IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI-AVENTIS U.S. LLC,
GENZYME CORP. AND
REGENERON PHARMACEUTICALS, INC.,
Petitioners

v.

IMMUNEX CORPORATION,
Patent Owner

Case IPR2017-01884
Patent 8,679,487

PATENT OWNER PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107(a)

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Patent Owner Immunex Corporation ("Immunex") provides this Preliminary Response to the Petition for *inter partes* review ("IPR") of claims 1-17 of U.S. Patent No. 8,679,487 ("the '487 Patent"; EX1001) filed by Petitioners Sanofi-Aventis U.S. LLC, Genzyme Corp., and Regeneron Pharmaceuticals, Inc. (collectively, "Sanofi").

I. Introduction

The present Petition is the third petition filed by Sanofi challenging the same claims of the '487 patent. These serial petitions followed on the heels of litigation initiated by Sanofi in the U.S. District Court for the District of Massachusetts seeking a declaratory judgment of non-infringement of the '487 patent, and in which Sanofi now challenges validity. In short, Sanofi has mounted a campaign of harassment of the '487 patent by filing challenges at every opportunity. The PTAB denied institution on Sanofi's first petition after finding that Sanofi had failed to show a reasonable likelihood of prevailing. The Board should also deny institution here.

Sanofi's staggered string of serial petitions, all challenging the same claims of the same patent, fly in the face of the Board's precedential decision in *General Plastic Industrial Co., Ltd. v. Canon Kabushiki Kaisha,* IPR2016-01357, Paper 19

(PTAB Sept. 6, 2017) ("*General Plastic*"). Sanofi deliberately waited for Immunex to file its Patent Owner Preliminary Response in IPR2017-01129, then used it as a roadmap to craft the present Petition. Meanwhile Sanofi provides no credible explanation for its staggered filings, and presents no evidence that the prior art references cited in its third IPR Petition were not known or available to Sanofi at the time of filing its first petition in March 2017. Because all of the *General Plastic* factors weigh against institution, the Board should exercise its discretion to deny Sanofi's petition under 35 U.S.C §314(a). *See* Section II below.

The Board should also exercise its discretion to deny institution under 35 U.S.C. § 325(d) because Sanofi has recycled *substantially the same arguments* as were presented during prosecution of the '487 patent. *See* Section III below. Sanofi's arguments rest on the same framework as that used during prosecution, specifically arguing that a person of ordinary skill in the art ("POSA") would have modified a prior art murine antibody using a prior art method. Sanofi even uses an antibody that was disclosed to the examiner (*i.e.*, MAb230) and art teaching a method that was disclosed to the examiner (*i.e.*, EX1007). The Board should not waste its valuable time and resources in revisiting the question.

In its denial of Sanofi's first petition against the '487 Patent, the Board was

"troubled by Petitioner's failure to inform [the Board] of its contention before the district court that the claims should be construed under 35 U.S.C. § 112 ¶ 6." IPR2017-01129, Paper 19, at 12. The Board should find the present Petition even more troubling because, even after reading Immunex's Patent Owner Preliminary Response to the first petition and Immunex's discussion of the issue, Sanofi *still* fails to inform the Board of Sanofi's §112 ¶6 claim construction position before the district court. Sanofi's claim construction failures are compounded by Sanofi's inconsistent positions regarding indefiniteness in the Petition and in district court, which create more ambiguity regarding Sanofi's shifting claim construction positions. Either of these defects alone warrants denying institution. *See* 35 U.S.C. § 314(a); 37 C.F.R. §42.104(b)(3); Section IV below.

The Board should also deny institution of Sanofi's Ground 1 for the separate and independent reason that it fails to present a prima facie case of obviousness under a proper construction of the term "human antibody." *See* Section V below. The Board gives claim terms their broadest reasonable interpretation in light of the claim language, specification, and file history, read from the perspective of a POSA. But it would not be reasonable to construe "human antibody" so broadly as to include murine antibodies modified to be more similar to human antibodies (*i.e.*,

humanized antibodies). *Id.* Because Sanofi's cited art, EX1007 ("Schering-Plough") and EX1401 ("Hart"), does not teach using human antibodies, Sanofi's Ground 1 has neither argued nor demonstrated that the cited art teaches all elements of the '487 patent claims.

Both of Sanofi's obviousness grounds must also fail because they are based on a hindsight-driven view of how a POSA theoretically could have arrived at the claimed invention by "humaniz[ing] [MAb230] to derive a potential therapeutic for allergic diseases." Pet., at 47; *see* Section VI, below. The MAb230 mouse antibody upon which Sanofi relies is a research tool that has never been suggested to have clinical applications. Sanofi has not demonstrated that a POSA would have selected the mouse antibody MAb230 to develop as a therapeutic, particularly given the many different approaches available for developing potential treatments and the wide range of mouse anti-IL-4R antibodies known in the prior art. Accordingly, Sanofi has not demonstrated that a POSA would have had reason to combine the cited references.

The Board should also deny institution of Sanofi's Petition because it fails to demonstrate that a POSA would have had a reasonable expectation of success in combining the cited references to arrive at a therapeutic antibody. *See* Section VII

below. Sanofi's obviousness arguments are premised on a POSA's desire to create a therapeutic agent, and accordingly Sanofi must demonstrate that "a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (quoting *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1070 (Fed. Cir. 2012)). Sanofi's reasonable expectation of success arguments are inapposite because they consider only whether a POSA would have expected "success in isolating" an antibody, and not whether a POSA would have reasonably expected to succeed in making the compound that allegedly motivated the modifications, *i.e.*, a therapeutically effective antibody. Pet., at 46.

Finally, the Board should deny the Petition because instituting IPR of the '487 Patent would deprive Immunex of its right to a jury trial under the Seventh Amendment. *See* Section VIII, below. IPR proceedings are a form of litigation over private property rights, and the Seventh Amendment preserves a Patent Owner's right to have litigation over its private property take place in an Article III Court, not before an administrative agency of the Executive Branch. Adjudicating the validity of the '487 Patent in this forum would violate Immunex's Seventh Amendment rights.

In sum, the Board should deny institution because the information presented in Sanofi's Petition and in this response shows that institution would result in undue inequities and prejudices to Immunex and that there is *not* a reasonable likelihood that the Sanofi would prevail in its challenges to claims 1-17. 35 U.S.C. §314.

II. The Board should deny institution under §314(a) because all *General Plastic* factors are met

The Board should exercise its discretion to deny institution under § 314(a) because Sanofi's Petition is part of an "abuse of the review process by repeated attacks on patents." *General Plastic,* IPR2016-01357, Paper 19, at 16-17 (PTAB, Sept. 6, 2017). In *General Plastic*, which the PTAB has designated a precedential decision, an expanded panel affirmed the previously-used list of seven non-exhaustive "factors that are considered in the exercise of the Board's discretion under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(a)." *Id.* at 4-5, 15-16; *see also*, *NVIDIA Corp. v. Samsung Elec. Co., Ltd.,* IPR2016-00134, Paper 9, at 6–7 (PTAB, May 4, 2016) ("*NVIDIA*")[1]. Those factors are:

[1] The *NVIDIA* decision issued on May 4, 2016—well before Sanofi decided to file its three staggered petitions challenging the same claims of the same patent.

1. whether the same petitioner previously filed a petition directed to the same claims of the same patent;

2. whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it;

3. whether at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition;

4. the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition;

5. whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent;

6. the finite resources of the Board; and

The *General Plastic* decision simply reiterates and reinforces the factors set forth in *NVIDIA*. *See General Plastic*, Paper 19, at 8-10.

> 7. the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than 1 year after the date on which the Director notices institution of review.

General Plastic, Paper 19, at 9-10, 16; *see also*, *NVIDIA*, Paper 9, at 6–7.

As described below, each and every *General Plastic* factor weighs against institution of this Petition.

A. Factor 1 supports denial of institution because Sanofi has filed two other petitions directed to the same claims Sanofi challenges here

Before filing this petition, Sanofi had already "previously filed a petition directed to the same claims of the same patent." *General Plastic*, Paper 19, at 16. The Petition in this case is Sanofi's third challenging claims 1-17 of the '487 patent.[2] In *General Plastic*, the Board "noted that the same claims of the same

[2] Sanofi challenged claims 1-17 of the '487 patent in its first petition (IPR2017-01129; "the first IPR"), filed on March 23, 2017. Sanofi challenged claims 1-14 and 16-17 of the '487 patent in its second petition (IPR2017-01879; "the second IPR"), filed on July 28, 2017. Accordingly, Sanofi's petition in this case challenging claims 1-17 is its third petition challenging claims 1-14 and 16-17 of the '487 patent, and its second challenging claim 15 of the '487 patent.

patent were at issue in the follow-on petitions as in the first-filed petitions, where institutions were denied." *General Plastic*, Paper 19, at 10. The same applies here. As the Board explained in *Nautilus Hyosung, Inc. v. Diebold, Inc*., the petitioner already "*had an opportunity to be heard* with regard to the patentability of the claims challenged in the [follow-on] Petition" when it filed the first petition. *Nautilus Hyosung, Inc. v. Diebold, Inc*., IPR2017-00426, Paper 17, at 12 (PTAB, June 22, 2017) (emphasis added). This "weighs toward [the Board] exercising [its] discretion not to institute." *Id.*

The fact that Sanofi's first petition was denied is of no moment here. Sanofi had its opportunity to be heard when it challenged the same claims of the same patent in its first petition; the Board's denial of institution in IPR2017-01129 makes *General Plastic* no less applicable here. Indeed, in both *General Plastic* and *NVIDIA*, the Board previously denied institution on the petitioners' first petitions before exercising its discretion to deny the subsequent petitions. *General Plastic*, Paper 19, at 2-3; *NVIDIA*, Paper 9, at 2.

