UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Patent No. 7,622,115 B2
Issue Date: November 24, 2009
Title: TREATMENT WITH ANTI-VEGF ANTIBODIES

Inter Partes Review No. 2016-01771

PATENT OWNER RESPONSE

Pursuant to 37 C.F.R. § 42.120, Patent Owner, Genentech, Inc., submits this Patent Owner Response to the Petition for *Inter Partes* Review of U.S. Patent No. 7,622,115 filed by Petitioner, Hospira, Inc.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

FEDERAL CASES

OTHER AUTHORITIES

Genentech revolutionized the treatment of certain cancers when it invented Avastin® (bevacizumab), a humanized monoclonal antibody that inhibits tumor progression. Since 2004, Avastin® has been widely prescribed, in combination with various chemotherapy regimens, for the treatment of many forms of cancer, including cancer of the colon, kidneys, cervix, ovaries, and lungs. *See* Ex. 2008 at 1. Avastin® binds VEGF, a protein involved in angiogenesis, the body's process for creating new blood vessels from existing vasculature that is critical to tumor growth. By inhibiting angiogenesis, Avastin® impedes tumor growth, thereby improving and often extending the lives of patients treated with it.

The patent at issue, U.S. Patent No. 7,622,115 ("the Fyfe Patent") involves a method of treating patients with Avastin® in light of Genentech's discovery that patients being treated with the medicine have a significantly increased risk of gastrointestinal ("GI") perforation. The Fyfe Patent teaches that oncologists should "assess[] . . . for gastrointestinal perforation during treatment with bevacizumab." Ex. 1001 at 40. Hospira challenges as anticipated and obvious claims that incorporate this limitation but in doing so proposes a construction—"evaluating the patient in any way that may provide information about whether the patient may be experiencing a GI perforation," Pet. 15 (citing Ex. 1002 ¶¶ 91–94)—so broad as to remove all meaning from the phrase. Hospira's own expert admitted that under this proposed construction, he, his medical students, and his

nurse practitioners have "assess[ed] . . . for [GI] perforation" every patient they have ever physically examined. *See* Ex. 2013 at 44, 190–93.

Hospira's construction also cannot be reconciled with the patent's prosecution history. The patent application originally recited a method comprising "*monitoring* the patient *for signs or symptoms* of gastrointestinal perforation." Ex. 1020 at 107 (emphases added). The examiner rejected those claims under § 102. Genentech, in response, amended its claims and limited its invention to a method of treatment comprising the step of "*assessing* the patient *for gastrointestinal perforation* during treatment with bevacizumab. Ex. 1020 at 107 (emphases added). Here again, the candor of Hospira's own expert undermines its Petition. He acknowledges that Hospira's proposed construction is functionally equivalent to the "monitoring . . . for signs or symptoms" language that Genentech disclaimed during prosecution. *See* Ex. 2013 at 155–58.

The appropriate construction of "*assessing* the patient *for gastrointestinal perforation* during treatment with bevacizumab" is narrower. Consistent with the understanding of the POSA and the meaning attached to it during prosecution, this claim language should be construed to mean *taking diagnostic steps to determine whether a GI perforation exists*. Nothing in the prior art described or suggested this invention. The two references underlying the Grounds at issue describe bevacizumab as well tolerated with mild to moderate toxicity, with no indication

its administration could cause this serious, often deadly, adverse event. The Examiner understood this, withdrew her rejection over similar art, and allowed the claims, a decision that would make no sense if Hospira's overly broad interpretation of the claims were the correct one. Just as the Examiner properly concluded that nothing in the art described or taught Genentech's invention, this Board should as well.

BACKGROUND

A. Avastin®.

Researchers long ago identified the crucial role angiogenesis plays in the growth and spread of tumors in patients suffering from certain cancers, and searched for years to identify agents capable of inhibiting this process. In 1989, Genentech reported the first successful effort to isolate VEGF, a protein that facilitates angiogenesis. Four years later the company disclosed that it had identified a mouse monoclonal antibody that bound to human VEGF, and three years after that announced that it had successfully humanized this antibody to make bevacizumab.

Extensive clinical testing followed to evaluate the safety and efficacy of bevacizumab for use as an anti-cancer therapy in humans. Given prior industry experience with anti-cancer drugs, certain toxicities uncovered in those trials were expected, including nausea and vomiting. *See* Ex. 2011 ¶¶ 32, 80–81. GI

perforation was not one of them. It was not until years after clinical testing started that the inventors unexpectedly discovered that patients being treated with bevacizumab suffered this serious adverse effect at rates sufficiently high to cause alarm. Ex. 1001; Ex. 2021 at 3.

