

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EMPOWER CLINIC SERVICES, L.L.C.
(d/b/a Empower Pharmacy),
Petitioner,

v.

ELI LILLY & CO.,
Patent Owner.

Case IPR2025-01024
Patent US 9,474,780

EMPOWER PHARMACY'S OPPOSITION
TO LILLY'S DISCRETIONARY-DENIAL REQUEST

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I. INTRODUCTION

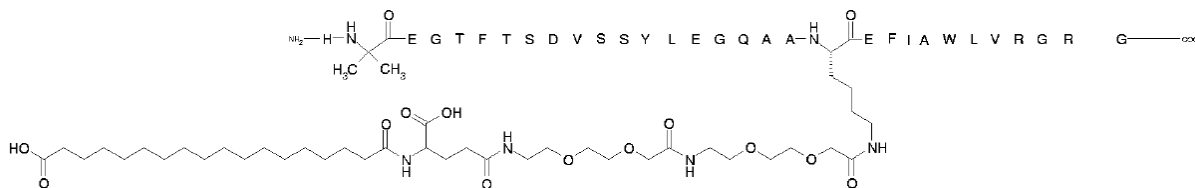
Using multiple prior-art references that Patent Owner (Lilly) omitted from the application file, Empower Pharmacy (Empower)'s petition materials raise new art and argument, and amply demonstrate examination error. For example, both EX1007 and EX1009 were never considered by the examiner (because Lilly failed to include them in an Information Disclosure Statement (IDS)), and they directly rebut the examiner's basis for allowance. The petition also cites multiple new and non-cumulative prior-art references (*e.g.*, EX1010, EX1075) that, while not identified as primary ground references, are relied upon in the ground as corroborating motivation and reasonable expectation of success. Under these circumstances, *Advanced Bionics* favors referral for merits consideration.

First, the examiner believed during examination that the operational peptide sequence for GIP/GLP-1 dual agonism recited in the challenged claims (specifically the GLN (Q) at position 24) was absent from the prior art. Critically, however, Lilly did not inform the examiner that this same sequence—including Gln²⁴—was previously disclosed in Lilly's much earlier patent application publication from a different family. EX1007, 2:12-25.

Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-
5 10
Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa¹-Val-Gln-Trp-Leu-Ile-Ala-
15 20 25

Nor did Lilly inform the examiner that this unconsidered prior art identified this operational peptide sequence as a lead compound for (high-dose) therapeutic use and expressly proposed its further modification to increase its half-life during clinical administration. EX1002, ¶¶143-145; EX1007, Abstract, 5:24-27, Claims 1-12.

Not only did Lilly fail to inform the examiner that Lilly's claims followed Lilly's prior-art lead compound, but Lilly invited a second error. Specifically, Lilly failed to inform the examiner that Lilly's claim also used the same albumin-binding moiety that Novo Nordisk already had used successfully in the prior art (at Lys²⁰) to achieve once-weekly dosing.



EX1002, ¶¶159, 162-165; EX1009, 47:4-12 (Example 4); EX1010, 1:21-23. Lilly thus improperly sought to extend its patent exclusivity **years** beyond its original patent application (EX1007) by making an obvious variation, the synthesis of which was admittedly simple and routine. Pet., 1-2, 7-8.

Despite Lilly being fully aware that the prosecution record was incomplete and that the basis of allowance was erroneous, Lilly asked the Office to issue the challenged claims anyway. Empower thus presented new prior art and arguments

that were not previously considered **and** demonstrated material error in examination.

As discussed in detail below, Lilly's Discretionary Denial Brief ("DDB," Paper 6) does little more than demonstrate Lilly's **knowledge** that the examiner's reasons for allowance could not be relied upon. Lilly clearly knew that it had copied the peptide sequence from its own prior-art lead compound (EX1007). Lilly knew this peptide expressly included Gln at position 24 (the first feature the examiner believed was missing from the prior art). Lilly's DDB essentially admits examination error by arguing the examiner should have reviewed this reference (while failing to point to any evidence that the examiner actually did so). Despite Lilly mentioning EX1007 in the specification (**without** reference to the sequence disclosed therein), Lilly failed to identify EX1007 on any IDS (despite submitting other, less salient, references). Lilly fails to identify anywhere in the examination record where the examiner indicated **any** consideration of EX1007, much less consideration of its peptide sequence (including Gln²⁴), or of its express suggestion to modify the peptide for increased half-life in clinical administration.

Lilly's DDB papers similarly make clear that Lilly knew the claimed albumin-binding moiety was in the prior art, but failed to alert the examiner. As explained repeatedly in the petition, mere weeks before Lilly filed its application for the instant patent, Lilly's biggest GLP-1 competitor (Novo Nordisk) disclosed in the prior art (EX1010) that it had successfully used the albumin-binding moiety (disclosed in

EX1009) to achieve once-weekly administration. Pet., 14, 20, 24, 45, 73. These previously unconsidered prior-art references thus provided a fresh solution (and motivation) to accomplish the express suggestion of EX1007: increase half-life of the operational peptide for clinical administration.

Lilly does not even assert EX1010 was previously considered or is cumulative. Instead, Lilly concedes to being aware that the claimed albumin-binding moiety was in the prior art and that the examiner should have considered that structure, but fails to identify any evidence the examiner did so. This too was error.

Instead of acknowledging its own complicity in inviting examination error, Lilly attempts to distract by speculating. First, Lilly speculates that the examiner ***could have*** obtained and considered EX1007 despite Lilly's failure to submit the reference for consideration. Second, Lilly speculates that the examiner ***could have*** identified the structure of semaglutide (as disclosed in EX1009). But what Lilly never does (and, in fact, cannot do) is identify anything in the examination record indicating that the examiner did any of these things. In other words, Lilly's DDB arguments merely confirm that examination failed to consider the art and arguments presented by the petition materials. In its blatant efforts to blame the examiner for failing to identify information of which Lilly admittedly was aware, Lilly fails to show entitlement to discretionary denial relief. Lilly instead merely demonstrates it had no settled expectations in the issued claims because it was aware of, and had in

fact invited, issuance based on examination insufficiencies.

Having failed to demonstrate entitlement to relief under section 325(d) (and not even asserting any basis under *Fintiv*), Lilly retreats to inviting new errors. Lilly attempts to read out from the prior art a lead compound that was expressly suggested for additional modification for clinical development. Lilly's purported justification is that other lead compounds might have been even more favorable (though it fails to identify any). This illogical argument was never the law. Nor should it be. Lilly would effectively rewrite the statute to create a *per se* exception to obviousness law for pharmaceutical compounds. Such an approach not only is contrary to law, but would improperly tie the hands of the Executive from correcting examination error in the face of waste, fraud, and abuse.

Lilly's other "settled expectation arguments" similarly are unpersuasive. Lilly relies on "average" clinical trial spending and other practices (*e.g.*, Orange Book Listings) that are generic to pharmaceutical patents rather than specifically showing **Lilly's** settled expectations **in the challenged patent**. Meanwhile, Lilly's clinical trials lack nexus because they relate to titration protocols that the challenged patent does not claim (Lilly claims them in later patents). Most notably, Lilly does not even argue that making the claimed invention (as opposed to what it claims as later inventions) involved any significant investment. Given that Lilly used the lead compound from its prior-art patent (EX1007), and then rapidly employed Novo's

Lys²⁰-conjugated albumin-binding moiety to impart once-weekly dosing (EX1009), Lilly would be hard-pressed to do so. Lilly has no settled expectations in propagating or continuing examination errors, especially not examination errors that Lilly itself invited.

Lilly's lack of settled expectations also is demonstrated by rapidly evolving boundaries, as Lilly recently decided to enter a new market (and attacks legal compounding pharmacies using the Lanham Act). Empower's prompt defensive action in response to Lilly's announced expansion is no excuse to shield Lilly's *patent* from Executive review. Empower should not be required to sit back and wait under the continuing threat of an infringement lawsuit while none is pending. Indeed, Lilly has no settled expectations in a patent that it has studiously avoided asserting *for years*, allowing millions of American taxpayers, patients, doctors, and pharmacies to come to rely on the availability of tirzepatide from non-Lilly sources. EX1079, 1-2 ("industry officials estimate that several large compounding pharmacies like his are provisioning up to 2 million American patients with regular doses of" GLP-1 semaglutide and tirzepatide). Lilly's DDB is just another attempt to hide what it has known since examination: the patent is invalid and unenforceable and affords Lilly no settled expectations.

Finally, Lilly has no settled expectations in requiring the Executive to cede his Article II Power to a district court judge of Lilly's future choosing to decide

questions of national importance, particularly where Lilly's prosecution error costs the Executive and American taxpayers billions of dollars each year (an epitome of waste, fraud, and abuse). In the face of Lilly's attempt to ignore the settled expectations of Empower and the American people, the Executive must not unilaterally disarm himself against Lilly's machinations. Lilly's request for discretionary denial of institution should be *denied*.

II. FACTUAL BACKGROUND

As explained in the petition materials, the challenged claims were allowed with minimal examination scrutiny and through examination error. Pet., 7-8; EX1002, ¶¶41-51. They were allowed just six months after application filing. EX1004, 22; EX1002, ¶42. An earlier European search report (EX1005) and written opinion (EX1006) considered only three references. EX1002, ¶42. The U.S. examiner considered a total of thirteen publications, all identified by the applicant in an IDS. EX1004, 36-39; EX1002, ¶43. These references did not include EX1007, EX1009, EX1010, or EX1075, among others.

The examiner discussed only a subset of disclosures from one reference, focused on a large genus. EX1002, ¶44 ("the Examiner cited disclosure only from paragraphs [0044] and [0111], Tables 1-2, and Formulae II(b)-(d) of the U.S. patent publication" (EX1012)). The primary bases for distinguishing over the reference was that it did not disclose Gln (Q) at position 24 or the claimed albumin-binding moiety,

and the examiner was unaware of any teaching or suggestion in the reference to make either modification:

The closest prior art of Just et al. (US 2015/0299281 A1; WO

2013/164483) teaches GIP-GLP1 dual acting receptor agonists, which are closely related to the instantly claimed compounds. The genus of GIP-GLP1 co-agonists taught in the prior art (Formula I, para. [0044]) **differs from the compounds claimed in this application at position 24**. The prior art defines position 24 as Asn, Glu, Arg, or Lys, whereas the instant claims require position 24 to be Gln. Just et al. do not teach or suggest substituting Gln for the amino acids at position 24.

Just et al. teach that the GIP-GLP1 co-agonists can be conjugated with a lipophilic substituent to one or more of amino acid positions 16, 17, 19, 20, 24, 27, 28, 30 and 32 (para. [0111]), but do not teach the specific lipophilic substituent recited in the instant application.

In order to arrive at the instantly claimed compounds, one of ordinary skill in the art would have to **substitute Gln at position 24 and a moiety** of ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H as the lipophilic substituent. There is no teaching or suggestion in Just et al. to do so. Even if there were, it would require

EX1002, ¶51; EX1004, 28. The examiner did not identify or discuss any teaching in the prior art that Gln (Q) was an appropriate amino-acid residue at position 24.