B. Factor 2 supports denial of institution because Sanofi knew or should have known of the art asserted in the third petition when it filed its first and second petitions

The Board has stated that, "[o]ut of concern for fundamental fairness, in

determining whether to deny institution on subsequent petitions challenging the same claims of the same patent, we look to whether a petitioner knew or should have known of the prior art asserted in its later case when it filed the earlier one." *Apple, Inc. v. Immersion Corp*., IPR2017-00887, Paper 7, at 6-7 (PTAB, Aug. 25, 2017); *see also*, *General Plastic*, Paper 19, at 10.

Here, Sanofi[3] had long known or should have known of all three references asserted in its obviousness grounds. Sanofi had used EX1007 ("Hart") and EX1401 ("Schering-Plough") as part of previous challenges to the '487 patent and a related European patent. And given that Sanofi asserts EX1402 ("Hoogenboom") issued on October 15, 1996, it should have been aware of Hoogenboom as a readily available patent publication that could have been identified with a diligent search. *General Plastic*, Paper 19, at 20 (stating that when considering what a party should have known, "[t]he relevant issue under factor 2 is . . . whether the prior art

[3] For convenience, Immunex refers to all three petitioners collectively as "Sanofi," and discussion of "knowledge" in this context refers to the collective knowledge of all three entities. For discussion of a single petitioner's knowledge or activity, Immunex refers to the full name of that entity.

references relied on in the follow-on petitions . . . could have been found with reasonable diligence").

Sanofi (*i.e.*, co-petitioner Sanofi-Aventis U.S. LLC) knew of Hart and relied upon it in its July 4, 2016 opposition to Immunex's related European patent, EP2292665. IMX2120, §§3.1, 3.2.3. Sanofi was therefore undeniably aware of Hart, which is cited in both grounds of its Petition, more than twelve months before the current Petition was filed and at least eight months before the first petition was filed. And beyond simply being aware of Hart, Sanofi even cited Hart in a challenge to Immunex's anti-IL4R antibody patent family well before filing its first petition. *Id.*

Sanofi was also aware of Schering-Plough, the other reference cited in both grounds, at least nine months before it filed its first petition. Co-petitioner Regeneron Pharmaceuticals, Inc. relied upon Schering-Plough in its own opposition to Immunex's EP2292665, filed June 4, 2016. IMX2121, §7, Annex A §1.1. Additionally, Sanofi cannot deny prior knowledge of Schering-Plough because it cited it as EX1007 in its first petition filed on March 23, 2017. IPR2017-01129, Paper 1, at iv, 13-14.

Finally, Sanofi should have been aware of Hoogenboom before it filed its

first petition. While Sanofi's first petition did not cite to Hoogenboom, the record here, as in *General Plastic*, "is devoid of any explanation why Petitioner could not have found the newly asserted prior art in any earlier search(es) through the exercise of reasonable diligence." *General Plastic*, Paper 19, at 20. And because Hoogenboom is an issued U.S. patent, it would have been indexed and accessible using any number of search tools.

No other references were cited as part of Sanofi's grounds. Therefore, "because Petitioner knew or should have known of the primary references[, indeed, *all* references] it uses to support its challenges, and provided no explanation of why it could not have raised the other reference in the First Petition, this factor weighs against institution." *Apple, Inc. v. Immersion Corp.*, IPR2017-00887, Paper 7, at 6-7 (PTAB, Aug. 25, 2017); *General Plastic*, Paper 19, at 16.

C. Factor 3 supports denial of institution because Sanofi had already received Immunex's Preliminary Response in IPR2017-01129 when it filed the present Petition and used it to reshape its arguments

Whether the petitioner has received the Patent Owner's Preliminary Response at the time of filing a later petition is a factor that the Board considers because of the risk that a petitioner will "benefit from receiving and having the opportunity to study Patent Owner's Preliminary Response." *General Plastic*,

Paper 19, at 16-17. Here, the risk of such gamesmanship is not merely theoretical. Immunex filed its Patent Owner Preliminary Response in IPR2017-01129 on July 6, 2017. Over three weeks later, on July 31, 2017, Sanofi filed the present Petition. Thus, Sanofi had the benefit of Immunex's Patent Owner Preliminary Response in IPR2017-01129 when it filed the present Petition. Moreover, Sanofi blatantly attempts to rebut arguments raised in Immunex's preliminary response in the first IPR—a practice the Board unequivocally admonished in *General Plastic*. *See* IPR2016-01357, Paper 19, at 16-17; *NVIDIA*, Paper 9, at 7–8.

For example, in its first petition, Sanofi offered no construction of the term "antibody," a fact that Immunex brought to the Board's attention in the Patent Owner Preliminary Response for IPR2017-01129. *See* IPR2017-01129, Paper 1, at 24-25; Paper 14, at 15-22. Attempting to correct the glaring deficiencies in its first petition, Sanofi's third petition now conveniently construes the term "antibody." Pet., at 21-22. Sanofi has clearly "modified its challenges in the follow-on petitions in an attempt to cure the deficiencies" that Immunex identified in its Patent Owner Preliminary Response in IPR2017-01129. *General Plastic*, Paper 19, at 11.

Moreover, Sanofi impermissibly uses this third Petition as a *de facto* reply brief on this issue by providing two pages of *rebuttal arguments* to Immunex's

Patent Owner Preliminary Response to the first petition. *See* Pet., at 21-22, n.6. In the present Petition, Sanofi explicitly refers to Immunex's Patent Owner Preliminary Response from IPR2017-01129 and alleges that "Patent Owner incorrectly argue[d]" certain points in the first preliminary response. *Id.* This rebuttal argument is highly improper and prejudicial to Immunex because Sanofi has adjusted its arguments and attempted to address flaws in its first petition after reviewing Immunex's positions. This is also prejudicial to Immunex because Sanofi is essentially filing a Reply to Immunex's Patent Owner Preliminary Response in IPR2017-01129—a request that was flatly denied by the Board in its email of July 25, 2017. *See* IMX2005. Sanofi's having "the opportunity to read Patent Owner's Preliminary Response [to a petition filed by the same petitioner against the same patent], prior to filing the Petition here, is unjust." *Toyota Motor Corp. v. Cellport Systems, Inc.*, IPR2015-01423, Paper 7, at 8 (Oct. 28, 2015).

Accordingly, the third *General Plastic* factor weighs heavily against institution because "at the time of filing of the [third] petition the petitioner already received patent owner's preliminary response to the first petition" and used that response to craft its later petition. *General Plastic*, Paper 19, at 16-17.

D. Factor 4 supports denial of institution because Sanofi was aware of the primary references asserted in this Petition for more than a year before filing

Sanofi was aware of the primary references asserted in this Petition for more than a year before filing the Petition in this case, and at least eight months before filing its first petition. Sanofi has cited Schering-Plough in both of its previous IPR petitions. IPR2017-01129, Paper 1, at iv and 13-14; IPR2017-01879, Paper 1, at iv and 15-16. And, more generally, Sanofi has been using both Hart and Schering-Plough as part of challenges to the patentability of related patents during that same period as part of its strategy of launching multiple attacks against the '487 patent family. IMX2120, §§3.1, 3.2.3; IMX2121, §7, Annexe A §1.1; IPR2017-01129, Paper 1, at iv and 13-14; IPR2017-01879, Paper 1, at iv and 15-16.

The Board has considered knowledge of a publication "about one month prior to filing of the petition" to be a factor in why "it would be unjust to Patent Owner to institute" a follow-on petition. *NVIDIA*, Paper 9, at 11; *see also*, *Alarm.com Inc. v. Vivint, Inc.*, IPR2016-01091, Paper 11, at 9-10 (PTAB Nov. 23, 2016). In this case, more than one year passed between Sanofi's first presentation of its references and the filing of the current Petition. Accordingly, the fourth *General Plastic* factor weighs against institution because of "the length of time that

elapsed between the time petitioner learned of the prior art asserted in the [current] petition and filing of the [current] petition." *General Plastic*, Paper 19, at 16.