At the time of this discovery, Genentech, the National Cancer Institute (NCI), and various oncology cooperative groups were still collaborating on a number of bevacizumab clinical trials, and changes were immediately implemented in response to the inventors' work. Ex. 2021 at 1. For example, clinical investigators in the NCI-administered studies received a strongly-worded Action Letter, "to alert [them] to two unexpected serious adverse events (Bowel Perforation and Bowel Anastomotic Dehiscence) that occurred in association with bevacizumab in studies sponsored by the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD) and by Genentech, Inc." *Id.* at 1. The NCI instructed them that "[a] revision to the protocol and the informed consent form is required by the NCI," and that investigators were to submit these proposed changes within thirty days. *Id.* at 1–2. Genentech's discovery also yielded an FDA-mandated "black box" warning for Avastin® directing physicians and patients to be on the lookout for this risk.

B. The Fyfe Patent.

The Fyfe Patent issued on November 24, 2009 and claims priority to a provisional application filed on May 30, 2003. Ex. 1001 at 1. Example 1 in its specification details the findings of the pivotal Phase III study of bevacizumab in patients suffering from metastatic colorectal cancer. *Id.* at 34–38. The patent discloses that six patients (1.5%) receiving bevacizumab therapy experienced a GI perforation event. *Id.* at 37. It explains that this "new potential adverse effect" was "uncommon and had variable clinical presentations." *Id.* at 38. Example 2 reports on a different trial where two patients receiving bevacizumab also experienced a GI perforation. *Id.* at 39.

A GI perforation is a hole or tear in the wall of the GI tract.[1] Ex. 2011 ¶¶ 29–35; Ex. 2012 ¶¶ 13–16. Sometimes perforation allows the contents of the GI tract—*e.g.*, food, stool, stomach acid, and gas—to enter the abdominal cavity with potentially devastating effects, including peritonitis, sepsis, and hemodynamic collapse. Ex. 2011 ¶¶ 29–35; Ex. 2012 ¶¶ 13–16. In many cases, these events can be fatal. Ex. 2011 ¶¶ 29–35; Ex. 2012 ¶¶ 13–16. Speedy detection of a GI

[1] The GI tract includes the esophagus, stomach, small intestine (duodenum, jejunum, and ileum), and large intestine (cecum, colon, rectum, and anal canal). Ex. 2011 ¶ 29.

perforation can substantially improve the odds of a positive outcome. *See, e.g.*, Ex. 2011 ¶ 30; Ex. 2012 ¶ 16; Ex. 1002 ¶ 102.

Claim 1 recites a new method of treatment that accounts for Genentech's discovery:

> A method for treating cancer in a patient comprising administering an effective amount of bevacizumab and assessing the patient for gastrointestinal perforation during treatment with bevacizumab.

Ex. 1001 at 40. The remaining claims depend from claim 1 and cover specific types of cancer (claim 2), combination therapy with a chemotherapeutic agent (claim 3), combination therapy with specific chemotherapeutic agents (claim 4), and administration at about 5–15 mg/kg every 2–3 weeks (claim 5). *Id.*

C. Detection of GI Perforations.

It is common ground between the parties that when a patient undergoing cancer treatment visits a medical oncologist, the medical oncologist will perform a routine examination of the patient. Ex. 2011 ¶ 44; Ex. 1002 ¶¶ 106–07. This will often include discussing with the patient how they are feeling, asking whether they are experiencing any side effects, and performing a relatively brief physical examination. Ex. 2011 ¶ 44; Ex. 1002 ¶¶ 105–07.

As Exhibit 2011, the declaration of Duke University Hospital oncologist Dr. Michael Morse, explains, with these sorts of office examinations oncologists can

neither confirm the presence, nor establish the absence of, a GI perforation. Ex. 2011 ¶¶ 45–47; *see also id.* ¶¶ 31–34. Symptoms that a physician might notice that are consistent with the presence of a GI perforation—*e.g.*, abdominal pain, nausea, and vomiting—are also consistent with a variety of other conditions, many of which are far more common than GI perforations. *Id.* ¶¶ 31–34, 45–47, 80–81. Observation of such symptoms does not allow a physician to know if a patient in fact is suffering from a GI perforation. *See id.* Dr. Neugut concurs in this view. Ex. 2013 at 77 ("[A] GI perforation requires testing and evaluation in the emergency room to make . . . the diagnosis"); *see also* Ex. 2013 at 75–78. At the same time, the absence of observable symptoms does not allow a physician to rule out the presence of a GI perforation. Ex. 2011 ¶¶ 45–47. That is because some perforations will be so small or short-lived that they cause little harm and may even go entirely unnoticed, unless they progress to causing ill effects for the patient. *Id.* ¶¶ 31–34, 45–47.