EX1002, ¶45. The examiner likewise failed to identify any teaching in the prior art identifying the specific conjugated moiety recited in the claims, or recognizing its use in the prior art for the very same purpose as in the challenged patent. EX1004, 27; EX1002, ¶¶48, 50.

The examiner thus erroneously allowed the claims without rejection, including by:

- Failing to identify prior-art (at least EX1007) teaching Gln as an appropriate residue at position 24 for preparation of an effective dual GIP/GLP-1 agonist or that its employment was strongly supported by the known, prior-art structure-activity relationship (SAR) for GIP/GLP-1 dual agonism. *E.g.*, EX1002, ¶45.
- Specifically failing to cite and discuss the disclosures of the '657 Publication (EX1007) providing a therapeutic peptide for clinical applications using the operative peptide sequence (including Gln²⁴) that Lilly used in the challenged claim to achieve GIP/GLP-1 dual agonism, and proposing to modify that peptide to increase half-life. *E.g.*, EX1002, ¶¶43, 50, 102, 108, 109.
- Failing to identify prior-art disclosure of the claimed albumin-binding moiety, though this specific albumin-binding moiety was in fact disclosed in the prior art for the same purpose for which the challenged patent employed it (at least EX1009 and EX1010). *E.g.*, EX1002, ¶48.
- Specifically failing to cite and discuss the disclosures of the '537 Publication (EX1009) providing the albumin-binding moiety that Lilly adopted in the challenged claim to achieve once-weekly dosing. *E.g.*, EX1002, ¶¶43, 50, 82, 130-133.
- Specifically failing to cite and discuss the disclosures of the '727

Publication (EX1010) that the claimed albumin-binding moiety in EX1009 had, in fact, achieved once-weekly dosing. *E.g.*, EX1002, ¶¶82, 130, 165; Pet., 14, 20, 24, 45, 73, 75.

- Specifically failing to cite and discuss the disclosures of the '715 Publication (EX1075) that this albumin-binding moiety had been widely used to increase half-life of GIP/GLP-1 receptor dual agonists, including when employing the C-terminal motif. *E.g.*, EX1002, ¶¶98, 165; Pet., 15, 74.

In further discussion of the large genus disclosure that the examiner considered during examination, the examiner concluded this large genus alone failed to anticipate or render obvious the claimed peptide sequence absent additional prior-art direction. In particular, the examiner reasoned that although “the broad genus of Just et al. encompasses the claimed compounds” with the exceptions noted above, “the ***preferred*** embodiments, sub-genera, and species have several more differences.” EX1002, ¶51 (“all of the ***preferred*** embodiments”) (quoting EX1004, 28); EX1004, 28 (“***preferably*** lysine, not isoleucine”; “***preferably*** Leu, Glu or Val, no[t] isoleucine”; “***preferably*** Gln or Ala, not Gly”; “***most of the species*** disclose[d] in Just et al. lack the GPSSGAPPPS sequence”). The examiner thus erroneously allowed the claims without rejection, including by:

- Limiting its analysis to “preferred” and actually-reduced-to-practice

embodiments of a single reference rather than what the reference teaches as a whole and what a person of ordinary skill in the art would have understood in combination with other prior-art references. *E.g.*, EX1002, ¶44.

- Failing to consider the known, prior-art structure-activity-relationship (SAR) that strongly indicated the entire claimed peptide sequence for dual GIP/GLP-1 agonism was effective for treating diabetes and obesity. EX1002, ¶¶44, 47, 49, 50, 148; Pet., 29-30.

Table A

GIP	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	SIP	GLP-5		
GLP-1	Y	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	V	N	W	X	L	A	Q	K	K	K	N	D	W	K	H	N	T	S							
Ulagitide	H	A	C	G	T	T	S	D	V	S	S	Y	E	G	Q	A	A	K	E				I	A	W	L	V	K	G	R	G	NH2														
Exenatide	H	A	C	G	T	T	S	D	V	S	S	Y	E	G	Q	A	A	K	E				I	A	W	L	V	K	G	R	G															
Compound 2	Y	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	V	N	W	X	L	A	Q	K	K	K	N	D	W	K	H	N	T	S							
Compound 3	Y	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	V	N	W	X	L	A	Q	K	K	K	N	D	W	K	H	N	T	S							
Compound 55	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	G	Q	A	A	K	E				I	A	W	L	V	K	G	R	G	S	S	G	A	P	P	P	S	NH2		0.0046	0.015			
Compound 119	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	G	Q	A	A	K	E				I	A	W	L	V	K	G	R	G	S	S	G	A	P	P	P	S	NH2		0.0072	0.0067			
Compound 43	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	K	K	A	Q	K	E				I	E	W	L	L	S	A	NH2											0.0063	0.011				
Compound 127	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	K	K	A	K	A	K	E				I	E	W	L	L	S	A	NH2											0.0095	0.017			
Compound 138	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	K	K	A	K	A	K	E				I	E	W	L	L	S	A	NH2											0.0097	0.018			
Compound 40	Y	Ab	C	G	T	T	S	D	V	S	S	Y	A	D	K	**	A	Q	K	E				I	E	W	L	L	S	Ab	NH2	P	S	S	G	A	P	P	P	S	NH2		0.0099	0.015		
Compound 122	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	A	Q	K	E				I	E	W	L	L	S	A	NH2											0.011	0.022			
Compound 41	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	**	A	Q	K	E				I	E	W	L	L	A	Q	K	G	P	S	S	G	A	P	P	P	S	NH2		0.012	0.018	
Compound 13	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	S	K	K	A	K	H	D				I	E	W	L	L	S	A	NH2											0.013	0.011			
Compound 119	Y	Ab	C	G	T	T	S	D	V	S	S	Y	A	D	K	K	A	Q	K	E				I	E	W	L	L	A	Q	K	G	P	S	S	G	A	P	P	P	S	NH2		0.015	0.022	
Compound 48	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	A	Q	K	E				I	E	W	L	L	S	Ab	NH2											0.015	0.0075			
Compound 17	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	A	Q	K	E				I	E	W	L	L	S	A	NH2											0.016	0.013			
Compound 21	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	A	Q	K	E				I	E	W	L	L	A	Ab	K	NH2									0.021	0.0074				
Compound 29	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	**	A	Q	K	E				I	E	W	L	L	A	Ab	K	NH2									0.022	0.026				
Compound 35	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	**	A	Q	K	E				I	E	W	L	L	A	Q	K	G	P	S	S	G	A	P	P	P	S	NH2		0.024	0.008
Compound 5	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	A	Q	K	E				I	E	W	L	L	A	Ab	K	NH2									0.026	0.022				
Compound 33	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	A	Q	K	E				I	E	W	L	L	A	Ab	K	NH2									0.033	0.023				
Compound 14	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	**	A	Q	K	E				I	E	W	L	L	A	Q	K	G	P	S	S	G	A	P	P	P	S	NH2		0.035	0.031	
Compound 34	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	K	K	**	A	K	E				I	E	W	L	L	A	Q	K	G	P	S	S	G	A	P	P	P	S	NH2		0.036	0.0087		
Compound 20	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	**	A	K	E				I	E	W	L	L	A	Q	K	G	P	S	S	G	A	P	P	P	S	NH2		0.037	0.013		
Compound 20	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	**	A	K	E				I	E	W	L	L	A	Q	K	G	P	S	S	G	A	P	P	P	S	NH2		0.045	0.031	
Compound 20	Y	Ab	C	G	T	T	S	D	V	S	S	Y	E	D	K	K	A	Q	K	E				I	E	W	L	L	A	Ab	K	NH2									0.049	0.0096				

Table B

[illegible]

Green = conserved across peptides

Light Blue = GIP

Dark Blue = GLP-1

Light Purple = Exenatide

- Failing to identify prior art teaching Ile as an appropriate residue at position 17 for preparation of an effective dual GIP/GLP-1 agonist (*e.g.*,

EX1007), especially when the Lys residue for linking to an albumin-binding moiety was situated at position 20 as expressly taught in the prior art (*e.g.*, EX1009). EX1002, ¶46; *see also, e.g.*, EX1002, Tables A-B above.

- Failing to identify prior-art disclosure that Ile and Gly worked well at positions 27 and 29, respectively, for dual GIP/GLP-1 agonism, and was strongly indicated to a POSA by known, prior-art SAR for dual GIP/GLP-1 agonism effective for treating diabetes and obesity. EX1002, ¶49; *see also, e.g.*, EX1007; EX1002, Tables A-B above.
- Failing to identify prior-art disclosure that the C-terminal motif (GGPSSGAPPPS) of the well-known prior-art GLP-1 receptor agonist exenatide worked well in *in vitro* and *in vivo* assays for dual GIP/GLP-1 agonism and was strongly indicated to a POSA by known, prior-art SAR for dual GIP/GLP-1 agonism effective for treating diabetes and obesity. EX1002, ¶47; *see also, e.g.*, EX1002, Tables A-B above.

Accordingly, the petition presented new argument and evidence, including the well-qualified testimony of Dr. Cornish, discussing these errors and how the previously unconsidered disclosures of new prior art (including EX1007, EX1009, EX1010, and EX1075) demonstrate the foregoing examination errors.

III. ***ADVANCED BIONICS*** FAVORS INSTITUTION

Lilly does not dispute that the petition presents new references that were never considered during examination. DDB, 23 (arguing only that “three references in the petition’s Ground” were either “considered or are cumulative”). In particular, Lilly does not assert that any of EX1007 or EX1009 was submitted in the application file or is listed on any IDS, much less an IDS marked considered by the examiner. Moreover, Lilly does not even argue that either EX1010 or EX1075 (relied on in the ground for motivation and reasonable expectation of success) was considered or is cumulative. Lilly does not address these latter exhibits at all.

Instead, Lilly argues only that the examiner should have obtained and reviewed a copy of EX1007 (which Lilly failed to submit during examination) to identify the salient teachings (which Lilly failed to identify during examination). DDB, 25-26. Lilly then argues that the examiner should have reviewed a copy of EX2045 (which Lilly failed to submit during examination) to analyze the structure of semaglutide (which Lilly failed to identify during examination). DDB, 28-29. With each argument, however, Lilly merely confirms the petition art and arguments are materially different than what was considered during examination because Lilly points to ***no evidence*** that the examiner actually considered EX1007, the albumin-binding moiety structure of semaglutide (disclosed in EX1009), or its achievement of once-weekly dosing (disclosed in EX1010). Lilly’s incomplete and erroneous

Section 325(d) analysis should therefore be rejected.

While Lilly fails to establish the examiner was aware of these critical prior-art disclosures during examination, Lilly does not dispute that **Lilly** was. In other words, Lilly effectively concedes facts demonstrating that Lilly invited the examination error that resulted in issuance of the challenged claims. Because the petition ground presents new and non-cumulative art and arguments that should have been considered during examination, and which provides ample new evidence of unpatentability, Lilly's request for discretionary denial should be denied.