E. Factor 5 supports denial of institution because Sanofi does not provide an adequate explanation for the time elapsed between filing its petitions

As part of "tak[ing] undue inequities and prejudices to Patent Owner into account," the *General Plastic* notes that the Board will "assess and weigh whether a petitioner should have or could have raised the new challenges earlier." *General Plastic*, Paper 19, at 17-18. The only explanation Sanofi offers with regard to its serial filings is the allegation that it "could not have filed this Petition sooner, because the testing of the prior art 230 antibody disclosed in Hart [for competition with the 12B5 reference antibody] was only recently completed on July 19, 2017." Pet., at 7-8. Sanofi offers no evidence to support this bald assertion. Further, this concocted rationale fails because it does not explain why it was necessary to file multiple petitions on multiple dates; rather, the timing of the IPR petition filings is only a reflection of Sanofi's tactical decisions. Sanofi could have performed testing at an earlier date, or Sanofi could have waited until testing was completed to file its earlier IPR petition(s)—but instead Sanofi chose to file serial petitions and Immunex should not bear the burden of that decision.

Sanofi's alleged rationale fails to explain the delay because Sanofi provides no reason why the testing to detect competition between MAb230 and 12B5 (*i.e.*, the '487 patent's reference antibody) could not have been performed earlier. To the contrary, Sanofi could have performed testing on MAb230 whenever it desired. MAb230 is a commercial product that has been available for approximately 20 years, and thus would have been available to test whenever Sanofi desired. *See, e.g.*, EX1206, 0017-0018 (disclosing the commercial availability of MAb230 as part of "the 1996 catalog"); IMX2116, 450-451 (disclosing having obtained and used MAb230 in a study submitted for publication in Dec. 1996). And Petitioner Regeneron Pharmaceuticals, Inc. has been performing competition assays with the 12B5 antibody for at least 10 years. For example, US 2008/0160035 to Stevens *et al.* (EX1006;"Stevens"), which was filed in October, 2007 and assigned to Regeneron Pharmaceuticals, Inc., disclosed testing a range of antibodies for competition with 12B5. EX1006, ¶¶[0065]-[0066]. Accordingly, the decision of when to begin and complete testing was entirely under Sanofi's control, and does not provide an adequate explanation for Sanofi's filing serial petitions. The Board should "hold [Sanofi] accountable for its own actions and inactions." *NVIDIA*, Paper 9, at 12.

Even if it were not possible for Sanofi to have completed testing before July 19, 2017 (though Sanofi has provided no evidence to support that assertion), that still would not justify Sanofi's serial petitions because the staggered filings are a result of Sanofi's tactical decision to make repeated attacks on Immunex's patent. Sanofi "does not explain why Petitioner could not have filed the petitions at the same time" or as a single petition. *Apple Inc. v Immersion Corp.*, IPR2017-01368, Paper 8, at 13-14 (PTAB Nov. 7, 2017). Sanofi was under no obligation to file its first petition. Sanofi's petitions were not filed in view of an imminent statutory bar. And the related district court litigation relating to the '487 patent began on March 20, 2017, when Sanofi filed a complaint for declaratory judgment. IMX2001. Just as the Board has previously stated, Immunex should not "be made to share a burden created exclusively by Petitioner's tactical decisions." *Hamilton Beach Brands, Inc. v. F'Real Foods, LLC,* IPR2017-00765, Paper 7, at 11 (PTAB July 31, 2017); *see also, General Plastic,* Paper 19, at 10-11.

Accordingly, the fifth *General Plastic* factor weighs against institution. *General Plastic*, Paper 19, at 16.

F. Factor 6 supports denial of institution because Sanofi's Petition would strain the finite resources of the Board

Another *General Plastic* factor is whether consideration of the petition will strain "the finite resources of the Board." *General Plastic*, Paper 19, at 16. This factor recognizes that "[t]he Board's resources would be more fairly expended on initial petitions, rather than on follow-on petitions, such as the Petition in this case. This is especially apparent when, as here, we are confronted with the third challenge to a patent . . . ." *Alarm.com Inc. v. Vivint, Inc.*, IPR2016-01091, Paper 11, at 13-14 (PTAB, Nov. 23, 2016). Rather than selecting and presenting their strongest arguments at one time, Sanofi has filed three petitions, so far, at different times over a four-month period, adding unnecessary strain to the Board's resources. As the Board has previously stated, it is more efficient to address a matter once:

> "No case, rule, or procedure compels the Board to expend judicial resources on consecutive unpatentability challenges by the same entity/ies, against the same claims of the same patent. Indeed, it is more efficient for the parties and the Board to address a matter once rather than twice."

Aruba Networks, Inc. v. Mobile Telecomm. Tech., IPR2017-00637, Paper 27, at 12-13 (PTAB, July 27, 2017) (internal quotations omitted); *see also, Samsung Elec.*

Co. v. Rembrandt Wireless Techs., LP, IPR2015-00114, Paper 14, at 7 (PTAB Jan. 28, 2015) ("[i]n this proceeding, however, we are not apprised of a reason that merits a second chance. Petitioner simply presents arguments now that it could have made in IPR '518, had it merely chosen to do so").

Sanofi had its opportunity to be heard in IPR2017-01129 and should not be afforded a second—or third—bite at the apple. "Permitting second chances in cases like this one ties up the Board's limited resources; [the Board] must be mindful not only of this proceeding, but of 'every proceeding'" *Samsung*, Paper 14, at 7. Accordingly, this factor also weighs against institution.

G. Factor 7 supports denial of institution because overlapping issues between three petitions would have complicated obtaining a final written determination less than one year from institution

Sanofi's three IPR petitions all relate to the same claims of the same patent, and issues such as claim construction are shared between the three petitions. At the time Sanofi filed the present Petition, Sanofi's tactics would have increased the burden on the Board to manage three staggered IPR proceedings, including three sets of briefing, and potentially three oral hearings—all for the same Petitioner challenging the same claims of the same patent. This would frustrate the Board's efforts to reach a Final Written Decision within one year from institution. Although

the Board recently denied institution in IPR2017-01129, Sanofi should not get a pass on *General Plastic* Factor 7. The premature filing of a deficient Petition should not buy Sanofi additional time to file others. The Board should still consider and weigh Sanofi's tactical decision to file three serial petitions because at the time Sanofi filed the present Petition, no decision on institution had been reached in IPR2017-01129. Accordingly, even in light of the Board's decision not to institute IPR2017-01129, the seventh *General Plastic* factor weighs against institution in this case. *General Plastic,* Paper 19, at 16.

* * * *

Even before *General Plastic*, Board panels have noted that "[t]hese factors guide [the Board's] decision to exercise discretion, but all factors need not be present, and [the Board] need not give equal weight to each factor in reaching our decision." *Alarm.com Inc. v. Vivint, Inc.*, IPR2016-01091, Paper 11, at 7 (PTAB Nov. 23, 2016); *Apple, Inc. v. Immersion Corp*., IPR2017-00887, Paper 7, at 6 (PTAB Aug. 25, 2017). Here, *all* of the above factors weigh against institution, and the weight of the combined factors justifies denying institution.

The Board has previously denied institution of follow-on petitions under circumstances highly similar to those present here. For example, in *NVIDIA*, the

Board denied institution when the petitioner filed a second petition (1) that was filed "approximately two months after Patent Owner filed its preliminary response," (2) that challenged the same claims using art that the "Petitioner identified and produced" in related litigation before the first petition was filed, and (3) that was delayed "with no apparent justification." *NVIDIA,* Paper 9, at 9-12. The *NVIDIA* Panel held that "it would be unjust to Patent Owner to institute review in this proceeding" and that "we hold Petitioner accountable for its own actions and inactions." *Id.* at 11.

Another example is *Nautilus Hyosung Inc. v Diebold, Inc.*, IPR2017-00426, in which the Board denied institution of a second petition directed to the same claims of the same patent when (1) "Petitioner has not explained why the arguments and evidence relied on in its Second Petition were not filed with the First Petition," (2) "Patent Owner provides persuasive evidence that Petitioner was aware of at least [two cited references] when Petitioner filed its First Petition," (3) "Petitioner had sufficient time to take advantage of Patent Owner's and the Board's responses to the First Petition," and (4) "Petitioner's explanation as to why it should be permitted another challenge to the same claims of the same patent under the circumstances of this case is conclusory and inaccurate," *Nautilus,* Paper 17, at

12-16.

The present case presents the epitome of what the *General Plastic* factors and §314 discretionary analysis are intended to prevent. Just as the Board's expanded panel concluded in its precedential *General Plastic* decision, the factors in the present case "strongly favor[] non-institution," and the Board should "exercise[] discretion and den[y] institution under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(a)." *General Plastic,* Paper 19, at 11. Doing otherwise would unduly burden the Board, greatly prejudice Immunex, and be contrary to the interests of justice. It would also endorse such tactics and encourage future petitioners to adopt them.

III. The Board should deny institution under §325(d) because substantially the same obviousness arguments were presented during prosecution

Sanofi's Petition alleges that the '487 patent claims are obvious in view of Hart's disclosure of the murine MAb230 antibody in combination with references disclosing methods of preparing human or humanized murine antibodies (*i.e.*, Hoogenboom and Schering-Plough, respectively). The Board should deny institution under 35 U.S.C. §325(d) because the Office already decided that the claims are patentable in view of combinations of art relating to mouse anti-IL-4R

antibodies with art disclosing methods of preparing human antibodies.