Given the limitations of these office-based examinations, the medical oncologist[2] needs to take additional diagnostic steps in order to determine whether

[2] "Medical oncologists are trained in the treatment of cancer using medications such as chemotherapy, targeted therapy, hormonal therapy, and biological

a patient has experienced a GI perforation. *Id.* ¶¶ 31–34, 45–47; Ex. 2012 ¶¶ 17–20. It is therefore common that an oncologist who suspects a patient may have suffered one will order medical imaging—in most cases CT ("computed tomography") scans—or alternative diagnostic steps to confirm the presence and ideally determine the location of the perforation.[3] Ex. 2012 ¶¶ 17–20; *see also* Ex. 2011 ¶¶ 31–34, 45–47. Acute GI perforations ordinarily require surgical intervention and repair, but, given its inherent risks, surgery is rarely undertaken without first confirming at least the presence of the perforation through one or more of these diagnostic techniques. Ex. 2011 ¶¶ 33–35; *see also* Ex. 2012 ¶ 20.

The effectiveness of CT scans in detecting a GI perforation can depend significantly on whether the radiologist is alerted ahead of time to look for this condition. Ex. 2012 ¶¶ 21–35. CT scans capture a large number of cross-sectional images of the patient's body. *Id.* ¶¶ 21–22. The radiologist conducting the test determines how these images are taken (*e.g.*, the thickness of the image "slices" and the perspective of the images relative to the patient's body), and will modify

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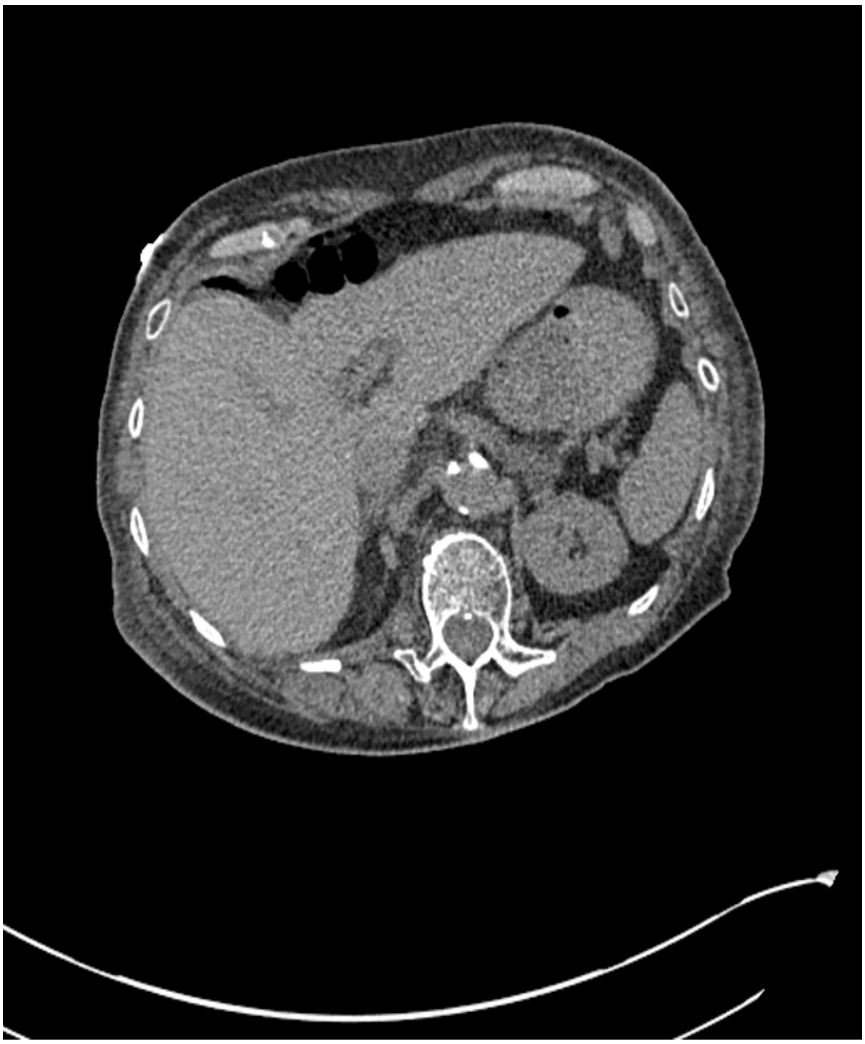
therapy." Ex. 2011 ¶ 40. Surgical oncologists, by comparison, specialize in performing biopsies and removing tumors. *Id.*

