case of obviousness, this too was material error.

As discussed above and in the Petition, the Examiner gave no reasons for allowing the claims, and therefore, the Examiner could have determined that despite a *prima facie* case of obviousness, Patent Owner's unexpected results arguments were sufficient to rebut this *prima facie* case.

Patent Owner paradoxically argues in its DDB that there could not have been a material error regarding its unexpected results arguments during prosecution because they were not made in the last Office Action response prior to allowance, thus suggesting that the Examiner already rejected Patent Owner's unexpected results argument prior to allowance. (DDB at 18-19.)

As much as Petitioner would like to believe that the Examiner rejected Patent Owner's unexpected arguments during prosecution (as the Examiner should

have since these arguments are in fact facially flawed), there is unfortunately enough ambiguity in the record which precludes outright disregard of these unexpected results arguments. For example, as noted, the Examiner did not give any reasons for allowance and never outright rejected Patent Owner's unexpected results argument. Moreover, in the last Office Action response prior to allowance, Patent Owner did again reference its prior unexpected results argument as a basis for traversing the obviousness rejection. (*See* EX1004, 298 ("Applicant respectfully traverses this rejection. Applicant argued against the previous obviousness rejection over D1 in view of D2, D3 and D4, and submitted that…(2) the ADC claimed in the present application is not obvious due to its unexpected superior property as demonstrated in Example 6 of the present application.").)

The Petition exhaustively demonstrated that Patent Owner's unexpected results arguments are flawed, and to the extent that the Examiner allowed the Challenged Claims by crediting these erroneous arguments, this too was material error which supports rejecting Patent Owner's request for discretionary denial.

For example, the Petition established that:

- The results of Example 6 of the '370 patent - allegedly showing that Patent Owner's cleavable linker ADC had a lower EC50 value compared to non-cleavable linker ADCs - ***was not unexpected but obvious.*** At the time of the filing of the '370 patent, there were multiple studies in the antibody

literature demonstrating that the vc cleavable linker used in Example 6 displays very potent efficacy both *in vitro* and *in vivo*, as well as favorable safety and stability.

- It was known in the prior art that drugs linked by cleavable linkers, such as vcMMAE (the cleavable linker-payload used in Example 6) were more likely to retain cytotoxic efficacy because drugs conjugated through a cleavable linker were more likely metabolized into their original unconjugated form to specifically target the intended tumor cells.
- The finding that neither MC-MMAE nor MCC-MMAE (which used non-cleavable linkers and were the subject of Example 6) have any activity was fully expected because the prior art taught that "MMAE, a protein-based anti-mitotic drug, is most potent in its native form and is therefore poorly suited for derivatization with non-cleavable linkers". (EX1002, 193; EX1015, 6.)
- As of the time of the filing of the Challenged Claims, there were only two FDA-approved ADCs—Mylotarg® (anti-CD33) and Adcetris® (anti-CD30)—for use in cancer treatments, yet **both** used cleavable linkers. (*See* EX1010, 3.) Moreover, there are currently fourteen FDA-approved ADCs available, twelve of which use cleavable linkers. Clearly, Patent Owner's argument ***that it was unexpected*** that ADCs using cleavable linkers would

be safe and effective defies the reality of the ADC scientific community and industry.

Pet. at 47-51.

Thus, to the extent that the Examiner allowed the Challenged Claims based on these faulty unexpected results arguments, this too was error by the Examiner which was material to the patentability of the Challenged Claims, which further compels declining Patent Owner's requested relief of discretionary denial.

C. None of Patent Owner's Purported "Other Factors" Support Discretionary Denial.

The additional factors identified in the Director's Memo do not provide any justification for discretionary denial in this case. Patent Owner identifies three such factors: the purported weakness of the unpatentability challenge in the Petition, purported compelling public health benefits related to the challenged patent, and a purported lack of changes in the law or judicial precedent. All three fail.

1. Patent Owner's arguments regarding the strength of the unpatentability challenge should not be considered.

The Director's Memo set up a "bifurcated" process to allow the Office to separately evaluate "(i) discretionary considerations [by the Director] and (ii) merits and other non-discretionary statutory considerations [by a PTAB panel of at least three APJs]." In its Request, Patent Owner fails to identify any purported weakness of the invalidity challenge. Instead, it solely relies on its "forthcoming

Patent Owner's Preliminary Response" which Patent Owner attempts to "incorporate[] by reference" into the Request.

First, Patent Owner's attempted incorporation of their nonexistent POPR is impermissible. *See* 37 C.F.R. §42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document. Combined … documents are not permitted.").