Section 325(d) gives the Board discretion to deny institution when the same or substantially the same arguments were previously presented to the Office. 35 U.S.C. §325(d); *see also R.J. Reynolds Vapor Co. v. Fontem Holdings 1 B.V.*, IPR2017-01118, Paper 8, at 4-5 (PTAB, Oct. 4, 2017) (holding that "the use of the word 'or' in 'prior art or arguments' indicates that the presence of previously presented prior art *or* arguments is sufficient to invoke Section 325(d)"); *Conopco, Inc. v. The Proctor & Gamble Co.*, Case IPR2014-00628, Paper 21, at 7–9 (PTAB, Oct. 20, 2014) (denying institution of grounds that "rel[ied] upon different prior art references . . . [but made] 'substantially the same' argument regarding anticipation"); *Toyota Motor Co. v. Adaptive Headlamp Techs., Inc.*, IPR2016-01740, Paper 7, at 9 (PTAB, March 10, 2017) (denying institution because, "even though [the ground in question] relies on a different primary reference, it still presents 'substantially the same . . . arguments [that] previously were presented to the Office'"). Indeed, the PTAB recently designated a trio of §325(d)-based decisions as "informative," further highlighting the importance of preventing petitioners from recycling prior arguments already considered by the Office during prosecution. *See Cultec, Inc. v. Stormtech LLC*, IPR2017-00777, Paper 7 (PTAB,

Aug. 22, 2017) (informative); *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739, Paper 16 (PTAB, July 27, 2017) (informative); *Unified Patents Inc. v. Berman*, IPR2016-01571, Paper 10 (PTAB, Dec. 14, 2016) (informative).

During prosecution, the Examiner considered arguments that were substantially the same as those in this IPR petition, particularly arguments relating to preparing human versions of murine antibodies. For example, the Examiner argued that it would have been obvious to "to modify/improve the [murine anti-IL-4R] antibodies of Mosley et al, by making fully human antibodies that bind to the extracellular domain of IL-4 receptor, because Jakobovits teaches a method of producing fully human antibodies with reduced immunogenicity." EX1002, 0047-0048 (discussing IMX2122 and IMX2123). Similarly, the Examiner argued that it would have been obvious "to modify/improve the antibodies of Tony et al, by making fully human antibodies that bind to the extracellular domain of IL-4 receptor, because Jakobovits teaches a method of producing fully human antibodies with reduced immunogenicity." EX1002, 0047-0048 (discussing EX1019 and IMX2123). Just as the Examiner asserted that Mosley (IMX2122) and Tony (EX1019) disclose murine anti-IL-4R antibodies, Sanofi asserts that Hart discloses a murine anti-IL-4R antibody. And just as the Examiner asserted that

Jakobovits (IMX2123) discloses methods of preparing human antibodies, Sanofi asserts that Schering-Plough and Hoogenboom disclose methods of producing a humanized and human antibodies, respectively. *Id.* A comparison of the asserted art from prosecution and the art from Sanofi's Petition are summarized in the table below:

	Examiner Arguments:	**Petition Arguments:**
Murine anti-IL-4R antibodies	"Mosley et al teach an isolated [murine] antibody that binds to the extracellular domain of human IL-4 receptor . . . . However, the Mosley et al reference does not teach human antibodies . . . ." EX1002, 0046-0047 (citing IMX2122) ***OR*** "The [murine] antibody of Tony et al binds to IL-4 receptor alpha and inhibits IL-4 or IL-13 activities with high affinity . . . . However, the Tony et al reference does not teach human antibodies that bind to the extracellular domain of human IL-4 receptor.." EX1002, 0049-0050 (citing EX1019)	"Hart (Ex. 1204), teaches MAb230---a prior art murine (mouse) antibody that potently blocks IL-4 and IL-13 activity . . . . Hart thus teaches an isolated antibody that is *murine,* rather than human . . . ." Pet., at 2 (citing EX1024)

Methods of producing antibodies	"Jakobovits discloses an efficient and reliable method of producing fully human antibodies." EX1002, 0047 (citing IMX2123)	"Hoogenboom (Ex. 1402), teaches epitope imprinted selection ("EIS"), which is a method for transforming a murine antibody into a *fully human* antibody." Pet., at 3 (emphasis original).

In combining Hart and Hoogenboom, all that Sanofi has done is make the same argument again using a different murine anti-IL-4R antibody and a different publication disclosing a method of preparing human antibodies. Sanofi also argues that the claims would have been obvious in view of Schering-Plough's method of generating humanized antibodies. As discussed in Section V below, a proper construction of the term "human" does not include humanized antibodies. If the claims did cover humanized antibodies, Sanofi's arguments would still be substantially the same as those presented during prosecution because they follow the same pattern of modifying a prior art murine antibody. Accordingly, Sanofi's obviousness arguments are substantially the same as the arguments presented during prosecution.

Further evidence that Sanofi's arguments are substantially the same as the arguments from prosecution is provided by the fact that the Examiner was aware of

the Schering-Plough reference and of R&D's MAb230 murine antibody during prosecution. Schering-Plough (*i.e.*, EP0604693) was disclosed during prosecution and listed on the face of the '487 patent. And the '487 patent specification notes that "[a]n anti-huIL-4R murine mAb (R&D Systems)" was available prior to filing. EX1001, 41:2-5; *see also,* EX1001, References Cited (listing R&D's 2008 MAb230 product data sheet). The Examiner saw no reason that references disclosing murine anti-IL-4R antibodies such as MAb230, in combination with references disclosing methods of modifying antibodies, negated the patentability of the '487 patent's claims. The Board need not use its limited resources to reconsider the issue.

Sanofi attempts to rely on data and testimony from Dr. Zurawski alleging competition between the mouse antibody MAb230 and 12B5, the human reference antibody in the '487 patent claims. Pet., at 31-35. But Sanofi's presentation of data relating to the MAb230 mouse antibody does not change the fact that Sanofi's arguments are substantially the same as the obviousness arguments presented during prosecution. Such data would not have been known to a person of ordinary skill in the art, do not alter the teachings of the art, would not have provided any reason to combine the references, and would not have provided any reasonable

expectation of success.

Because Sanofi asks the Board to consider the same or substantially the same issue that was already decided by the Office, the Board should "decline to revisit the Office's Decision" and exercise its discretion to deny institution under Section 325(d). *Huawei Tech. Co., Ltd. v. Pabst Licensing GmbH & Co. KG,* IPR2017-00449, Paper 7, at 9 (PTAB, June 12, 2017). Instituting IPR would waste the Board's valuable time and resources in revisiting the question of the alleged obviousness over art relied upon for disclosing an anti-IL-4R antibody and art relied upon for disclosing techniques to generate human antibodies. *Panacea Biotec, Ltd. v. Daiichi Sankyo Co. Ltd.,* IPR2015-01496, Paper 11, at 6 (PTAB, Jan. 7, 2016) (finding that the Board's "judicial resources are best spent elsewhere").

IV. The Board should deny institution because Sanofi has not construed the claims as required by 37 C.F.R. §42.104(b)(3)

Sanofi's Petition should be denied because Sanofi fails to explain how the challenged claims are to be construed, as required by 37 C.F.R. §42.104(b)(3).[4] In

[4] While Immunex has provided a construction of only a subset of claim terms here, construction of other terms is not needed to resolve the issues in this

particular, the Board should deny institution because Sanofi has taken inconsistent claim construction positions in the present proceeding and in district court, and has failed to adequately explain its inconsistent claim constructions despite having notice from Immunex's Preliminary Response in IPR2017-01129.

A. Sanofi again failed to inform the Board of its §112, ¶6 claim construction in district court and failed to reconcile its inconsistent constructions of "antibody."

The Board should deny institution because Sanofi failed to adequately explain its inconsistent claim constructions in district court litigation and the present proceeding. As with the petition in IPR2017-01129, Sanofi's omission of its district court construction in the Petition is troubling. In this proceeding, Sanofi argues that the term "antibody" should be broadly construed to encompass "whole antibodies and antigen binding fragments thereof," and "full-length antibodies of any isotype, antibody fragments, fusion proteins, and/or single chain antibodies."

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proceeding. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (holding that "claim terms need only be construed 'to the extent necessary to resolve he controversy'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Pet., at 21-22. In concurrent district court litigation concerning the '487 Patent, Sanofi has represented, and continues to represent, to the U.S. District Court for the District of Massachusetts *and* to the U.S. District Court for the Central District of California[5] that the term "antibody" recited in the *same claims* of the *same patent* "must be construed in accordance with 35 U.S.C. § 112 ¶6." IMX2001, ¶¶30-31; IMX2002, ¶¶66-67; IMX2003, ¶¶66-67; IMX2004, at 1. Sanofi's district court position is that, "[p]roperly construed, none of the claims of the '487 Patent cover matter beyond the structures specifically disclosed in the specification, *i.e.*, the sequences of mAbs 6-2, 12B5, 27A1, 5A1, 63, or 1B7, the only structures conceivably capable of performing the 'compet[ing]' function, or their equivalents."[6] IMX2001, ¶¶30-31; *see also*, IMX2002, ¶¶66-67; IMX2003, ¶¶66-67; IMX2004, at 1. Sanofi's first petition, in IPR2017-01129, offered no specific

[5] Sanofi has now quadrupled down on its §112, ¶6 argument in federal court, pushing its §112, ¶6 construction in at least four district court filings. *See* IMX1001, ¶¶30-31; IMX2002, ¶¶66-67; IMX2003, ¶¶66-67; IMX2004, at 1.