A. New Art and Arguments Warrant Institution

The petition ground's reliance on numerous references that were not considered or applied during examination warrants referral for institution. Determining whether "the same or substantially the same art" previously was "made of record by the Examiner" or "provided to the Office by an applicant" during "proceedings pertaining to the challenged patent" is a threshold inquiry before invoking discretionary denial of institution under 35 U.S.C. §325(d). *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 (2020) (precedential) at 7-8 (hereinafter "*Advanced Bionics*"); *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (2017) (precedential as to § III.C.5, first paragraph, Aug. 2, 2019) (hereinafter "*Becton*") (identifying six factors relevant to discretion under §325(d)).

Board precedents identify three factors relevant to this threshold inquiry: (a) 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; and (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. *Advanced Bionics*, at 9-10 & n.10. Here, none of EX1007, EX1009, EX1010, or EX1075 was considered or applied during examination, and Lilly points to no evidence to the contrary. Moreover, these references are materially different than the art and arguments considered during examination. Finally, the petition ground relies on EX1008 in a manner that is materially different (non-cumulative) to how EX1012 was considered during examination. Each of these material distinctions from examination warrant referral of the petition for institution, as discussed in detail below.

1. Lilly Fails to Demonstrate EX1007 Was Previously Considered or Is Cumulative.

As explained in the petition, Lilly (1) did not identify WO 2011/119,657 (EX1007, “’657 Publication”) on its IDS during examination; (2) did not submit it to the examiner for consideration; and (3) did not identify any teaching in the prior art that Gln (Q) was an appropriate amino acid residue at position 24, despite the ’657 Publication expressly teaching Gln at position 24. Pet., 7-8; EX1002, ¶¶44-47,

49; EX1007, 2:12-25. Even after the examiner expressed the belief (in the reasons for allowance) that the evaluated prior art of record did not teach Gln (Q) at position 24 (EX1004, 28; EX1002, ¶¶50-51), Lilly said nothing.

It is undisputed that, as explained in the petition, the '657 Publication was not cited or discussed during examination or applied in any rejection. Pet., 16. Also uncontested by Lilly, the '657 Publication disclosed the operational peptide sequence that Lilly employed in the claims—including specifically Gln (Q) at position 24—for clinical use (to achieve a favorable balance of both GLP-1 and GIP agonism. Pet., 16-17, 25, 34; EX1002, ¶¶155-157. Accordingly, *Becton* factors (a), (b), and (d) each alone, and collectively, warrant institution because the '657 Publication is materially different from the prior art involved during examination, is not cumulative in nature to the prior art (lacking Gln²⁴) evaluated during examination, and the petition materials rely on the '657 Publication to make a different argument than what was evaluated during examination.

Despite failing to contest the salient facts presented in the petition materials and summarized again above, Lilly argues the '657 Publication should have been placed “before the examiner during prosecution” because it is cited in the specification (for a different proposition than Gln²⁴) and because the MPEP asks the examiner to consider references cited in the “application or reexamination.” DDB, 25-26; citing MPEP §§707.05, 2103.

As an initial matter, Lilly misreads these provisions. Neither section of the MPEP requires the examiner to review every reference cited in the specification, as opposed to those references cited for consideration in the “application **or reexamination**.” An Information Disclosure Statement (IDS) is how the Applicant documents art the Applicant provided to the Office. *Id.*, 8; MPEP §609; 37 C.F.R. §1.97. The Applicant is obligated to list in an IDS “all patents, publications, applications, or other information submitted for consideration by the Office,” and must comply with certain formal requirements. 37 C.F.R. §1.98(a)(1). During examination, Lilly was obligated by “a duty to submit to the Office information which is material to patentability.” MPEP §609; 37 C.F.R. §1.56. To the extent Lilly desired to avoid submitting a reference it viewed as “substantively cumulative” to a submitted reference, Lilly was obligated to “state[] that these other patents or publications are cumulative.” 37 C.F.R. §1.98(c). The rules governing IDS submissions “provide certainty for the public by defining the requirements for submitting information disclosure statements to the Office so that the Office will consider information contained therein before a patent is granted.” MPEP §609. Even when submitted, an improperly filed IDS “will be placed in the file but will not be considered by the Office.” 37 C.F.R. §1.97(i). Of course, references never submitted are **not** placed in the file and consequently are **not** considered by the Office. Lilly’s proposed rule that every reference cited in every specification is

involved in examination regardless of any evidence to that effect rests on an illogical fiction that perversely undermines the Office's own disclosure rules.

Lilly's failure to submit the '657 Publication for consideration during examination is not the only evidence contradicting Lilly's fiction. Aligned with the USPTO goal of providing "certainty" for the public regarding which references have been considered in the application during examination (and which have not), the USPTO similarly requires the examiner to identify references considered during examination in addition to those listed on the Applicant's IDS(s). The examiner uses form PTO-892 to document such prior art. MPEP §707. The examiner is expected to identify any such references at least by name, date, and number. *Id.* Examiner-cited references are "placed in the application file" similar to those submitted by the Applicant. MPEP §707.05(a). Lilly identifies no evidence the examiner reviewed or considered the '657 Publication during examination, much less the disclosure in the '657 Publication of the claimed operational peptide sequence. Lilly's argument would turn on its head the "certainty" granted by USPTO rules to the public to rely on the official record of references considered as part of the application.

Contradicting Lilly's speculation that the examiner reviewed the '657 Publication despite Lilly's omission of it from the application file, the examination record tells us what the examiner considered during examination. Pet., 16. Examination was brief and limited, and there is no indication the '657 Publication

was ever involved. To the contrary, the examiner’s statement that allowance was appropriate because of the absence of prior-art teaching Gln²⁴ (EX1004, 28) further undermines Lilly’s speculation that the ’657 Publication was secretly considered during examination.

Lacking evidence of actual consideration, Lilly points to two non-precedential panel decisions, both of which granted institution and denied a request for discretionary denial. DDB at 25-26 (citing *Apotex Inc. v. Celgene Corp.*, IPR2023-00512, Paper 7 at 50 (2023) (hereinafter “*Apotex*”); *Precision Planting LLC v. Maschio Gaspardo S.p.A.*, IPR2024-0008, Paper 12 at 21 (2024) (hereinafter “*Precision*”). But neither of these cases examined the fictional-consideration argument Lilly makes here. Nor did they provide any reasoning or legal analysis in their brief discussion (which was not essential to the decision to institute in any case) to support Lilly’s argument. In *Precision* (at 21), the panel merely noted that applicant-admitted prior art “arguably” was before the examiner. In other words, the panel concluded that the words in the specification itself arguably may have been reviewed, not that references lacking any indication of examiner consideration somehow take on more weight than a rejected IDS.

Apotex similarly does not support Lilly’s fictional-consideration argument. In that case, the sole asserted reference in the primary (anticipation ground) was indisputably “before the Office” during examination. *Apotex* at 50-51. This reference

(Ionescu) was relied upon for teaching the alleged “missing element” that resulted in issuance. *Apotex* at 52-52. Prior consideration of Ionescu (the sole reference in the primary ground) necessitated evaluation of *Advanced Bionics* step 2. *Apotex* at 51. Accordingly, the minimal discussion in *Apotex* provides no basis for Lilly’s proposed rule.

Moreover, the circumstances of each of those cases are very different from the circumstances here and do not support Lilly’s argument in any event. In both *Apotex* and *Precision*, the specification of the challenged patent itself ascribed the relevant subject matter to the cited reference. DDB at 26 (“Arguably, applicant admitted prior art was before the Examiner because it is part of the Specification.” (quoting *Precision* at 21)); *Apotex* at 50 (“Gibson was expressly cited in the Specification of the ’628 patent for its disclosure of ‘conventional methods known to those skilled in the field of pharmaceutical formulation.’”). In other words, in those cases, reviewing the specification necessarily entailed consideration of the relied-upon teaching regardless of whether the examiner actually reviewed an underlying reference. There was thus no conflict between the absence of those references from the application file (if established) and the Office’s rules requiring express disclosure of the references considered.

Here, Lilly failed to apprise the public in the specification that it was copying its own, prior-art operational peptide sequence, specifically including the Gln²⁴

residue the examiner believed was missing from the prior art. Instead, the information provided by a review of the specification was limited to a discussion of immunogenicity of a co-agonist, but the sequence of that co-agonist was not discussed. *E.g.*, EX1001, 20:45-64 (“Immunogenicity Profiling”).¹ Unlike in *Precision* and *Apotex*, the specification of the challenged patent does not expressly disclose relied-upon subject matter as Applicant Admitted Prior Art or describe the relied-upon subject matter and incorporate it by reference. *Compare* *Precision* at 6 (Ground listing: “Applicant Admitted Prior Art”); EX1083, 9:45-49 (US 8,846,628 incorporating by reference in entirety); *with* EX1001 (no incorporation by reference of ’657 Publication). These cases thus do not support Lilly’s proposed fictional-consideration rule.

Ultimately, Lilly’s invocation of these cases merely undermines its arguments

¹ As explained in the petition materials, this immunogenicity resulted significantly from the use of PEGylation and the artificial C-terminal motif, both of which provided strong motivation to modify the peptide using a less immunogenic approach (e.g., exenatide C-terminal motif) to prolong duration of action. Pet., 35-36, 74-75; *id.*, 11, 14-15. In any case, the specification’s discussion of immunogenicity does nothing to demonstrate the examiner was aware of the successful use of the claimed operational unit peptide sequence, including Gln²⁴.

by demonstrating that failure to consider salient prior-art teachings warrants referral. In *Apotex*, Ionescu was indisputably considered by the Office during examination, but overlooking its teachings without commenting on their salience was “error material to the patentability of the claims.” *Apotex* at 50, 52-53; *see also Oticon Medical v. Cochlear Ltd.*, IPR2019-00975, Paper 15 (2019) (precedential as to § II.B and II.C, Mar. 24, 2020) (hereinafter “*Oticon*”), at 16 (overlooking salient reference is material error). Accordingly, the panel instituted review. *Apotex* at 53. In *Precision*, the panel similarly instituted review where the references relied upon to disclose the alleged “missing element” were both disclosed on an IDS because the examiner had “overlooked specific teachings” in the reference. *Precision* at Cover, 21-23. Accordingly, both *Apotex* and *Precision* undermine Lilly’s request for discretionary denial.

Ignoring the holdings of these cases, Lilly argues the ’657 Publication was cumulative to the U.S. publication discussed during examination (EX1012) because the examiner concluded a skilled artisan would need to “choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are different than those preferred and reduced to practice in Just,” in addition to substituting Gln at position 24. DDB at 26-27. But Lilly’s argument is itself sufficient to demonstrate differences material to patentability. The ’657 Publication discloses the operational peptide sequence that Lilly employed in the challenged claims (including Ile¹⁷ and

Ile²⁷). Accordingly, the '657 Publication closed the gap (*e.g.*, Gln²⁴, Ile¹⁷, and Ile²⁷) the examiner identified and is not cumulative. Lilly's argument also ignores the combination of references asserted here, including additional prior art expressly teaching the remaining amino acid sequences (*e.g.*, the familiar exenatide C-terminal motif at positions 29-39). *See* Sections III.A.2-3 below.