Second, even if such incorporation were permitted, which it is not, the allegedly incorporated document does not exist and Petitioner cannot reasonably be expected to respond to an argument Patent Owner has not made. Petitioner's instant response is due before Patent Owner's POPR and, thus Patent Owner's reliance on a nonexistent POPR deprives Petitioner of any notice or opportunity to respond to Patent Owner's arguments therein. Consequently, any consideration of Patent Owner's POPR arguments in the Acting Director's discretionary denial decision would violate Petitioner's constitutional and statutory due process rights. *See* 5 U.S.C. §553(c)(1) ("The agency shall give all interested parties opportunity for … the submission and consideration of facts [and] arguments.").

Notwithstanding the inclusion of the strength of the unpatentability challenge as a consideration, the Memo's bifurcated process contemplates that consideration of the merits is reserved for an appropriately constituted panel of

PTAB APJs. Certainly, the Memo does not contemplate allowing the Patent Owner to ignore the Office's rules and Petitioner's due process rights.

Third, the grounds of the Petition are strong and the strength of the unpatentability challenge weighs against discretionary denial. The claims of the '370 patent are unpatentable under 35 U.S.C. § 103 because they represent a routine and predictable combination of known elements disclosed in multiple prior art references that was evident to a POSA as of the '370 patent's effective filing date. Specifically, the claimed ADCs—comprising an anti-EGFR antibody covalently linked to a cytotoxic payload via a cleavable linker—would have been obvious to a POSA in view of Liu (which discloses the BA03 anti-EGFR antibody), in combination with Wei and/or Leanna (which disclose the use of cleavable linkers such as VC and cytotoxic agents such as MMAE in EGFR-targeting ADCs). Each component of the claimed invention was known in the art, and the references collectively teach their combination to form ADCs with therapeutic utility and improved properties, including reduced immunogenicity and potent cytotoxic activity. *See e.g.*, Pet. at 24.

Patent Owner's arguments during prosecution, including teaching away and unexpected results associated with cleavable linkers, are unavailing. The cited references expressly disclose the use of vc-MMAE linkers in EGFR-directed ADCs, and the alleged concerns are neither supported by scientific evidence nor

reflective of prevailing knowledge at the relevant time. *See id.* at 21, 41. Moreover, the widespread adoption of cleavable linkers in contemporaneous ADC development undermines any suggestion of teaching away or unpredictability. The combination of BA03 with a vc-MMAE linker–payload construct was the logical choice rendering the Challenged Claims obvious based on the prior art. *See id.* at 41-42. Accordingly, the claims of the ’370 patent should be found to have been obvious as of the effective filing date and invalid under § 103. In the absence of any permissible counter arguments, the strength of the unpatentability challenge weighs against discretionary denial.

2. Patent Owner’s arguments regarding compelling public health interests are pointless.

Patent Owner argues that its drug candidate, MRG003, has been granted Fast Track and Breakthrough Therapy designations by the FDA and states, without any evidence, that defending against the Petition would “create uncertainties on the Patent Owner’s ability to commercialize the MRG003 drug candidate.” (DDB at 20-21.) What Patent Owner does not do is explain how such regulatory designations ***require*** the maintenance of its excessively broad and undeserved exclusionary patent rights of the ’370 patent. Patent Owner’s drug has already received the Fast Track and Breakthrough Therapy designations and a review of the ’370 patent does not in any way impair Patent Owner’s ability to continue pursuing regulatory approval of its drug candidate.

It is notable that Patent Owner does not argue that the proceeds from MRG003 and its excessively broad exclusionary patent monopoly would fuel additional research and development into new treatments. Indeed, it cannot do so, because MRG003 is not currently on the market. As Patent Owner itself admits, there is no guarantee that MRG003 will even be a marketable drug. (*See* EX2003, 2 ("Warning: There is no assurance that the MRG003 will ultimately be successfully developed and marketed by the Company.").) Rather, Patent Owner appears to suggest that unexplained "uncertainties" related to its undeserved patent monopoly would cause ***it*** to decide against marketing MRG003. The Office should not consider this conclusory and unsupported claim. The implication here appears to be that, without the guarantee of an excessively broad exclusionary patent monopoly blocking all other therapies using the claimed antibody and its consequent windfall profits, Patent Owner ***itself*** would decide not to bring its alleged breakthrough cancer therapy to market. Plainly, such a position reveals that Patent Owner's incentive is not grounded in public health concerns, but rather in the ability to secure unwarranted monopoly profits. The Office should not credit arguments that place private gain above the public interest in promoting innovation and access to life-saving treatments.