[6] Immunex does not concede that any of Sanofi's conflicting statements regarding the scope of the claim term "antibody" are correct.

construction of the term "antibody," with *no mention* of its ongoing narrow and inconsistent construction of the same term in district court. The present Petition now conveniently offers a construction of "antibody," yet *still fails to inform the Board* of its inconsistent claim construction position in district court. The Petition never even mentions 'means-plus-function' or §112, ¶6.

The Board recently denied institution in *Facebook, Inc. v Sound View Innovations, LLC* ("*Facebook*"), based on the petitioner's seemingly inconsistent positions before the district court and the PTAB. *Facebook*, IPR2017-00998, Paper 13 (PTAB, Sept. 5, 2017). Just as here, the *Facebook* petitioner argued for a means-plus-function construction in district court, stated that no term needed construction in the IPR proceeding, and failed to inform the Board of its inconsistent claim construction position in district court. *Id.* at 8, 14-18. The *Facebook* Panel admonished the petitioner for failing to inform the Board of the inconsistent construction made in district court, and for its failure to explain its reasoning for not offering the same construction in the IPR:

> Clearly, based on its arguments to the district court, Petitioner believes that claim 19 "contains a means-plus-function … limitation." … Nevertheless, Petitioner chose not to provide us with the required construction….

> *Perhaps even more troubling, Petitioner chose not to inform us in its Petitions that it simultaneously was arguing a different treatment of the terms of claim 19 before the district court … nor did it explain the reason for Petitioner's change of heart regarding the presence of means-plus-function terms in claim 19*…. At the very least, Petitioner's failure to inform us of its differing claim construction arguments before the district court raises the specter of lack of candor.

Id. at 16-18 (emphasis added). Here, just as in *Facebook*, the Board should consider Sanofi's "failure to inform [the Board] of [Sanofi's] seemingly inconsistent claim construction positions or to provide [the Board] with means-plus-function constructions as required by [the] Rules" more than sufficient grounds for denial. *Id.* at 18.

Though district courts apply the *Phillips* standard and the PTO applies the BRI, the differences between these standards cannot be used to selectively invoke §112 ¶6 at Sanofi's will. As the Board acknowledged in its denial of Sanofi's first petition in IPR2017-01129, "[t]hat the broadest reasonable interpretation applies to construing claims in *inter partes* review proceedings does not justify taking a different position with respect to §112 ¶ 6 before the district court." IPR2017-

01129, Paper 19, at 12. Indeed, "[§ 112] paragraph six applies regardless of the context in which the interpretation of means-plus-function language arises, i.e., whether as part of a patentability determination in the PTO or as part of a validity or infringement determination in a court." *IPCOM GMbH & Co. v. HTC Corp.,* 861 F.3d 1362, 1369 (Fed. Cir. 2017) (citing *In re Donaldson Co., Inc*., 16 F.3d 1189, 1193 (Fed. Cir. 1994) (en banc)); *see also, Euro-Pro Operating LLC v. Acorne Enterprises, LLC*, IPR2014-00351, Paper 19, at 6-7 (July 10, 2014); *Facebook,* Paper 13, at 14-18. Thus, Sanofi's markedly different stance on construction of the term "antibody" in this proceeding cannot be excused simply because the BRI applies here.

In *Facebook,* the Board found "troubling" the petitioner's failure to inform the Board that it was arguing §112 ¶ 6 applies to the challenged claim in district court. *Facebook*, Paper 13, at 17-18. In IPR2017-01129, the Board similarly wrote that "[w]e are troubled by [Sanofi's] failure to inform us of its contention before the district court that the claims should be construed under 35 U.S.C. §112 ¶6." IPR2017-01129, Paper 19, at 12. Sanofi's present Petition suffers from the same deficiencies as those in *Facebook* and IPR2017-01129 because it *still* fails to inform the Board of its § 112 ¶ 6 contentions in district court. Accordingly, the

present Panel should use its discretion under §314(a) to deny institution, just as the Board did in *Facebook* and IPR2017-01129.

B. Sanofi has presented incompatible positions on claim definiteness in its Petition and in district court

In this proceeding, Sanofi "request[ed] that the claim terms be given their broadest reasonable interpretation," and stated that only the terms "human" and "antibody" "may need to be defined or further clarified." Pet., at 19-20. In contrast, Sanofi has repeatedly and consistently asserted in district court that "[o]ne or more of the claims of the '487 Patent are invalid as indefinite under 35 U.S.C. § 112 ¶ 2 for failing to particularly point out and distinctly claim the subject matter of the alleged invention claimed therein." IMX2002, 13; IMX1432. Sanofi is, in effect, requesting that the Board construe one or more claims that Sanofi is arguing to be indefinite, again creating ambiguity regarding Sanofi's position on claim construction. By failing to reconcile its inconsistent positions on claim construction, Sanofi improperly "shifts the burden of advancing a claim construction from the petitioner to the Board." *Palo Alto Networks v. Finjan, Inc.*, IPR2015-02000, Paper 9, at 4 (PTAB, May 20, 2016). This defect is fatal to Sanofi's Petition, and the Board should deny the Petition on this basis.

Sanofi's Petition does not disclose Sanofi's district court indefiniteness arguments—even though Sanofi had already asserted indefiniteness in district court before filing the present Petition. IMX2002, 13. Sanofi only belatedly informed the Board of its indefiniteness contentions by requesting to enter an exhibit, just three weeks prior to the due date for Immunex's preliminary response. IMX2002, 13; IMX2100; EX1432. Such belated disclosure is inadequate to address Sanofi's claim construction failures—Sanofi has not offered any way of reconciling its two positions despite concurrently arguing for both.

Immunex does not agree with Sanofi's district court contentions regarding the alleged indefiniteness of the claims, and is not addressing the merits of these arguments here because there were no such arguments presented in the Petition and because doing so is not necessary to resolve this proceeding. Nevertheless, it is significant that Sanofi has again created ambiguity regarding its position on claim construction because, as the PTAB has recognized, a patent may not, like a "nose of wax," be twisted "as it suits [the parties'] infringement and invalidity cases." *Google, Inc. v. Koninklijke Philips N.V.*, IPR2017-00411, Paper 11, at 13 (PTAB, May 24, 2017) (citing *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1351 (Fed. Cir. 2001)). Furthermore, though district courts apply the *Phillips*

standard and the PTAB applies the broadest reasonable interpretation, the differences between the standards cannot be used to argue that claims are definite under one standard but not the other. *See e.g., Ex Parte McAward*, Appeal No. 2015-006416 (PTAB, Aug. 25, 2017). It is illogical for Sanofi to assert that the ’487 Patent claims comply with the BRI standard of indefiniteness but not the *Phillips* standard, and Sanofi has not explained how one or more claims are somehow indefinite under the *Phillips* standard but not the BRI. Thus, Sanofi's different position in this proceeding on the definiteness of the claims cannot be brushed aside simply because the BRI applies here.

V. The Board should deny Ground 1 because it relies on an unreasonably broad construction of a "*human* antibody”

Sanofi's Ground 1 asserts that it would have been obvious to generate a *humanized* antibody based on MAb230. But the '487 patent claims are directed to "*human* antibodies." EX1001, Claim 1. And, under the broadest reasonable interpretation standard, a person of ordinary skill in the art would not have considered it reasonable to construe "human antibody" so broadly as to include murine antibodies modified to be more similar to human antibodies (*i.e.*, humanized antibodies). As discussed below, humanized antibodies are a separate

and distinct category of antibodies from human antibodies. Accordingly, Sanofi's arguments in Ground 1 are flawed because Sanofi has neither argued nor demonstrated that the cited art in Ground 1 taught "human antibodies."

A. Person of Ordinary Skill in the Art

"Under the broadest reasonable construction standard, claim terms are generally given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure." *Homeland Housewares, LLC v. Huiyang Allan Plastic & Electric Industries Co., LTD.*, IPR2016-00841, Paper 9, at 8 (PTAB, Oct. 7, 2016) (citing In re Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007)). A person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA in the field of immunology would have had knowledge of the scientific literature and have skills relating to that field, including the design and generation of antibodies before May 1, 2001. IMX2101, ¶14. A POSA would also have had knowledge of laboratory techniques and strategies used in immunology research, and would have known about practical applications of the same, such as research assays, pre-clinical applications, and clinical applications. *Id.* A POSA would

typically have had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, or a related discipline, with at least two years of experience in the field. *Id.* Also, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others on the team, *e.g.*, to solve a given problem. *Id.* For example, a clinician and a molecular biologist may have been part of a team. *Id.*

B. Sanofi's unreasonably broad construction of "human antibody" is inconsistent with the specification and prosecution history

In applying the broadest reasonable interpretation standard, "claims should always be read in light of the specification and teachings in the underlying patent. . . .[and] [t]he PTO should also consult the patent's prosecution history . . . ." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F. 3d 1292, 1298 (Fed. Cir. 2015). "That is not to say, however, that the Board may construe claims during IPR so broadly that its constructions are unreasonable under general claim construction principles." *Id.* Here, Sanofi has presented a construction of "human antibody" that is so broad as to be unreasonable—despite the different meanings of human antibody and humanized antibody, Sanofi has proposed a construction of human that would

encompass both types of antibody and effectively read the term "human" out of the claims.