Next, Lilly argues that the '657 Publication is cumulative to the '483 Publication because the latter teaches a genus that "essentially encompasses" the N-terminal peptide sequence of the former. DDB at 28. However, Lilly's illogical and legally erroneous argument demonstrates the opposite of what it asserts. The examiner considered whether disclosure of a peptide sequence genus in EX1012 disclosed a claimed peptide sequence species. The petition materials rely on a previously disclosed operational peptide sequence that Lilly employed again in its claims. The two arguments are materially distinct. The references are materially distinct. And Lilly's failure to present the previously disclosed operational peptide sequence to the examiner for consideration caused the examiner to overlook this distinct teaching that directly undermines the express basis for allowance.

2. Lilly Fails to Demonstrate EX1009, EX1010, or EX1075 Was Previously Considered or Is Cumulative.

As explained in the petition, the '537 Publication (EX1009) was identified in the prior art (*e.g.*, EX1010, WO 2014/202,727 (hereinafter "'727 Publication"),

1:21-23) in December 2014 as providing the structure for the once-weekly GLP-1-receptor agonist semaglutide in clinical development by Novo Nordisk. Pet., 19-20. The petition further explained that this same albumin-binding moiety (at Lys²⁰) already achieved once-weekly dosing for dual agonists in the prior art. Pet., 14-15 (citing EX1075, WO 2015/067, 715 (hereinafter “’715 Publication”). Each of EX1009, EX1010, and EX1075 is relied upon in the ground, including to support motivation to modify and reasonable expectation of success. *See, e.g.*, Pet., 24, 45, 73, 74, 75 (citing EX1009-EX1010); Pet., 74 (citing EX1075).

Lilly does not dispute that none of the ’537 Publication (EX1009), the ’727 Publication (EX1010), or the ’715 Publication (EX1075) was considered by the examiner. DDB at 28-30. Lilly does not even argue that the ’727 Publication or ’715 Publication was cumulative to any art that was considered or asserted by the examiner. Nor does Lilly assert that the ’537 Publication was cumulative to any art that was asserted by the examiner. Finally, Lilly does not identify any art asserted or considered during examination as disclosing that the Lys²⁰-conjugated albumin-binding moiety achieved once-weekly dosing, as was disclosed in the ’727 Publication.

Instead, Lilly asserts only that the ’537 Publication is cumulative to a document mentioned in the specification but never identified on an IDS or otherwise considered during examination. DDB at 28-29 (arguing the structure can be found

in EX2045). But Lilly identifies no evidence the examiner considered EX2045 or any other document disclosing the structure of semaglutide. Lilly (1) does not assert that the specification actually discloses the structure of semaglutide (as opposed to that it can be found outside the application); and (2) does not assert that the specification discloses that this albumin-binding moiety achieved once-weekly dosing in prior art GLP-1 and GIP/GLP-1 dual agonists, both of which the petition demonstrated were disclosed in the prior art. Accordingly, Lilly's so-called "cumulative" argument fails.

Becton factors (a), (b), and (d) again each alone and collectively warrant referral because the '537 Publication, '727 Publication, and '715 Publication (1) are each (and collectively) materially different from the prior art involved during examination; (2) are not cumulative to the prior art evaluated during examination; and (3) the petition materials rely on these references to make a materially different argument than that considered during examination.

Next, Lilly notes (but does not dispute) the petition arguments (Pet., 40-47) that the claimed albumin-binding moiety is specifically disclosed in the prior-art '537 Publication but is consistent with the genus in the '483 Publication. DDB at 29-30. Lilly then argues that the '537 Publication "adds little to the obviousness analysis" and is cumulative to the '483 Publication because it allegedly discloses "many different options for linkers" and fatty acids. But Lilly does not argue that the

'483 Publication discloses the claimed albumin-binding moiety.² Nor does Lilly dispute that the '537 Publication does, or that the '727 Publication specifically called out that particular structure from among others in the '537 Publication as achieving once-weekly dosing. Accordingly, there is no genuine dispute that the '537 Publication's "relevant disclosure" was not before the examiner and that the '537 Publication called out by the '727 Publication is not cumulative.

Finally, Lilly makes the conclusory argument that the '483 Publication "provided more guidance to a person of skill in the art than" the '537 Publication because the former, but not the latter, includes *in vitro* and *in vivo* test results. DDB at 30. But this argument once again ignores the asserted art (*e.g.*, EX1010) teaching successful *in vitro* and *in vivo* use of the claimed albumin-binding moiety advanced into clinical development. Lilly's argument that the '537 Publication is cumulative to the '483 Publication thus erroneously ignores material differences between the references asserted and what was considered during examination.

Lilly's reliance on the *Dr. Reddy's* decision (DDB at 30) is similarly unavailing. In *Dr. Reddy's*, the only reference not before the examiner did not disclose the claim element for which it was relied upon and thus added "little, if

² To the contrary, Lilly avers that Just et al. did not disclose Gln at position 24 or the claimed lipophilic substituent. DDB at 32, 35-36.

anything, to the obviousness analysis.” *Dr. Reddy’s Labs. S.A. v. Indivior UK Ltd.*, IPR2019-00328, Paper 21 at 16-18 (2019) (hereinafter “*Dr. Reddy’s*”) (“FDA IIG does not disclose information about the amount of citric acid or sodium citrate in Suboxone® tablets”).³ In contrast, here, it is undisputed that the ’537 Publication discloses the claimed albumin-binding moiety that was indisputably missing from the reference considered during examination, and that the ’727 Publication called that structure out as achieving once-weekly dosing just weeks before Lilly adopted it. Lilly does not allege, much less demonstrate, that the claimed albumin-binding moiety was disclosed in the ’483 Publication. Accordingly, Lilly’s reliance on *Dr. Reddy’s* to label the ’537 Publication cumulative fails.

3. Lilly Ignores Material Differences in How EX1008 Is Relied Upon Versus Examination.

Lilly argues that the ’483 Publication (EX1008) was considered during

³ In *Dr. Reddy’s* (at 17), the Board noted that pointing to a reference that failed to disclose the missing claim element and making unsupported arguments that the missing claim element could be derived by making unsupported assumptions about the reference “suggests hindsight reconstruction.” Here, the petition ground is based on the actual disclosures of the prior art, which were not previously considered and which no one contends were present in the previously-asserted art.

examination and was “explicitly distinguished by the Examiner in the Reasons for Allowance” on the basis that its disclosures, standing alone, contained no teaching or suggestion to use Gln at position 24 or to use the claimed albumin-binding moiety “as a lipophilic substituent.” DDB at 23-25. But Lilly’s argument misses the point. The ground does not rely on the ’483 Publication to disclose Gln²⁴ or the claimed albumin-binding moiety. As the petition materials explained, the ’657 and ’537 Publications (EX1007 and EX1009) were not considered during examination, much less in combination with the ’483 Publication. Pet., 7-8. Lilly does not dispute that they disclose both these previously missing elements. Accordingly, the art and argument asserted herein are materially different from what was considered during examination (whether Just et al. alone demonstrated patentability).

The petition also cites multiple new prior-art reference that, while not identified as primary ground references, are relied upon in the ground as corroborating motivation and reasonable expectation of success. As also explained above, the ground further relies on EX1010 and EX1075 for providing non-hindsight reasoning for using the claimed prior-art albumin-binding moiety for the very same purpose for which it was disclosed in the prior art. Lilly does not even allege either reference was considered during examination or was cumulative to any reference that was. The multiple references that were never considered or applied during examination warrant referral for institution and trial. *Oticon* at 10, 16 institution

warranted where reference not previously of record “provide[s] motivation”).

Because the petition uses new references that supply the missing elements and reason to combine, the argument presented now is not cumulative to that presented (and failed) during examination. Lilly argues that the examiner concluded “it would require hindsight reasoning to make the compounds claimed in this application” based the ’483 Publication alone “because all of the preferred embodiments and species disclosed [therein] differ from the instant compounds at additional positions[.]” DDB at 24. But the present ground does not rely on the ’483 publication alone. As explained above (*see* Sections III.A.1-2), new references (EX1007, EX1009, EX1010, and EX1075) close the gaps. The ground does not rely on the ’483 Publication the same way it was applied during examination.

Lilly does not even purport to address the teachings of the ’483 Publication that are materially distinct from those considered and relied upon during examination. During examination, the examiner only discussed paragraphs [0044] and [0111], Tables 1-2, and Formulae II(b)-(d) of the U.S. patent publication (EX1012), and examined patentability from the perspective of whether the broad genus disclosed a narrower species. EX1002, ¶44; EX1004, 27-29. As Dr. Cornish explained, however, [“t]he Examiner’s brief exploration of this single reference did not identify important prior-art teachings establishing effective structure-activity relationships (SARs) for dual GIP/GLP-1 agonism effective for treating diabetes and

obesity.” EX1002, ¶44; *see also, e.g.*, EX1002, Tables A-B above.

Lilly presents no showing that the paragraphs of EX1012 relied upon during examination render cumulative the prior-art disclosures relied upon in the present ground. For example, there is no discussion in the examiner’s treatment of EX1012 that it teaches a structure-activity relationship (SAR) elucidating locations that are amenable to specific substitution or that the peptide can predictably and successfully be truncated at position 28 or substituted with the familiar exenatide C-terminal motif. *E.g.*, Pet., 18-19, 26-28. Nor does Lilly identify any discussion by the examiner that benefits of employing the familiar exenatide C-terminal motif were well recognized in the art. *E.g.*, Pet., 27-28 (reduced clearance and increased metabolic stability without unduly sacrificing activity when motif was successfully appended to DPP-IV-resistant GLP-1 and GIP agonists to improve metabolic stability while retaining favorable potency). Lilly presents no evidence the examiner considered the SAR from the data in the ’483 Publication (*see* Section II above), presents no evidence the examiner analyzed the prior-art SAR by sorting activity data (Pet., 28-30), and fails to explain how consulting prior-art SAR data somehow demonstrates improper hindsight. Lilly’s unsupported speculation and conjecture should be rejected.

B. Material Examination Error Warrants Referral

Even when the same or substantially the same art and argument previously

was presented to the Office, discretionary denial is not warranted where the petitioner has demonstrated that the Office erred in a manner material to patentability. *Advanced Bionics* at 8. Paradigmatic examples of material error expressly include “misapprehending or overlooking specific teachings of the relevant prior art where those teaching impact patentability of the challenged claims” or making “an error of law.” *Id.*, n.8; *Oticon* at 19-20 (finding examination error material to issuance because it “seems that the Examiner was simply not aware of Choi’s [non-cumulative] teachings” that were “deal[ing] with similar problems” as the challenged patent). That is the case here, at least with respect to EX1007, EX1009, EX1010, and EX1075. *See* Sections II and III.A.1-2 above. Lilly does not even contest that (1) EX1010 and EX1075 are new and non-cumulative; (2) that EX1009 was not before the examiner; and (3) that neither Lilly nor the examiner ever identified EX1007 as a considered reference.