To the contrary, deciding ***not*** to adjudicate Petitioner's unpatentability grounds would stifle the market for a host of other therapies which are markedly

different from Patent Owner's MRG003, yet fall within the overly broad scope of the '370 patent. As stated in Patent Owner's documents, "MRG003 is an ADC comprised of an EGFR-targeted monoclonal antibody conjugated with the potent microtubulin inhibiting payload monomethyl auristatin E [MMAE] via a valine-citrulline [VC] linker." (EX2003, 2.) Challenged Claim 1, however, is not limited to an MMAE payload and a VC cleavable linker. Rather, claim 1 blocks ***all*** ADCs comprising, not just the specific anti-EGFR antibody of Patent Owner's product, but the claimed antibody CDR sequences, which only constitute a limited subset of sequences of the actual BA03 antibody, linked with ***any*** cytotoxic agent by ***any*** cleavable linker. (*See* EX1001, 33:2-11.) Thus, even assuming, arguendo, that Patent Owner could identify any public health benefits tied to its patent rights, the '370 patent would effectively prevent any other therapy utilizing an ADC with these limited CDR antibody sequences, with ***any*** cytotoxic agent and ***any*** cleavable linker from reaching the market – even when the ADC is not indicated for the same disease.

Indeed, Patent Owner has produced no evidence that any drug candidate produced by Petitioner would have the same indication as its MGR003 drug candidate.

Moreover, Petitioner and its real parties-in-interest have made substantial investments in the development of their ADC cancer therapies (e.g., SYS6010, also

known as CPO301). For example, in April 2025, they initiated a Phase III, randomized, open-label, multi-center clinical trial (ClinicalTrials.gov Identifier: NCT06927986) comparing SYS6010 to standard platinum-based chemotherapy (cisplatin or carboplatin combined with pemetrexed) in patients with EGFR-mutated, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed following EGFR tyrosine kinase inhibitor (TKI) therapy. (EX1101, 1.) In addition, they are conducting a Phase 1b/2 clinical trial (ClinicalTrials.gov Identifier: NCT06775236) evaluating SYS6010 compared to chemotherapy in patients with advanced breast cancer and other EGFR-expressing solid tumors. (EX1102, 1.) In fact, Petitioner's SYS6010 is further along in clinical development within the United States. According to ClinicalTrials.gov, there are currently no active clinical studies for Patent Owner's MRG003 in the U.S. In contrast, Petitioner and its real parties-in-interest have initiated a first-in-human, multicenter, open-label, dose-escalation Phase I clinical trial in the United States (ClinicalTrials.gov Identifier: NCT05948865) to evaluate the safety, tolerability, and pharmacokinetics (PK) of SYS6010. (EX1103, 1, 3, 5.)

Notably, Petitioner's ADC product, SYS6010, has received three Fast Track Designations from the FDA: in June 2023 for EGFR-mutant metastatic non-small cell lung cancer (NSCLC) after EGFR-targeted therapies; in September 2024 for EGFR-overexpressing squamous NSCLC after chemotherapy and anti-PD-L1

therapy; and in May 2025 for advanced non-squamous NSCLC without EGFR mutations or other actionable genomic alterations (AGAs) after chemotherapy and anti-PD-L1 treatment. (EX1100, 1.)

As previously noted, Patent Owner's self-serving public health interest arguments collapse under the most basic scrutiny. Contrary to Patent Owner's unsupported assertions otherwise, it faces no genuine uncertainty regarding its ability to market its drug, regardless of the outcome of this proceeding. However, if discretionary denial is granted and Petitioner is unable to pursue its challenge of the '370 patent, Patent Owner would retain the ability to use its impermissibly broad exclusionary patent rights to block Petitioner's cancer treatments from the market. This uncertainty would place ***Petitioner's*** investments in its groundbreaking cancer therapies and the interests of patients in need of innovative treatment options at dire risk.

Far from contributing to any purported public health benefits, allowing Patent Owner's invalid blocking patent to remain unreviewed would ***suppress*** therapeutic innovation and ***limit*** patient access to potentially life-saving treatments and would cause serious harm to public health. Thus, public health considerations strongly weigh against discretionary denial.

3. The lack of any change in law or judicial precedent does not favor discretionary denial when the patent challenge is not based on a change in applicable law.

Without citing any authority, Patent Owner argues that the lack of any change in law or judicial precedent "favors discretionary denial." Petitioner does not argue that the '370 patent is invalid because of a change in applicable law. Petitioner, instead, argues that under the applicable law in-force as of the effective filing date of the '370 patent, it is invalid and should not have been issued. Further, Patent Owner has not argued for any settled expectations based on the length of time the patent has been in-force nor has it permissibly argued that the unpatentability challenge in the Petition is weak (since it is based entirely on impermissible incorporation by reference). At most, this factor is neutral to whether discretionary denial should be granted. Indeed, the applicable law as of the effective filing date compels a finding of unpatentability of the Challenged Claims for the reasons laid out in the Petition.