Claim 1 of the '487 patent, the sole independent claim, claims "[a]n isolated *human* antibody…." EX1001, 77:26. Sanofi asserts that the broadest reasonable interpretation of a "human" antibody is an antibody that is "partially or fully human." Pet., at 20. And Sanofi asserts that this definition should encompass humanized antibodies. Pet., at 3, 21. Contrary to Sanofi's assertions, the specification does not describe "human antibodies" as including "humanized antibodies." As discussed below, the proper construction in view of the specification and prosecution history is that "human antibodies" are antibodies in which the amino acid sequence is consistent with the amino acid sequences of antibodies produced by the human immune system. IMX2101, ¶¶15-19. A POSA would have understood that "humanized antibodies" have sequences that have characteristics that are inconsistent with antibodies produced by the human immune system, and therefore are not "human antibodies." IMX2101, ¶¶20-21.

The '487 patent's specification describes both human and humanized antibodies, and characterizes them as distinct and non-overlapping categories of antibodies. The '487 patent's abstract refers to "human antibodies" that are

"generated by procedures involving immunization of transgenic mice." EX1001, Abstract. The specification provides detail regarding such transgenic methods, which involve using mice in which "[h]uman immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes . . . [and] immunizing [the] transgenic non-human animals with an IL-4R polypeptide." EX1001, 19:38-20:8. These descriptions are consistent with the convention in the field of referring to antibodies by their species of origin. IMX2101, ¶17; EX1402, 13:5-28; IMX2103, 128, 130:Table 1, 140-141. Accordingly, as confirmed by Immunex's expert Dr. Wayne Marasco, who has almost thirty years of antibody design and engineering experience, a POSA would have understood that, in the context of the '487 patent, that a "human antibody" is an antibody that, because it is derived from a human sequence, will have amino acid sequence characteristics that are reflective of its production by the human immune system. IMX2101, ¶¶15-19.

In contrast, the '487 patent specification describes "humanized antibodies" as "versions of murine monoclonal antibodies." EX1001, 19:21-22. Humanized antibodies are antibodies derived from a non-human sequence that has been modified to include some human sequences—thus, humanized antibodies are only partially human antibodies and retain some non-human antibody characteristics.

IMX2101, ¶21; IMX2104, 65. The '487 patent describes the process of humanization as combining "variable region[s] of a murine antibody" with "constant region[s] derived from a human antibody." EX1001, 19:21-37. As noted by Sanofi's expert Dr. Zurawski, a humanized antibody "is based" on a murine antibody, and "the [murine parent] CDRs and other [murine parent] binding-determinant residues are retained in a successfully humanized antibody." EX1400, ¶56. A POSA would have understood, based on this understanding of how humanized antibodies are constructed, that humanized antibodies retain sequences that are consistent with murine antibodies. IMX2101, ¶21.

The different meanings of human and humanized, as outlined above, are consistent with the plain language in the claims of the '487 patent. The claims refer to "human" antibodies, not to "partially human" or "chimeric" antibodies. And the claims also refer to the claimed antibodies binding to and facilitating signaling though "human" IL-4R when the '487 patent's disclosures all relate to signals from the native human protein (*i.e.*, the fully human protein). *See* EX1001, Claims 2-10, Examples 7-9.

The different meanings of human antibody and humanized antibody, as outlined above, are also supported by treatment of the terms during prosecution of

the '487 patent. During prosecution of U.S. Appl. No. 12/291,702 (the parent application from which the '487 patent was a continuation), the application included a dependent claim requiring that the "antibody is a human, partially human, humanized, or chimeric antibody." IMX2105, 139 (Claim 39 in 8-21-09 claim set); IMX2101, ¶21. The delineation of "human" as a distinct category from "humanized" indicates that human antibodies are a distinct category of antibodies that is an alternative to humanized antibodies. The Examiner's recognition of these distinct categories is reflected in the examiner citing art teaching methods of preparing "fully human" antibodies (*i.e.*, Jakobovits, IMX2123); notably, the Examiner did not cite art disclosing the humanization of an antibody. EX1002, 0047-0048. And the distinct and non-overlapping nature of human and humanized antibodies is further seen in the '487 specification's statement that an anti-IL-5 antibody could be "human *or* humanized." EX1001, 31:31-33 (emphasis added).

In contrast, the language Sanofi cites from the '487 patent does not support its position with regard to the construction of "human antibody." Sanofi highlights quotes referring to both "partially human" and "fully human" antibodies being antibodies of the claimed invention. EX1001, 20:57-60, 19:41-44, 21:1-2; Pet., at 20. This language only demonstrates that the specification contemplated antibodies

with varying degrees of human-derived sequence content. The language Sanofi cites does not indicate that the term "human antibody" without any modifier should mean anything other than the plain and ordinary meaning of "human antibody," and they do not indicate that antibodies with sequences derived from mice or other non-humans should be considered to be "human antibodies." Therefore, Sanofi's construction is not supported by the cited disclosure of different antibody types.

The case law Sanofi has cited also does not support its claim construction arguments. Sanofi points to *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295 (Fed. Cir. 2007), and it statement that "[w]hen a patent thus describes the features of the 'present invention' as a whole, this description limits the scope of the invention." *Id.* at 1308; Pet., at 20. The import of this statement is that if an invention as a whole is described as including a particular feature, then the claims to that invention should be construed as being ***limited*** to embodiments that include that feature. Sanofi is improperly trying to do something entirely different—arguing that claim scope should be ***expanded*** to include alternative embodiments because both are described in the specification. But there is no requirement that all embodiments in a specification be claimed. Indeed, "the claims of the patent need not encompass all disclosed embodiments. [The Federal Circuit's] precedent is

replete with examples of subject matter that is included in the specification, but is not claimed." *Tip Systems, LLC v. Phillips & Brooks/Gladwin*, 529 F. 3d 1364, 1373 (Fed. Cir. 2008) (internal citations omitted). Sanofi cites a previous Board panel's guidance that "a general principle of claim construction counsels against interpreting claim terms in a way that excludes embodiments disclosed in the specification." *Nissan N. Am., Inc. v. Norman IP Holdings, LLC*, IPR2014-00564, Paper 36, at 7 (PTAB, Aug. 26, 2015); Pet., at 21. But claiming one category of antibodies (*i.e.*, human) does not "exclude" other categories (*i.e.*, partially human) from also being considered part of the invention. Sanofi improperly conflates "not claiming" embodiments in the '487 patent with "excluding" embodiments of the invention.

C. Under the proper construction of "human antibody," Sanofi's Ground 1 fails because it is directed to generating humanized antibodies

Ground 1 of the Petition fails because it relies on Sanofi's overly broad construction of the term "human antibody," which improperly includes humanized antibodies. Sanofi's premise in Ground 1 is that "it would have been obvious for a POSITA to modify Hart's MAb230 with Schering-Plough's *humanization techniques* to derive a potential therapeutic for allergic diseases." Pet., at 36

(emphasis added). But as discussed above, the claim term "human antibodies" does not include humanized (*i.e.*, partially human) antibodies. Because claim 1, the sole independent claim of the '487 patent, is directed to "human antibodies," no claims of the '487 patent cover humanized antibodies.

Sanofi has neither argued nor demonstrated that the cited art in Ground 1 teaches "human antibodies" as that term is properly construed. Sanofi asserts that Hart "teaches MAb230, a murine anti-hIL-4R blocking antibody." Pet., at 35. Schering-Plough discloses starting with "*non-human* monoclonal antibodies." EX1007, 2:20-23 (emphasis added). And Sanofi admits that Schering-Plough as "teaches techniques for humanizing *murine* anti-hIL-4R blocking antibodies." Pet., at 36 (emphasis added). Because it starts with murine (*i.e.*, non-human antibodies), antibodies generated using Schering-Plough's method will retain CDR's and other sequences characteristic of murine antibodies. IMX2101, ¶21. Neither Hart nor Schering-Plough discloses generating antibodies with fully human character, much less human antibodies that compete with the described reference antibody. Accordingly, even if a POSA would have had a reason to modify MAb230 to make a partially human antibody according to Schering-Plough's method (which they would not, as discussed below), a POSA nonetheless would not have arrived at an

embodiment within the scope of the claims as properly construed.