Lilly’s arguments that EX1007 or EX2045 could have been considered (because they were referenced in the specification but not in an IDS) or that EX1009 is cumulative to EX2045, are all unavailing because, at most, they demonstrate the error of overlooking prior-art that should have been applied.

Indeed, the Office recently reiterated that a petitioner “satisfies the second part of *Advanced Bionics* because the asserted prior art was not a basis for rejection during examination, is not substantially the same as prior art the Examiner applied,

and includes specific teachings that ‘impact patentability of the challenged claims.’” *Ecto World, LLC v. Rai Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 5 (USPTO Dir. 2025) (precedential) (hereinafter “*Ecto World*”) (quoting *Advanced Bionics* at 8 n.9). “A petitioner also may point to the fact that even though the asserted prior-art is listed on an IDS, the Examiner did not issue any prior-art rejections during examination, so the Examiner materially erred by overlooking certain teachings in the prior art on the IDS.” *Ecto World* at 5-6. Accordingly, examiner error is demonstrated here by the failure to apply the asserted references even if they are deemed to have been considered *sub silentio*, as Lilly proposes.

Indeed, just as in the present case, the Office has repeatedly concluded it was material examination error to allow claims over a single reference where teachings of other references were overlooked, including failing to assert them in combination with the considered reference. See *Microsoft Corp. v. X1 Discovery, Inc.*, IPR2025-00253 Paper 13 at 2 (USPTO Dir. 2025) (Office error warranted referral where cited prior-art taught a feature that the examiner had identified as not being taught in the prior art); *Xencor, Inc. v. Merus N.V.*, IPR2025-00604 Paper 12 at 2-3 (USPTO Dir. 2025) (similar); *Microsoft v. Partec Cluster Competence Center*, IPR2025-00318, Paper 9 at 2-3 (USPTO Dir. 2025) (similar); *Anthony Inc. v. ControlTec, LLC*, IPR2025-00559, Paper 12 at 2 (USPTO Dir. 2025) (material error to fail to find missing element in a reference never considered by the examiner). These are

precisely the types of examination error that occurred here, as summarized above. See Section II.

Furthermore, as discussed in detail below, Lilly's arguments that the present challenge is cumulative to the examiner's consideration of Just et al. merely demonstrates how different they are. See Section III.B *infra*. Moreover, Lilly's discussion of the examiner's consideration of Just et al. reveals additional examination errors, discussed further below. See Section III.C

1. Lilly Repeatedly Ignores Disclosures of Previously Unasserted Art.

Lilly argues that the Office should “defer to previous Office evaluations of the evidence of record unless material error is shown” and that it cannot be said there is error material to patentability if reasonable minds can disagree about the examiner's prior evaluation of the prior art of record. DDB at 37. But here, it is undisputed that there is no evidence the examiner evaluated EX1007, EX1009, EX1010, or EX1075. Failure to consider salient references is examiner error under *Advanced Bionics*, *Oticon*, and recent decisions from the Director's Office (discussed above). Lilly identifies no justification for overturning these precedents.

Next, Lilly argues that there was no error during examination because the examiner evaluated Just et al. during examination and distinguished it on the additional bases that “making the claimed compounds would require several specific

changes—and no others—” and “that doing so would require hindsight.” DDB at 32. As discussed at length above in Section III.A, however, Lilly’s argument ignores the disclosures of the new references (*e.g.*, EX1007, EX1009, EX1010, and EX1075), which close the gap.

Lilly’s argument (DDB at 33-34) that a skilled artisan “would have had to add the precise lipophilic substituent with the precise linker (neither of which was disclosed by [EX1007]), at the right location (also not disclosed by [EX1007])” ignores that this element is expressly disclosed by EX1009, and reason to combine with reasonable expectation of success is supported by EX1010 and EX1075, none of which were considered during examination. Failure to consider and apply or distinguish these references during examination was material error warranting institution.

2. Lilly Ignores Prior-Art Rationale.

Lilly offers conclusory “hindsight” and “lead compound” arguments. DDB at 36 (citing *Sanofi-Aventis U.S., LLC v. Dr. Reddy’s Labs., Inc.*, 933 F.3d 1367, 1375-80 (Fed. Cir. 2019); *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019)). But Lilly’s arguments fails to address the ground actually presented. The previously unconsidered EX1010 and EX1075 provide non-hindsight-based rationale and reasonable expectation of success for applying the prior-art Lys²⁰-conjugated albumin-binding moiety to the prior-art operational

peptide sequence to achieve favorable half-life without the known downsides of PEGylation. EX1010, 1:21-23 (Lys²⁰-conjugated albumin-binding moiety achieved once-weekly dosing) (cited at, *e.g.*, Pet., 14, 24, 45); EX1075, Abstract, 2:21-25, 19:28-37, 25:25-26:6, 36:7-10, 38:6-10, 49-51 (Table 1), 58 (Table 4) (the same albumin-binding moiety routinely increased the half-life of GIP/GLP-1 agonists comprising the exenatide C-terminal motif, achieving half-lives similar to or longer than semaglutide) (cited at Pet., 15-16, 74); EX1002, ¶165 (cited at Pet., 43-46). The demonstrated structure-activity relationship (SAR) for GIP/GLP-1 dual agonism and the known benefits of the exenatide C-terminal motif provided non-hindsight-based rationale for employing that motif in place of Lilly's idiosyncratic C-terminus (at positions 29-39). EX1002, ¶¶158 (cited at Pet., 36), 165 (cited at Pet., 45, 74), 190 (cited at Pet., 78-79). Though Lilly argues (DDB at 36) the examiner concluded that modifications like those proposed in the petition require hindsight, as explained in Section III.A above, the examiner never expressed any conclusions about modifications to EX1007 in view of EX1009 (because the examiner never considered it).

Lilly next argues that there is nothing new in Dr. Cornish's expert declaration because the petition allegedly "fails to identify any specific prior-art teaching of a SAR relationship for dual GIP/GLP-1 receptor agonism in the prior art that the Examiner allegedly misapprehended or overlooked." DDB at 34-35. But Lilly

ignores Dr. Cornish's extensive discussion of the SAR, including as illustrated in Tables A and B, and as cited at length above. *See, e.g.*, Section II above.

Lilly asserts that it will argue in the POPR that SAR relationships are complex and unpredictable, and that SAR studies are iterative and experimentally onerous. DDB at 35. As a threshold matter, Lilly should not be permitted to avoid opposition scrutiny by holding back its rationale until Empower has no opportunity to respond. Moreover, Lilly does not dispute herein that the '483 Publication performed such an iterative and "experimentally onerous" analysis, but that the examiner failed to discuss it and lacked the benefit of Dr. Cornish's testimony regarding how a skilled artisan would have understood it. To the extent Lilly seeks to attack rationale to combine or reasonable expectation of success by raising new fact disputes about the predictability of the SAR disclosed in the prior art and relied upon in the petition, this merely demonstrates that the arguments presented in the petition are materially distinct from the sole argument considered during examination and that institution should be granted to consider Lilly's new arguments.

3. Lilly's Hindsight Arguments Highlight Examination Error.

Lilly argues that the examiner allowed the claims because a skilled artisan relying exclusively on Just et al. "would have had to 'choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are different from those preferred and reduced to practice'" therein, but the examiner found no

rationale other than “hindsight” to go from the “‘preferred embodiments and species’ in Just et al.’s broad genera” to the “instant compounds[.]” DDB at 32-33. But, of course, the current ground does not rely primarily or exclusively on the broad genera, or the preferred embodiments and species disclosed in Just et al. As explained in the petition materials and above, the ’657 Publication discloses the operational peptide sequence, the ’537 Publication discloses the Lys²⁰-conjugated albumin-binding moiety, and these prior-art disclosure close the gap.

Moreover, Lilly’s argument also highlights material examination error (a legal error), and invites the Director to adopt that legal error. For example, Lilly argues that the basis for allowance was the examiner’s belief that it is legally permissible to exclude from the disclosure of the prior-art express embodiments “that are different than those preferred and reduced to practice[.]” DDB at 27-28. Lilly thus explicitly bases its nonobviousness argument on fundamental legal error by the examiner, which Lilly amplifies in its brief and encourages the Director to repeat.

Lilly urges, “[w]ith respect to Just, the Examiner explained that to make the claimed compounds, a skilled artisan would have had ‘to choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation ***that are different from those preferred and reduced to practice in [Just].***’” DDB at 13, 24, 27, 32-33, all citing EX1004, 28 (emphasis added). This examiner analysis commits long-established legal error. *See, e.g., In re Lemelson*, 397 F.2d 1006, 1009 (CCPA

1968) (“The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain.”); *see also EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985) (“A reference must be considered for everything it *teaches* by way of technology and is not limited to the particular *invention* it is describing and attempting to protect.” (original italics)), *cited with approval in Netflix, Inc. v. DivX, LLC*, 2023 U.S. App. LEXIS 4926 *12-*13 (Fed. Cir. 2023) (nonprecedential) (“The Board’s...substituting a focus on Chen’s own inventive ‘system’ for the petition’s focus on particular Chen disclosures about pre-Chen art...was a fundamental legal error.”).

Lilly extends this fundamental error to attack the ’657 Publication (EX1007). DDB at 27 (“Alsina-Fernandez [EX1007] is cumulative of Just.”). But, of course, repeating a fundamental legal error just compounds—rather than cures—that error. Correcting fundamental examiner error is an appropriate use of Board resources. *Padagis US v. Neurelis, Inc.*, IPR2025-00464, Paper 12 at 3 (USPTO Dir. 2025) (“[T]he patent examiner’s conclusion...raises concerns of material error such that review of the challenged patents is an appropriate use of Office resources.”).

Next, Lilly argues that the ’657 Publication likewise discloses a genus of compounds depending on whether one employs the Nal or F amino acid at position 22, whether one employs optional cysteine amino acids at positions 43-44, and

whether the C-terminus is “optionally amidated.” DDB at 33. Lilly’s argument once again misses the mark. Lilly’s claims encompass the use of Nal or F at position 22 as well as optional amidation of the C-terminus. These options provide no basis to distinguish the claims from the prior art. That leaves only one of Lilly’s three proposed choices (cysteines at positions 43-44), but even Lilly concedes that these residues are “optional.” DDB at 33. As explained in the petition, the cysteines are employed only for the purposes of PEGylation, and there was good reason in the prior art to employ the prior-art albumin-binding moiety for improved half-life instead of PEGylation. Pet., 14-15, EX1002, ¶¶102 (cited at Pet., 16), 144 (cited at Pet., 26, 74). Lilly’s arguments are meritless.