4. Settled Expectations of Petitioner Weigh Strongly Against Discretionary Denial.

As previously noted, the Director's Memo lists several considerations for evaluating whether a petition should be discretionarily denied. Patent Owner only briefed three, and all three fail to support discretionary denial as explained above. *See supra* Sections II and III.C, incorporated here. Petitioner additionally raises its own settled expectations in pursuing a proactive and early challenge of the '370

patent to protect its ability to market its ADC-based drug candidates in the United States.

The Office has recently granted discretionary denial on petitions challenging patents that have been in force for seven years or more without an invalidity challenge creating purportedly settled expectations on the Patent Owner. *See Dabico Airport Sols. Inc. v. AXA Power APS*, IPR2025-00408, Paper 21 at 2 (PTAB June 18, 2025) ("the challenged patent has been in force almost eight years, creating settled expectations"); *iRhythm, Inc. v. Welch Allyn, Inc.*, IPR2025-00363, Paper 10 at 3 (PTAB June 6, 2025) (since "one of the patents has been in force since as early as 2012 and Petitioner was aware of it as early as 2013," settled expectations supported denying institution). Most relevant to Petitioner's settled expectations in this case, the Office issued two decisions addressing discretionary denial in a series of five IPRs filed by the same petitioner against the same patent owner. The Office discretionarily denied two petitions challenging patents that "have been in force for nine and seven years, respectively." *Cambridge Indus.s USA Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00433, Paper 11 at 3 (PTAB June 26, 2025). The same day, the Office allowed three petitions to proceed to a merits panel challenging patents that "have not been in force for a significant period of time (issued in 2020, 2019, and 2019), and, accordingly, Patent Owner has not developed strong settled expectations that favor discretionary denial as to

at least those patents." *Cambridge Indus. USA Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00434, Paper 11 at 2-3 (PTAB June 26, 2025).

Here, Patent Owner has not argued any settled expectations based on the length of time the patent has been in force. The challenged patent issued in October of 2020, thus is within the statutory damages period of 35 U.S.C. §286. In view of the Office's recent decisions, Petitioner's settled expectation that proactive challenges will be reviewed on the merits strongly disfavors discretionary denial.

Additionally, Petitioner and its real parties-in-interest to the Petition have made use of the AIA trial system by proactively filing other petitions for review before the Patent Trial and Appeal Board to protect the market for its products. *See CSPC Pharm. Grp. Ltd. et al v. Ipsen Biopharm Ltd.*, IPR2025-00505, Paper 1 (PTAB Jan. 17, 2025) (challenged patent issued May 31, 2022). Both the instant petition and IPR2025-00505 were filed prior to the Memo's issuance and Petitioner, therefore, had settled expectations that its petitions would be reviewed in accordance with more than a decade of PTAB procedural precedent. These expectations also weigh against discretionary denial.

IV. CONCLUSION

Based on the foregoing, the Board should decline to exercise discretionary denial under § 325(d).

Dated: July 7, 2025

By: /s/ Joe Chen

Joe G. Chen, Ph.D.
(Reg. No. 70,066)
joechen@foxrothschild.com
Fox Rothschild LLP
212 Carnegie Center, Suite 400
Princeton, NJ 08540
Tel: (609) 844-3024
Fax: (609) 896-1469

Howard S. Suh (pro hac vice to be filed)
hsuh@foxrothschild.com
Fox Rothschild LLP
101 Park Avenue, 17th Floor
New York, NY 10178
Tel: (212) 878-7914
Fax: (212) 692-0940

Ryan N. Miller (Reg. No. 68,262)
rmiller@foxrothschild.com
2001 Market Street, Suite 1700
Philadelphia, PA 19103
Tel: (215)299-2901
Fax: (215)299-2150
Counsel for Petitioners

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioners' Response to Patent Owner's Request for Discretionary Denial of Institution contains, as measured by the word-processing system used to prepare this paper, 9604 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: July 7, 2025

By: /Joe Chen/
Joe G. Chen, Ph.D.
Reg. No. 70,066
Counsel for Petitioners

CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e), I hereby certify that on July 7, 2025, I caused a true and correct copy of the foregoing Petitioners' Response to Patent Owner's Request for Discretionary Denial of Institution to be served by electronic mail, as authorized by Patent Owner, at the following email addresses:

Lead Counsel

Christopher Ponder (Reg. No. 77,167)
cponder@sheppardmullin.com

Backup Counsel

Alex Nie, Reg. (Reg. No. 60,523)
anie@sheppardmullin.com

Fangzhou Qiu, (Reg. No. 82,810)
fqiu@sheppardmullin.com

Dated: July 7, 2025

By: /Joe Chen/
Joe G. Chen, Ph.D.
Reg. No. 70,066
Counsel for Petitioners