VI. Sanofi's obviousness arguments in Ground 1 and Ground 2 are based on impermissible hindsight

Sanofi's obviousness arguments in Ground 1 and Ground 2 fail because they rely on impermissible hindsight to arrive at the claimed invention, irrespective of the proper construction. "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007). Sanofi's Petition references IL-4's "role in the development of allergic disorders," and uses that role as a justification for alleging that a POSA would have had a reason to combine the cited art. Pet., at 23, 36, 43. However, Sanofi's Petition and Sanofi's expert Dr. Zurawski ignore the wide range of therapeutic options that were under development for allergic inflammation and allergic disorders, and ignore the large number of other murine anti-IL-4R antibodies known in the art. IMX2101, ¶¶22-35. Instead, Sanofi relies on hindsight to conveniently pick MAb230 out of a sea of options and conclude that it would be used to develop a therapeutic candidate. Sanofi chose MAb230 despite a lack of evidence that anyone has ever considered MAb230 a clinical candidate in the 20 years since it became

commercially available. *Id.* Because Sanofi's Petition picks and chooses disclosures from the art and uses *ex post* reasoning in an attempt to reconstruct the '487 patent claims, the Board should deny institution.

Sanofi's hindsight reconstruction is apparent in its failure to consider the wide range of different therapeutic strategies and targets discussed as potential treatments for allergic disorders in the prior art. IMX2101, ¶¶24-26. For example, neither Sanofi nor Dr. Zurawski discussed any of the "many kinds of drugs" already used for treating allergic disorders that could have served as the starting point for developing new therapeutics. IMX2106, 275-276; IMX2101, ¶25. Similarly, neither Sanofi nor Dr. Zurawski discussed other candidate strategies and therapeutics that were being investigated as new candidates before May 1, 2001. IMX2101, ¶¶25-26. But, as noted by Dr. Marasco (IMX2101, ¶25), a POSA would have been aware of numerous such candidate strategies and therapeutics:

- "Recent advances in the understanding of the inflammatory and immunological mechanisms of allergic diseases [had] illuminated ***many potential therapeutic strategies*** that may prevent or even reverse the abnormalities of allergic inflammation." IMX2110, Abstract (emphasis added).

- "***Many new therapeutic agents*** have been developed either to attenuate the pro-inflammatory processes in asthma or to augment the host anti-inflammatory mechanisms . . . include[ing] heparin and inhibitors of PDEs, tyrosine kinases, and NF-kappaB, as well as antibodies and soluble receptors directed against IgE, IL-4, and IL-5." IMX2107, Abstract (emphasis added).
- "There are ***numerous therapies*** in clinical development that combat the inflammation found in asthma, specifically targeting eosinophils, IgE, adhesion molecules, cytokines (interleukin-4, -5, -13) and chemokines, inflammatory mediators, and cell signaling (kinase inhibitors)." IMX2108, Abstract (emphasis added);
- "The novel ***targets for therapy*** suggested by the current conceptual model for the activation and effector phases ***of the response to allergen are numerous***. They include : cytokine inhibitors (anti-IL-4, IL-5, IL-13 or TNF-α), chemokine inhibitors (anti-CCR3 receptor), cell adhesion blockers (antibodies against or inhibitors of selectins, ICAM-1, VACAM-1, VLA-4), anti-inflammatory cytokines (IL-10, IFN-γ, IL-12, IL-18), transcription factor inhibitors (of NFκB, of NF-AT, of MAP-kinases, of Tyrosine kinases, of STAT-6)." IMX2109, 338 (emphasis altered)

Even if a POSA were to consider targeting IL-4R signaling as a therapeutic strategy (though Sanofi has not demonstrated that one would), Sanofi's hindsight-driven analysis is further apparent in Sanofi's failure to indicate why a POSA would have chosen to develop an anti-IL-4R antibody as a method of targeting IL-4R. IMX2101, ¶¶27-31. A POSA would have been aware of a range of different strategies to modulate the effects of IL-4R signaling including using soluble IL-4R protein, using soluble IL-13 protein, antibodies that bind IL-4, antibodies that bind IL-13, IL-4 muteins that bind to IL-4R but do not induce a biological response, IL-13 muteins, molecules that inhibit IL-4-induced signal transduction, and targeting downstream aspects of IL-4 signaling (*e.g.*, the control of transcription factors of the IL-4 gene such as STAT-6). EX1011, 409-410; EX1429, 2:12-15; IMX2110, 1043; IMX2101, ¶29. Of the range of different strategies, the most clinically advanced strategy was targeting soluble IL-4R extracellular domain ("sIL-4R") to block endogenous cytokine signaling. IMX2109, 339; EX1011, 411; IMX2101, ¶28. Clinical trials with sIL-4R were "promising" and "tantalizing," and "support[ed] the potential therapeutic use of sIL-4R in allergic inflammation." IMX2109, 339; EX1011, 411; IMX2101, ¶28. Dr. Zurawski himself had investigated IL-4 muteins and stated that "it is likely that antagonistic mutant IL-4

proteins [(*i.e.*, IL-4 muteins)] may have potential clinical use in the treatment of IgE-mediated allergic diseases." IMX2128, Abstract; EX1400, ¶9; IMX2101, ¶29.

In contrast to the pre-clinical testing done with sIL-4R, most reviews in the field did not even mention anti-IL-4R antibodies. IMX2101, ¶30. For example, in 2001 Tokura *et al.* published a six series of essays answering the question: "What are the most promising strategies for the therapeutic immunomodulation of allergic diseases?" IMX2113. None of the essays mentioned anti-IL-4R antibodies, despite discussing a wide range of other therapeutic strategies. *Id.* Other review articles published just before the May 1, 2001, priority date) similarly ignored anti-IL-4R antibodies in their extensive discussions of current and future targets of allergic disease and asthma treatments. *See, e.g.*, IMX2110, 1043; IMX2108, 167; IMX2109, 339; IMX2112. S588:Table II. Rather than addressing why a POSA would have selected anti-IL-4R antibodies as a therapeutic strategy, Sanofi's hindsight-driven arguments simply ignore the strategies discussed in the art.

Finally, even if a POSA were to consider anti-IL-4R antibodies as a therapeutic strategy (though Sanofi has not demonstrated that one would), Sanofi's hindsight-driven analysis is further apparent in Sanofi's failure to indicate why a POSA would have selected MAb230 from the range of known murine anti-IL-4R

antibodies. IMX2101, ¶¶32-35. IL-4R was known in the art before May, 2001, and, as Sanofi has previously admitted, "a large number of murine antibodies have been described in the prior art that specifically bind to the extracellular domain of hIL-4R." IMX2120, ¶6.1.1. For example, Schering-Plough discloses nine different murine anti-IL-4R antibodies (*i.e.*, murine antibodies produced from hybridomas S103, 0361, S17, 0296, S456, S924, S697, 0497 and 0735). EX1007, Abstract, 2:32-33. Despite the fact that Dr. Zurawski was involved in the development of these nine antibodies, neither Sanofi nor Dr. Zurawski discuss them as candidate therapeutics. EX1010, 13874:Table 1; IMX2101, ¶33. And neither Sanofi nor Dr. Zurawski discuss other murine anti-IL-4R antibodies disclosed in the prior art. *See, e.g.*, EX1019, Abstract (describing the X2/45 anti-IL-4R antibody); EX1205, 59:16-30 (describing the M57 anti-IL-4R antibody); IMX2125, 5054 (describing the CDw124 "monoclonal mouse IgG1 anti-human IL-4 receptor"); IMX2101, ¶¶32-33.

Despite Sanofi's sole rationale to modify MAb230 being linked to an alleged desire to make a therapeutic, and despite MAb230 being commercially available for over 20 years, Sanofi has not identified any publication that suggests modifying MAb230 to make a therapeutic antibody. IMX2101, ¶34. To the contrary, R&D

Systems, which manufactured MAb230, stated in bold terms in its catalog that MAb230 is for "RESEARCH USE ONLY," specifically for assays such as "neutralization," "ELISA" and "Western Blot." EX1206, 0010, 0018. And Hart describes using MAb230 in a method of "[a]ssessment of functional responses to IL-13." EX1401, 2094.

Further, numerous publications mentioning MAb230 before May 1, 2001, described MAb230 only in terms of its use as a research tool or reagent. IMX2101, ¶34; IMX2114, 1453 (using MAb230 "in flow cytometry"); IMX2115, 31448 (using MAb230 to purify recombinant proteins); IMX2116, 5660 (using MAb230 for "Flow cytometric analysis and FACS"); IMX2117, 451, 454 (using MAb230 in flow cytometry and as a signal blocking reagent); IMX2118, 630 (using MAb230 "to block endogenous cytokines"); IMX2119, 414, 416 (using MAb230 for immunohistochemistry); IMX1401, 2094 (using MAb230 in a method of "[a]ssessment of functional responses to IL-13").