4. Lilly’s Attempts to Silence Opposition Should Be Rejected.

Lilly argues that Empower’s discussion of examiner error in the petition was “conclusory” and that Empower should be precluded from addressing examiner error “in forthcoming briefs.” DDB at 31-32 n.6. Lilly’s argument is a thin reed at best, and is actually frivolous. As an initial matter, the petition amply demonstrated examiner error, as illustrated by the numerous petition cites discussed above. Lilly’s attempt to restrict the petition materials’ demonstration of examiner error to the summary of the examination history should be squarely rejected.

Even more importantly, however, Lilly’s attempt to preclude Empower briefing on discretionary denial contravenes the Office’s own directives for

petitioners to address discretionary-denial factors in the discretionary-denial briefing. USPTO, *Interim Director Discretionary Process* (last visited Sept. 13, 2025) at §I.B.C, *available at* <https://www.uspto.gov/patents/ptab/interim-director-discretionary-process> (“The petitioner may file a brief that opposes the patent owner’s request and explains why the Office should review the challenged patent in view of discretionary considerations.”). Lilly asks to preclude Empower from addressing Lilly’s arguments while also attempting (DDB at 38) wholesale incorporation by reference of merits arguments from its yet as-filed preliminary response—presumably hoping to preclude thereby any ability to respond to those arguments. Lilly’s repeated attempts to deprive Empower of any opportunity to respond merely serves to underscore that Lilly is desperate to hide its prosecution conduct from scrutiny.

C. Lilly Invites Further Legal Error

1. The Lead Compound Is Not Missing From The Petition.

Lilly’s lead compound arguments (DDB at 38-44) invite the Director to commit legal errors at least by (1) requiring a demonstration that there is only one-true lead compound; and (2) ignoring the legal rule that lead-compound analysis is not always required, such as when the prior art expressly suggests a compound for clinical development. Controlling case law has repudiated Lilly’s lead-compound canards, yet Lilly invites the Director to engage in legal error. Ultimately, Lilly

ignores that the petition satisfies the lead compound analysis under controlling caselaw and identifies no reason dissuading a POSA from the lead compound disclosed in the '657 Publication.

Lilly insists that “Petitioner does not even attempt to show that a skilled artisan would have selected the lead compound over other prior-art compounds, as Federal Circuit caselaw requires.” DDB at 3; *see also* DDB at 39, 40-43. Lilly, however, misreads precedent to construct a rigid **only-one-true-lead-compound** test that would run afoul of the flexibility that precedent demands. *KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 415 (2007) (requiring a “an expansive and flexible approach” to obviousness). Indeed, “that the prior art must point to only a single lead compound for further development efforts [is a] restrictive view of the lead compound test [that] would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*.” *Altana Pharma v. Teva Pharmaceuticals*, 566 F.3d 999, 1008 (Fed. Cir. 2009); *Daiichi Sankyo v. Matrix Labs.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (the lead-compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a *single*, best lead compound); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012) (holding that lead compound is an appropriate approach but noting that structural similarity is “generally” the appropriate approach). *Otsuka*, 678 F.3d at 1292 (“[o]ur analysis focuses on those proposed lead **compounds** ... that the skilled

artisan would have had a reason to select from the panoply of known compounds in the prior art” (emphasis added)).

Altana is a Hatch-Waxman case in which Altana sought a preliminary injunction that the district court denied after finding a substantial question of invalidity. 566 F.3d at 1004-05. On appeal, Altana urged error because “the prior art suggested the availability of numerous other compounds that were at least as promising to modify.” *Id.* at 1006. The Federal Circuit rejected the patentee’s argument, explaining “[o]bviousness based on structural similarity may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound.” *Id.* at 1007. Indeed, it is “sufficient” to show that the claimed and prior-art compounds possess “a sufficiently close relationship” to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old. *Id.* at 1007 (citing *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir.1990) (en banc)). The Federal Circuit affirmed the district court for employing “a flexible approach ... and found that the defendants had raised a substantial question that one of skill in the art would have used the more potent **compounds** of the [reference], **including** compound 12, as a starting point from which to pursue further development efforts.” *Id.* at 1008-09 (emphasis added).

Similarly, the petition here identifies a prior-art compound with a sufficiently

similar structure and express reasons to modify. As the petition explained, the '657 Publication relies on *in vitro* and *in vivo* data to demonstrate SEQ ID NO:1 has utility as a GIP/GLP-1 dual agonist, including for glycemic control and weight loss, and expressly teaches its use for clinical treatment. Pet., 25; EX1007, 13:7-8, 15:1-3, 17:1-19:7, 22:15-30 & Tables 1-7 (data); EX1007, Abstract (“treatment of diabetes”), 2⁴:12-25 (“GLP-1 is a 37-amino acid peptide that protects pancreatic beta cells and inhibits glucagon secretion, gastric emptying and food intake which lead to weight loss.”), 5:24-27 (“treatment of obesity.”), Claims 1-12. Lilly identifies no reason that the petition arguments and evidence fail to satisfy the applicable legal standard.

Nor is Lilly correct that a lead-compound analysis is always required. Indeed, “case law ***has not*** suggested that lead compound analysis is *always* required.” *Cytiva Bioprocess R&D AB v. JSR Corp.*, 122 F.4th 876, 884 (Fed. Cir. 2024) (original italics, emphasis added), *citing KSR*. In *Cytiva*, the patentee argued “the Board erred by failing to conduct this lead-compound analysis[.]” 122 F.4th at 884. The Federal Circuit explained that:

⁴ The page number cited is the document page number rather than the native pagination.

When it applies, the lead-compound analysis typically proceeds with a two-part inquiry. First, [determine] whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts. * * * [Second, determine] whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success."

Id. Indeed, as the court explained, "[a] lead-compound analysis is not required where the prior-art references expressly suggest the proposed modification." *Id.* This makes sense, of course: why go through a rigid lead-compound analysis when a reference has already done the requisite work of the lead-compound analysis by expressly identifying a compound as a suitable starting point for the same use and even suggested appropriate modifications. Such is the case here.

The petition explained how the '657 Publication disclosed "a most promising GIP/GLP-1 dual agonist peptide sequence useful for treating diabetes and/or reducing body weight." Pet., 25, citing EX1007, Abstract, 2:12-25, 5:24-27, Claims 1-12. Note: it did not simply identify a "lead compound," but actually identified a compound that was promising for the same purpose as the claimed compound. Indeed, "[t]he '657 Publication relies on *in vitro* and *in vivo* data to demonstrate SEQ ID NO:1 has utility as a GIP/GLP-1 dual agonist, including for glycemic control and weight loss." Pet., 25 (citing EX1007, 13:7-8, 15:1-3, 17:1-19:7, 22:15-30 & Tables

1-7). Hence, the suggestion in the prior art was not some blue-sky speculation, but actual, real-world results.

Moreover, not only was it “most promising GIP/GLP-1 dual agonism properties” but it was also likely “that this compound would be favorably improved through further modification, including use of the exenatide C-terminal motif and Lys²⁰-conjugation to a promising albumin-binding moiety.” Pet., 26 (citing EX1002, ¶¶139, 144, 114, 135). Dr. Cornish explained how the ’657 Publication suggested C-terminal modifications and “reports that in vivo administration of these less potent PEGylated peptides still resulted in dose-dependent decreases in weight, fat mass, food intake, blood glucose, triglycerides, and cholesterol as compared to vehicle.” EX1002, ¶144, citing EX1007, Tables 6-7, 22:15-30. Thus, the ’657 Publication meets *Cytiva*’s criteria by specifically identifying the lead compound and suggesting modification.

Instead of addressing the case the petition actually made, Lilly cherry-picks language from a few lead-compound cases to conjure a universal requirement to identify other lead compounds and then explain why the chosen one was the best. DDB at 3 (accusing the petition of failing to “show that a skilled artisan would have selected the lead compound over other prior art compounds, as Federal Circuit caselaw requires [sic].”); DDB at 39-41, 43 (same). As *Altana*, *Daiichi*, and *Cytiva* all confirm, however, there is no legal requirement to justify selection of one lead

compound over another lead compound. Because Lilly focuses exclusively on its legally-erroneous *per se* rule, it fails to address the merits of the petition’s analysis, which starts with an express teaching of a compound selected for modification for clinical use coupled with express suggestions to modify. *E.g.*, Pet., 26 (citing EX1007); *Cytiva*, 122 F.4th at 884 (lead-compound analysis not required where the prior-art references expressly suggests modification).

Additionally, Lilly argues (DDB at 20) “there has been no change in the law of structural obviousness or the ‘lead compound’ test” as reason to deny institution but—to the extent Lilly’s misreading of lead-compound precedent as a set of rigid requirements ever had any currency—recent cases like *Cytiva* have confirmed Lilly’s misreading is no longer tenable.

Two related arguments are also worth refuting: (1) Lilly argues that the prior-art lead compound is a genus and implies (without support) that this is a problem; and (2) Lilly reports that its “research” shows patents are almost never invalidated under a lead-compound analysis. Both arguments are wrong.

First, Lilly repeatedly argues that the lead compound is a genus. DDB at 22-23 n.5 (noting “SEQ ID NO:1 as Petitioner’s ‘lead compound,’ but Petitioner’s lead compound is a genus covering 28 distinct compounds.”); 33 (“actually a genus of compounds, requiring a skilled artisan to choose from multiple options”). As an initial matter, the same is true of the claims (*e.g.*, amino acid at position 22 and

optional amidation), such that Lilly's exaggerated description of genus size has no material distinction for the petition, as discussed above.

Moreover, Lilly is wrong that a lead compound coupled with express teachings to modify makes the lead compound itself a genus—rather it remains a specific lead compound with a genus of anticipated modifications. Additionally, Lilly does not (and cannot) show that the genus of compounds here is a problem because the caselaw that Lilly itself cherry-picked recognizes that “lead compounds” are an acceptable part of the analysis. DDB at 39 (quoting *Otsuka*, 678 F.3d at 1291 (“First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as **lead compounds, or starting points**, for further development efforts.” (emphasis added))). This makes real-world sense, of course: it can hardly be true that **more** promising, related (in the same genus) starting points paradoxically makes a purported invention (in the same genus) **less** obvious.

Second, Lilly reports its “research yielded only three cases finding a novel pharmaceutical compound claim obvious based on a ‘lead compound’ analysis.” DDB 46. Lilly purported failure to find contrary relevant cases like *Altana* and *Cytiva* simply highlights how crabbed and unreliable Lilly has made its analysis in an effort to insulate pharmaceutical claims from Executive power. Once again, Lilly invites the Director to commit legal error. Once again, the Director should decline.