Sanofi's hindsight-driven focus on MAb230 is exemplified by Dr. Zurawski's immediate focus, without justification, on MAb230 in his discussion of anti-IL-4R antibodies:

> Prior to May 1, 2001, it was well-known that antibodies could be raised against IL-4Rα. One such anti-h1L-4Rα antibody that was well-known to skilled artisans before May 1, 2001 is disclosed in Ex. 1204 ("Hart"). . . . Hart describes the use of a mouse anti-h1L-4Rα antibody called MAb230 (also known as clone 25463.11) to investigate the signaling complexes induced by IL-4 and IL-13 in monocytes and monocyte-derived macrophages ("MDMac").

EX1400, ¶¶43-44 (internal citations omitted); IMX2101, ¶32. Only hindsight allowed Dr. Zurawski to leap straight to discussing Mab230, given all of the other known murine anti-IL-4R antibodies.

Sanofi's assertion that "[e]very murine antibody is both a laboratory reagent and potential parent to a humanized antibody with therapeutic potential" is misleading and irrelevant. Pet., at 47. Sanofi bears the burden of demonstrating that MAb230 has characteristics that would be desirable as a therapeutic. Despite its blustering, Sanofi has not demonstrated that the prior art provides any reason "to generate a humanized version of MAb230 as a potential therapeutic for allergic diseases," let alone a human version of MAb230 as required by the claims. Pet., at 48. That assertion is solely the product of Sanofi's hindsight.

Sanofi's alleged reasons to use MAb230 are incomplete and unsupported because Sanofi points to properties of MAb230, but does not demonstrate that those properties would have led a POSA to consider MAb230 a good candidate for developing a therapeutic. For example, Sanofi alleges that a POSA would have had a reason to humanize because MAb230 is "able to block both IL-4 and IL-13 signaling activity." Pet., at 43-44. But other antibodies also shared this characteristic, and Sanofi has not demonstrated that the art preferred MAb230. *See, e.g.*, EX1019, Abstract. Sanofi also alleges that a POSA would have selected MAb230 because it has "a 50% neutralization constant ("ND_{50}") of 0.003-0.006 μg/mL," a value higher than the therapeutic candidates in Schering-Plough. Pet., at 44 (citing EX1400, ¶148). While Sanofi asserts that the ability to bind tightly is desirable or a characteristic of a good therapeutic candidate, this assertion is based entirely on a conclusory expert statement *without any citations to the prior art*. *Id.*

But perhaps the bluntest repudiation of Sanofi's arguments that it would have been obvious to humanize MAb230 is seen in Sanofi's own actions. Regeneron's initial efforts to develop a therapeutic inhibitor of IL-4 signaling, in the May 2001 time frame, used soluble IL-4R fragments, not an anti-IL-4-R antibody. IMX2111, 47. At the time, Regeneron publicly extolled the virtues of

this approach. IMX2126. Only later did Regeneron attempt to develop an anti-IL-4R antibody to target "IL-4 related disorders." EX1006, ¶[0030]. And even then, rather than humanizing MAb230—which Sanofi with hindsight argues was an obvious choice based upon art available as early as 1999—Sanofi instead relied on Immunex's disclosure of the 12B5 antibody in the published patent application that led to the '487 patent. *See, e.g.*, EX1006, ¶¶[0003], [0065], FIG. 1A-1C (disclosing using 12B5 as a "control" antibody in multiple assays); IMX2124, 14:5-57, Tables 1-3. Accordingly, Sanofi's hindsight obviousness arguments are undone by its own contemporaneous decisions and actions.

VII. Sanofi has failed to show that a POSA would have had a reasonable expectation of success in generating the claimed anti-IL4R antibodies

Both of Sanofi's obviousness grounds (Ground 1 and Ground 2) also fail because Sanofi has not met its burden to show that a POSA would have had a reasonable expectation of success.

Sanofi's Petition (in both grounds) argues that the motivation to combine the cited art is to develop a therapeutic antibody. For example, Sanofi's Petition argues that "Schering-Plough expressly motivates a POSITA to humanize murine anti-IL-4R blocking antibodies *to derive potential therapeutics*." Pet., at 43 (emphasis

added). Indeed, the Petition is littered with references to the alleged therapeutic applicability of anti-IL-4R antibodies, and devotes an entire section to the "Need for Therapeutic Antibodies that Block IL-4 and IL-13 Signaling." *See, e.g.*, Pet., at 2-3, 11, 23-24, 25, 36, 42-45, 47-48, 57-58. Certainly, the Petition does not assert any non-clinical reasons to combine the cited art; as noted by Sanofi's expert, Dr. Zurawski, "[o]ne humanizes a mouse antibody to decrease the likelihood that the antibody triggers [an immune] reaction when injected into a human." EX1400, ¶214.

While Sanofi's sole reason to combine the cited art is to create a therapeutically effective monoclonal antibody, Sanofi fails to show that a POSA would have had a reasonable expectation of success in so doing. As the Federal Circuit has explained, when the sole alleged reason to combine the prior art is to develop a potential therapeutic, a demonstration of obviousness requires that "a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective." *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (quoting *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1070 (Fed. Cir. 2012)); *see also*, *Bristol-Myers Squibb v. Teva Pharmaceuticals USA*, 769 F. 3d 1339, 1355 (Fed. Cir. 2014)

(Taranto joined by Lourie and Reyna) (dissenting in the denial of a rehearing en banc to consider whether evidence postdating the invention may be used to establish unexpected results) (discussing how "[t]he success that must be reasonably expected in this case would, I think, have to be success in what motivated the investment in the research—an acceptable safety/efficacy profile for human-therapeutic use"); *see also, Phigenix, Inc. v. Immunogen, Inc.*, IPR2014-00676, Paper 39, at 21 (PTAB, Oct. 27, 2015) (holding that "Petitioner's rationale . . . was to make an immunoconjugate useful in treating tumors in human patients . . . [and] Petitioner does not persuade us that a preponderance of the evidence establishes that a skilled artisan would have had a reasonable expectation of success . . . in the treatment of breast tumors in humans").

Here, Sanofi's Petition fails to demonstrate that a POSA would have reasonably expected to succeed in its efforts to produce a therapeutically effective modified MAb230, *i.e.*, the antibody allegedly motivated the modifications. Sanofi's reasonable expectation of success arguments fail because, instead of providing evidence regarding the expectation of success in the therapeutic context, Sanofi merely argued that a POSA could have successfully performed the *process* of altering MAb230 to "isolat[e] at least one species of the '487 Patent's claimed

genus of antibodies." Pet., at 47. Accordingly, Sanofi has not demonstrated that a POSA would have had a reasonable expectation of success in modifying the teachings in the art in accordance with the alleged motivations to combine the art.

VIII. Should the Supreme Court Hold that *Inter Partes* Review trials are unconstitutional, the Board should vacate and terminate this proceeding

The Supreme Court recently granted a certiorari petition in *Oil States Energy Services LLC v. Greene's Energy Group, LLC* to decide whether the IPR statute violates the U.S. Constitution by granting the Board the authority to extinguish private property rights in a non-Article III forum without a jury. *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, 639 F. App'x 639 (Fed. Cir. 2016) (Mem.), *cert. granted*, 137 S. Ct. 2239 (2017). Immunex respectfully objects to this tribunal's exercise of jurisdiction to adjudicate the validity of the '487 Patent because it would violate Immunex's right to a jury trial under the Seventh Amendment. If the Supreme Court disturbs the Federal Circuit's precedent in this area, Immunex will advise the Board and seek dismissal of this matter.

IX. Sanofi's arguments fail for multiple reasons

In summary, the entire Petition hinges on §103 attacks to the challenged claims that are defective in multiple ways, and these defects compel denying

institution both individually and in aggregate. The defects include:

- Sanofi's Petition is an improper serial petition challenging the '487 patent that constitutes an abuse of the system and harassment of Immunex (*see* Section II, *supra*);
- Substantially the same issue regarding the obviousness of the claims has already been squarely before the Office during prosecution—a fact Sanofi neither discloses nor disputes in its Petition (*see* Section III, *supra*);
- Sanofi fails to clarify its ambiguous positions on claim construction—even though claim construction is a predicate to obviousness analyses (*see* Section IV, *supra*);
- Sanofi's Ground 1 fails to make a prima facie case of obviousness because it is dependent on an unreasonably broad construction of "human" antibodies (*see* Section V, *supra*);
- Sanofi's Ground 1 and Ground 2 obviousness arguments are based on an impermissible hindsight reconstruction of the claims (*see* Section VI, *supra*); and
- Sanofi fails to demonstrate that a POSA would have had a reasonable expectation of success in arriving at the IL-4R antibody that Sanofi alleges a

POSA was motivated to make (*see* Section VII, *supra*).

X. Conclusion

The Petition fails to show a reasonable likelihood that any of the challenged claims is unpatentable as obvious in view of the cited art and, therefore, the Board should deny institution.

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that Immunex Corp.'s Patent Owner Preliminary Response contains 12,380 words as counted by the word-processing program used to generate this reply. This total does not include the table of contents, the table of authorities, appendix of exhibits, certificate of service, or this certificate of word count.

Respectfully submitted,
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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned "Patent Owner Preliminary Response" was served in its entirety on November 16, 2017, upon the following parties via electronic mail:

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