2. Another Examiner Legal Error: “And No Other Change.”

Lilly invites yet another legal error by repeating and expanding on the examiner’s holding that hindsight would be required to make the proposed changes “but not make any other changes.” EX1004, 28; DDB at 13, 32. This reason for allowance contradicts well-established precedent rejecting the idea that obviousness can only produce a single outcome. *Janssen Pharms. v. Teva Pharms.*, 97 F.4th 915, 930 (Fed. Cir. 2024) (“A POSA can be motivated to do more than one thing...and [the challenger] did not need to show that a POSA would be singularly motivated” to do only one of them), *citing Bayer Pharma AG v. Watson Labs.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) (“[O]bviousness does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away.” (simplified; original italics)). Rather than warranting denial, the examination error that Lilly highlights provides additional ***reason to refer*** the question for trial. *Padagis*, IPR2025-00464, Paper 12 at 3 (“[T]he patent examiner’s conclusion ... raises concerns of material error such that review of the challenged patents is an appropriate use of Office resources.”).

Lilly embraces and expands upon the examiner’s legal error in arguing the petition must have used improper hindsight. DDB at 27-28, 43-44. Because Lilly’s argument is based on a fundamental mistake in obviousness law, its argument is unavailing. In any case, as discussed in the previous section, the principal references

provide express teaching of a lead compound's relevance to a problem in the art and express suggestion to further modify, rendering Lilly's nonspecific and legally-erroneous argument even less tenable. Once again, Lilly invites legal error, and once again the Director should decline Lilly's invitation and instead refer the case for trial.

IV. LILLY HAS NO LEGITIMATELY SETTLED EXPECTATIONS

The Director's guidance for discretionary denial based on settled expectations is clear: cases turn on individual facts—such as material error by the Office and efficient use of Board resources—rather than categorical rules. *E.g.*, *Anthony*, IPR2025-00559, Paper 12 at 2 (“Although the challenged patents have been in force for approximately eighteen and seventeen years, Petitioner appears to show a material error by the Office, and it is an appropriate use of Office resources to review the potential error.”); *Eunsung Global v. HydraFacial LLC*, IPR2025-00445, Paper 14 at 3 (USPTO Dir. 2025) (“Petitioner persuasively demonstrates that the patent examiner overlooked certain teachings ... that appear to disclose the allowable features of the claims[, so d]iscretionary denial is not appropriate....”); *Azurity Pharms., Inc. v. Helsinn, Healthcare S.A.*, IPR2025-00945 et seq., Paper 11, at 2-3 (USPTO Dir. Sep. 19, 2025) (“*Azurity*”) (examiner error warrants referral of pharmaceutical patent issued in 2014). Despite this clear guidance, Lilly's “settled expectation” arguments are premised on its erroneous proposed policy that pharmaceutical patents are categorically exempt from Executive review. Lilly

further argues that age of the patent alone is dispositive in insulating Lilly's invited examination error from review. But both of Lilly's proposed categorical rules are wrong and must be rejected. And, once the individual facts of this patent and Lilly's actions related thereto are considered, it becomes apparent that Lilly cannot immunize this patent from Executive review based on alleged settled expectations.

A. Lilly's Pharmaceutical-Product Exception Should Be Rejected.

Rather than focusing on the individual patent at issue and demonstrating that Lilly legitimately relied on settled expectations in that particular patent, Lilly makes overbroad arguments that apply categorically to patents for pharmaceutical compounds as a whole. For example, Lilly argues that it published clinical-trial results, obtained FDA approval, and listed the challenged patent in the Orange Book. DDB at 15, 19-20. Of course, Lilly is just describing the regulatory scheme for FDA approval in the U.S., the reward for which is NCE exclusivity, not immunization of erroneously granted patents. Lilly's arguments apply equally to all patents related to pharmaceutical products and, as such, they prove too much. If Lilly is correct that these factors categorically establish settled expectations and immunize each Orange Book-listed patent from Executive review, Lilly is effectively asking the Executive to unilaterally disarm himself against pharmaceutical patents issued in error.

That cannot be the law. Of course, the Executive is not categorically precluded from revisiting examination error when there is an FDA approval, especially when

Lilly invited the error (as is the case here, as explained above). It is inconsistent for Lilly even to argue that availing itself of Executive power to obtain NCE exclusivity somehow immunizes Lilly's erroneously granted patent from Executive power to review that patent grant. Lilly already received the Executive's reward for FDA approval: NCE exclusivity. Lilly's proposed policy is particularly unjustifiable because it would disempower the Executive to correct the errors of bureaucrat carryover from prior administrations, treating the current Executive as somehow disfavored as compared to prior holders of the same office. Lilly's dead-hand argument should be dead on arrival.

Lilly's request that the Executive unilaterally disarm himself against examination error in pharmaceutical patents also makes especially little sense in this particular case given that it contravenes the Executive's directive to root out waste, fraud, and abuse. E.O. 14273, *Lowering Drug Prices by Once Again Putting Americans First*, 90 Fed. Reg. 16441 (2025) ("It is the policy of the United States that Federal ... intellectual property protections... are optimized to provide access to prescription drugs at lower costs to American patients and taxpayers."). Extracting unjustified monopoly rents from the Executive is the very definition of waste, fraud and abuse.

Tying its once-weekly GLP-1 products to its pre-existing auto-injector pen, Lilly extracts billions of dollars from the Executive and the American taxpayers, and

seeks tens of billions more. EX1076, 2 (Table: \$12.42 billion in US spending on Mounjaro and \$17.57 billion for Trulicity in 2023:), 2 (Figure: depicting Trulicity share decreasing from 2021 to 2023 as share for Mounjaro expands); EX2002 (uses Lilly’s already “well-established auto-injector pen”);⁵ EX1077, 7-8 & Fig. 1 (“Medicare makes up 24 percent of total US market prescriptions and Medicaid makes up 10 percent.”); *id.*, 6-7 (73 percent of Medicare enrollees with obesity already have access to GLP-1 treatment, CBO estimated rule change would add additional 2 percent in the first year, increasing Medicare expenditures “around \$1.4-1.5 billion” in the first year and \$35.5 billion over a nine-year period while increasing federal Medicaid spending by \$11 billion over a ten-year period). GLP-1 prices in the United States “are significantly higher in the U.S. than in peer nations[.]” EX1082, 1-2; (tirzepatide: U.S.: \$1,023; Japan: \$319; Netherlands: \$444)). Given this Administration’s commitment to lowering prices for Americans, Lilly’s arguments are ironic at best. Exec. Order 14,297, 90 Fed. Reg. 20749 (May 15, 2025) (“The United States has for too long turned its back on Americans, who unwittingly sponsor both drug manufacturers and other countries.”); 35 U.S.C. 316(b) (requiring consideration of “the effect [of PTAB rules] on the economy” as

⁵ This video illustrates how to use the auto-injector pen: https://www.youtube.com/watch?v=6_0l6xWhk1k (last visited Sep. 19, 2025).

well as the integrity of the patent system).

Though Lilly recognized its ability to demand astronomical prices was coming to an end—introducing lower-priced tirzepatide “vial” products shortly after the petition was filed—those prices are still higher in the U.S. than prices for GLP-1-containing auto-injector pens in foreign countries (discussed above). EX1078 (\$500-\$1049/month for “Zepbound vial” treatment without auto-injector pen), EX1084 (similar). Lilly’s recent decision to chase compounders by offering “vial” products provides no reason to divest the Executive of his Constitutional and statutory error-correction power now.

Moreover, Lilly’s argument completely ignores the settled expectations of millions of Americans who understand their President is empowered to root out waste, fraud, and abuse to lower drug prices. The President campaigned on his ability to do so. As discussed in detail below, Lilly permitted millions of Americans to obtain GLP-1 vials from non-Lilly sources without interference from the challenged patent *for years*. EX1079, 1-2, 5 (Novo blamed shortage of auto-injectors for millions turning to compounders). Depriving the Executive of his Constitutional and statutory authority to correct past bureaucratic errors thus would not only unsettle the expectations of the President, but that of millions of Americans. Lilly cites no case where settled expectations were found, much less found sufficient to warrant denial of institution, in similar circumstances.

B. Age Is Not Dispositive.

Lilly assumes mere age is dispositive, arguing that the challenged patent issued in October 2016, almost nine years before the petition was filed, and that this “passage of time alone” justifies discretionary denial because Petitioner should have sought “earlier review.” DDB at 13-20. Despite being warned that each case must be addressed individually based on its facts, Lilly supports its erroneous assertion that the passage of time alone is dispositive with an unexplained string citation merely enumerating the number of years that patents in other cases with different facts had been in existence. DDB at 13-15 (citing cases).

Lilly is incorrect in asserting that age of an issued patent insulates that patent from Executive review of demonstrated Office error. The Office has repeatedly held that material examination error voids even long-settled expectations. *E.g.*, *Anthony*, IPR2025-00559, Paper 12 at 2 (“Although the challenged patents have been in force for approximately eighteen and seventeen years, Petitioner appears to show a material error by the Office, and it is an appropriate use of Office resources to review the potential error.”); *Xencor*, IPR2025-00604, Paper 12 at 2-3 (“strong settled expectations” outweighed by petitioner demonstrating a reference cited in an IDS during examination taught the feature that was believed at allowance to be missing from the prior art); *Eunsung*, IPR2025-00445, Paper 14 at 3 (similar); *Activision Blizzard v. Milestone Entertainment*, IPR2025-00708, Paper 13 at 2-3 (USPTO Dir.

2025) (examination error outweighs “strong settled expectations”); *Azurity* at 2-3 (referring 11-year old patent for examination error despite “strong settled expectations”). The Office has established that it is an appropriate use of resources to review challenges such as this where there was material Office error during examination. *Partec*, IPR2025-00318, Paper 9 at 3; *see also Padagis*, IPR2025-00464, Paper 12 at 3 (“concerns of material error [raised] such that review of the challenged patents is an appropriate use of Office resources.”), *citing Advanced Bionics*.

Significantly, as explained in Section III above, Lilly’s brief failed to address the material differences between the art and arguments presented in the petition and the limited examination. Moreover, Lilly essentially demonstrates material examination error by illustrating that the examiner ***should have*** considered the art and arguments presented in the petition, but there is ***no evidence*** that it was considered. Instead of taking responsibility for inviting claim allowance on an incomplete and erroneous examination record, Lilly blames the examiner for failing to suss out and request the materials Lilly admittedly knew about but omitted from the file (materially significant disclosures that the relevant peptide sequence and albumin-binding moiety were in the prior art). DDB, 9-11. But Congress expressly authorized the Executive to correct errors through IPRs, putting the Executive at the apex of his Article II Power. *See Youngstown Sheet & Tube Co. v. Sawyer*, 343 U.S.

579, 635-636 (1952) (Jackson, J., concurring) (“When the President acts pursuant to an express or implied authorization of Congress, his authority is at its maximum, for it includes all that he possesses in his own right plus all that Congress can delegate. In these circumstances...may he be said (for what it may be worth) to personify the federal sovereignty.”). The Executive should not be baited into punting his own correction process to another branch of government. Federalist No. 78 (“the judiciary, from the nature of its functions, will always be the least” of the three branches of government because it should have “neither FORCE nor Will”). Each examination error Lilly invited confirms Lilly has no legitimately settled expectation.

C. Lilly Undermines Its Settled Expectations Arguments.

Moving beyond Lilly’s erroneous categorical exceptions to Executive power, Lilly’s arguments also fail on their specific facts. Beginning with Lilly’s Orange Book argument, for example, Lilly’s listing undermines Lilly’s settled expectations argument rather than support it.

Lilly’s EX2044 illustrates that the statutory reward for FDA approval is NCE exclusivity, which Lilly asserts extends from approval until May 13, 2027. In other words, Lilly never relied on the existence of the challenged patent to exclude anyone from making tirzepatide from the very beginning until today.

Lilly’s lack of settled expectations in the challenged patent is further

illustrated in this particular case because Lilly's failure to supply adequate quantities of tirzepatide led the U.S. Government to suspend Lilly's exclusivity. EX1079, 3 ("enduring shortages" began "in December 2022 for tirzepatide" while "the U.S. health care system has come to depend on compounding pharmacies...to plug supply holes"). Beginning in 2022, millions of Americans came to rely on alternative suppliers. *Id.*, 2 ("large compounding pharmacies...are provisioning up to 2 million American patients with regular doses" of the weight loss drugs). That reliance continued unabated for years. EX1085, 1 (shortage authorization continued from 2022 through 2025); EX1086, 1 ("compounding remains a legal and vital part of personalized medicine" today). But Lilly never asserted the challenged patent against any of them.

Some compounding patients understandably want to continue with their existing treatments, causing Lilly recently to issue threats against compounders. Rather than having nine years of notice that the challenged patent threatened permitted compounding practices (as Lilly alleges), Empower had only a matter of months. Though Lilly's U.S. tirzepatide sales have co-existed with compounders essentially since 2022 (essentially since they began), Lilly now threatens to drive compounders away by any means at its disposal. But even now, Lilly continues to shy away from asserting the challenged patent (presumably to insulate it from invalidity challenge in district court). Instead, Lilly relied on frivolous accusations

under the Lanham Act. Lilly argues this somehow demonstrates Empower is misusing the petition. DDB at 49-51. What it demonstrates is that Lilly very recently threatened permitted compounding practices, and that Empower promptly responded legitimately to Lilly's saber rattling. But Lilly simply has no settled expectations in the challenged patent that it strategically avoided asserting **for years** (essentially coinciding with the entire duration of Lilly's marketing of tirzepatide). It is Lilly, not Empower, that has recently attempted to disrupt the status quo.

Lilly's clinical trial arguments similarly undermine its settled expectations assertions in this particular case. Lilly attempts to rely on the average and median costs of clinical trials in the industry to establish settled expectations (rather than proving up any actual investments tied specifically to the challenged patent). DDB at 15. For example, Lilly trumpets the number of clinical trials it says it has performed (83), with some of them published in "prestigious journals," being deemed by Lilly collaborators as providing "impressive" results, or resulting in share price increases. DDB at 15-18. Rather than demonstrate settled expectations **in the challenged patent**, however, the volume of Lilly's trials actually do the opposite.

The bulk of Lilly's studies relate to dosing protocols that are not the

“invention” of the challenged patent, including prior-art⁶ high dose (*e.g.*, 15 X then-existing GLP-1 dose) and dose-titration protocols that reduce adverse event profiles. In particular, the unclaimed titration protocol reduced the nausea and vomiting observed to be comparable to the rest of the GLP-1 class. EX2021, 513 (“The dose-escalation scheme in the current trial...was associated with a better gastrointestinal-related side-effect profile than the scheme in the phase 2 trial, which involved more rapid escalation.”); EX2022, 11 (“Gastrointestinal events (nausea, diarrhoea, and vomiting)...were the most frequent TEAEs in the tirzepatide groups.... When gastrointestinal events were analysed within 4-week intervals, these events were most frequent during the dose-escalation period....”), 14 (“The incidences of nausea, diarrhoea, and vomiting were lower than those in a phase 2 study of tirzepatide, and similar to those in SURPASS-2 and GLP-1 receptor agonist class.”); EX2023, 213-214 (“As typically observed with these medications, transient, mostly mild-to-moderate gastrointestinal events were the most frequently reported adverse events, occurring primarily during the dose-escalation period.”); EX2024, 2917 (“The

⁶ The prior art ’657 Publication discloses high-dose administration encompassing the doses used in Lilly’s clinical trials. EX1007, 25:10-20 (“dosages per week fall within the range of 1 to 24 mg of peptide conjugate”); EX2024, Abstract (maximum tolerated dose of 10-15 mg).

allowance of dose de- and re-escalation during the titration phase helped to maximize tolerability and reflected dose adjustment strategies that may be relevant for clinical practice.”). These dosing protocols are not claimed in the challenged patent.

Instead, Lilly’s Orange Book listing demonstrates that Lilly obtained additional patents between June 2022 and July 2025, which Lilly asserts will not expire until *years* after the ’780 patent. EX2044 (listing U.S. Patent Nos. 12,295,987 and 12,343,382). It is these later patents (not the challenged patent) that claim the dosing regimens from Lilly’s clinical trials that Lilly purports to rely upon for settled expectations in the challenged patent. EX1080, Claim 1 (“wherein the first dose is about 25% of the fourth dose, the second dose is about 50% of the fourth dose and the third dose is about 75% of the fourth dose.”); EX1081, Claim 1 (“administering an escalation dose about once weekly for a minimum of at least about two weeks...of tirzepatide”). In this particular case, Lilly’s trials undermine rather than support Lilly’s assertion of settled expectations.

Indeed, it appears that Lilly was so desperate to extend its data exclusivity—rather than rely on the challenged patent—that Lilly aggressively studied new indications (DDB at 16, 18-19; EX2049-EX2050, EX2002; EX2042; EX2043) in addition to the unclaimed dosing protocols (DDB at 15-18). Lilly admits that these efforts continue even today. DDB at 16. Lilly’s own evidence thus demonstrates that

the trials it conducted lack nexus to the challenged patent and instead support Lilly's efforts to obtain later data exclusivity and later patents. Lilly's studies thus demonstrate a lack of settled expectations in the challenged patent.

D. Empower's First-Mover Petition Favors Institution.

Lilly admits it has not asserted the challenged patent in parallel litigation and that Empower is the first to challenge the patent despite growing public interest in doing so (due to Lilly's recent encroachment). DDB at 50, 5 n.1 (identifying later challenger). Absence of parallel litigation ordinarily favors institution. *See Amgen v. Bristol-Myers Squibb*, IPR2025-00601, Paper 9 at 2 (USPTO Dir. 2025) (“[T]he parties are not currently engaged in a parallel proceeding involving the challenged patents....As a result, there is currently no concern of inconsistent outcomes and duplication of efforts resulting from two proceedings operating in parallel.”). Here, Empower's early filing without any parallel litigation over the patent weighs even more strongly in favor of institution because it occurred very quickly after Lilly's encroachment against compounding pharmacies). *See Home Depot U.S.A., Inc. v. H2 Intellect LLC*, IPR2025-00480, Paper 11 at 2-3 (USPTO Dir. 2025) (where petitioner files promptly after Patent Owner newly threatens Petitioner's market, this weighs against Patent Owner's settled expectations and in favor of Petitioner's expectations); *cf. Sig Sauer Inc. v. Lone Star Future Weapons, Inc.*, IPR2025-00410, Paper 13 at 2 (2025) (“the parties are engaged in related litigation” declaratory

judgment of non-infringement).

Though Lilly lacked sufficient expectations of validity or enforceability in the challenged patent to assert it when its NCE exclusivity was suspended, its very recent, aggressive posture against permitted compounding-pharmacy practices demonstrated that Lilly intends to displace GLP-1 compounders, which it had not previously done. Lilly counterintuitively complains about the speed with which Empower responded to Lilly's threats, as if promptly petitioning the Executive for relief is something to be discouraged. But this is no hold-up operation by Empower. Lilly's saber-rattling newly threatened Empower's market, causing new awareness and a prompt response. Given Lilly's threatening entrance and refusal to grant Empower a covenant not to sue on the challenged patent, Lilly cannot complain that its patent is now subject to Executive scrutiny for waste, fraud, and abuse. In this context, it is astonishing for Lilly to imply that the Director should cede Article II power to cure a bureaucratic error caused by holdovers from a prior administration.

V. CONCLUSION

Lilly's request for discretionary denial should be *denied*.

Respectfully submitted,

Dated: September 22, 2025

/Jad A. Mills/

Jad A. Mills, Reg. No. 63,344

Counsel for Empower Pharmaceuticals,
Inc.

VI. EXHIBIT LIST - §42.63(E)

Exhibit No	Description
1001	U.S. Patent No. 9,474,780.
1002	Declaration of Dr. Virginia W. Cornish, Ph.D.
1003	<i>Curriculum Vitae</i> of Dr. Virginia W. Cornish, Ph.D.
1004	Prosecution History (Excerpts) of U.S. Patent No. 9,474,780.
1005	WO 2016/111,971 Search Report.
1006	WO 2016/111,971 Written Opinion.
1007	WO 2011/119,657 A1 Publication.
1008	WO 2013/164,483 A1 Publication.
1009	WO 2006/097,537 A2 Publication.
1010	WO 2014/202,727 A1 Publication.
1011	Gregg B. Fields, <i>Introduction to Peptide Synthesis</i> , 26 CURRENT PROTOCOLS IN PROTEIN SCI., 18.1.1-18.1.9 (2002).
1012	U.S. Patent Publication No. 2015/0299281 A1.
1013	SAXENDA (liraglutide) injection drug label (Dec. 2014) (“SAXENDA”) <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf .

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Exhibit No	Description
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1080	U.S. Patent No. 12,295,987.

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1081	U.S. Patent No. 12,343,382.
1082	Amin, K. et al., <i>How do prices of drugs for weight loss in the U.S. compare to peer nations' prices?</i> , HEALTH SYSTEM TRACKER (Aug. 17, 2023), available at https://www.healthsystemtracker.org/brief/prices-of-drugs-for-weight-loss-in-the-us-and-peer-nations/
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VII. CERTIFICATIONS

A. Word Count

I certify that this discretionary-denial opposition complies with the type-volume limitation of Rule 42.24 and Webpage, *Interim Director Discretionary Process*, §III.C.iii6 (“ For discretionary denial requests due before September 1, 2025, a petitioner’s opposition to the patent owner’s discretionary denial brief is limited to 14,000 words....”). The word count for this paper is 13,847 words.

B. Rule 42.6(e)(4) Certificate of Service

I certify that today this paper and exhibits 1076-1086 were served electronically on Eli Lilly & Co.’s counsel at michael.morin@lw.com; david.frazier@lw.com; michelle.ernst@lw.com; inge.osman@lw.com; raghav.bajaj@lw.com; ashley.fry@lw.com; hostettler_danica@lilly.com; barkoff_aaron@lilly.com. See Paper 8 (PO Updated Mand. Not.).

C. Declaration

All statements in this certificate of service made of my own knowledge are true and all statements made on information and belief are believed to be true. I acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of this proceeding.

Dated: September 22, 2025

/ Yawen Wang /
Yawen Wang