[3] This practice was the same in May 2003. Ex. 2011 ¶¶ 34, 42–51; Ex. 2012 ¶¶ 10, 21–35.

these settings depending on what condition he or she is looking for or suspects. *Id.* ¶¶ 21, 24–35. When presented with a patient who might be experiencing a GI perforation, radiologists typically employ a "lung window" rather than the standard "soft tissue window," applying settings normally reserved for CT scans of the lung that are better able to reflect the classic diagnostic sign of perforation, the presence of "free air" in the abdominal cavity. *Id.* ¶¶ 26–35. This can mean the difference between detecting a GI perforation and missing one. *Id.* ¶¶ 28–35.

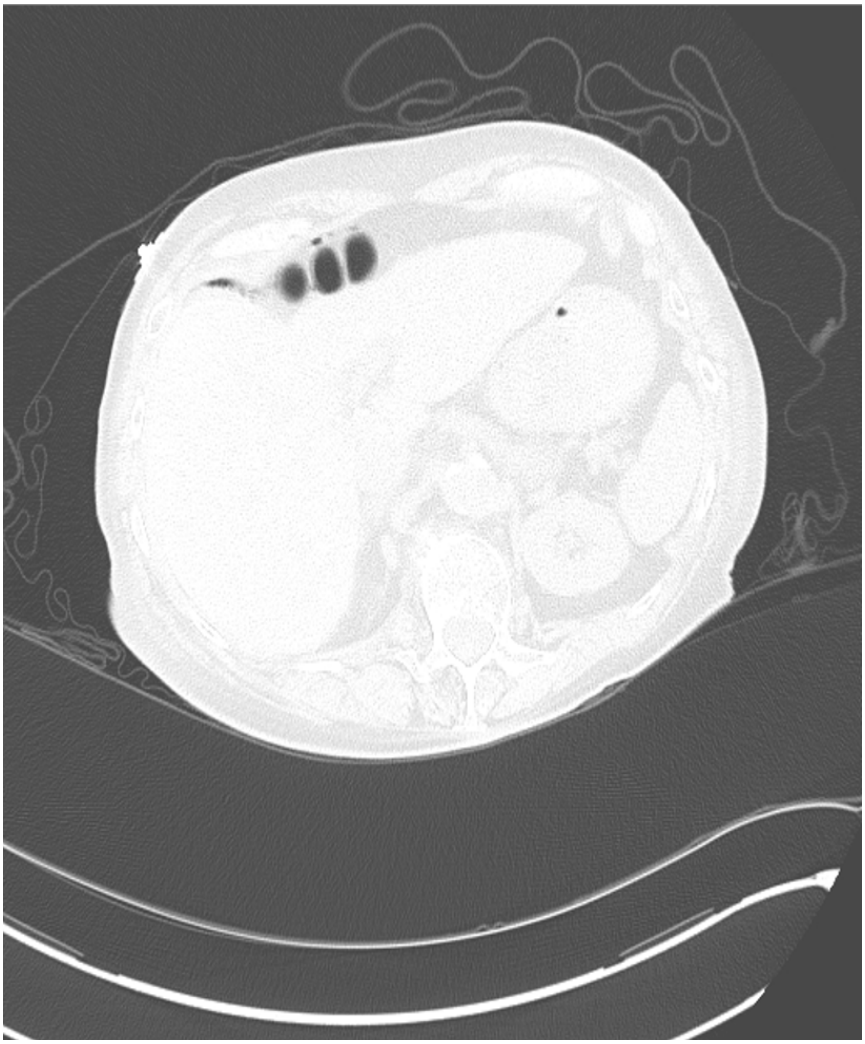
Exhibit 2012, the declaration of Georgetown University radiology professor Dr. Angela Levy, explains and illustrates the difference, using sample CT scans from patients with a GI perforation. In the soft tissue window, air appears as dark black, while tissue appears as varying shades of gray or lighter black and bone appears as white. *Id.* ¶ 29. In this view, large pockets of air, like those ordinarily found within the colon, are easily detectable but small amounts of "free air" outside the walls of the GI tract—a telltale sign of GI perforation—can blend into the background of dark gray or even black fat. *Id.* ¶ 29–35. In this scan from an actual patient who suffered a GI perforation, the free air is difficult to detect in the soft tissue window:



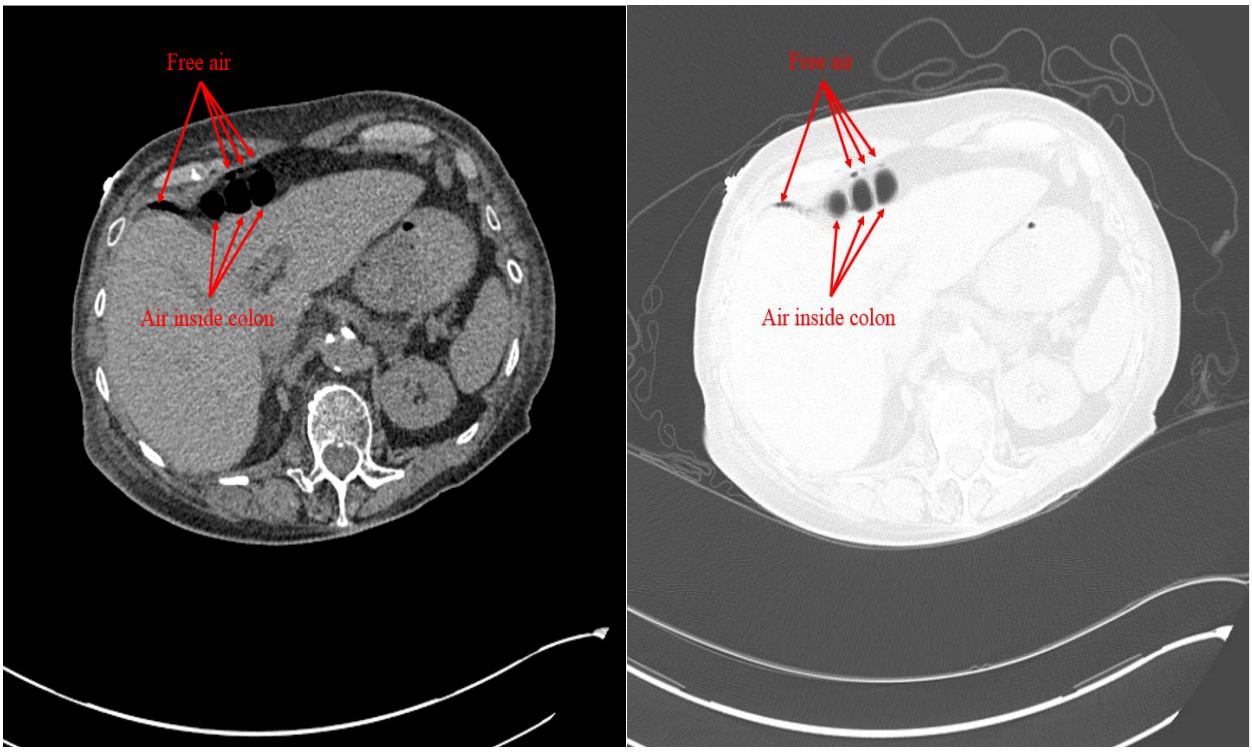
Id. ¶¶ 33–34.

When the radiologist chooses instead to have the CT equipment provide a lung window, the scan depicts air as black and everything else as white or light gray, allowing the radiologist to more easily differentiate air from tissue and determine whether any of that air has entered the abdominal cavity. *Id.* ¶ 27–35. The following image, for example, is the identical scan as above, only presented in

a lung window, permitting the small volumes of free air anterior to the three circle-shaped pockets of air collected in the colon to be more easily identified:



Id. ¶¶ 33–34. In the side-by-side images below, Dr. Levy has added arrows identifying the key features of these scans:



Id. As Dr. Levy explains, programming the equipment to provide the radiologist with a lung window dramatically increases the chance of detecting the pockets of free air and diagnosing the perforation, particularly given the limited time a radiologist ordinarily examines a set of scans. *Id.* ¶¶ 26–28, 35.

D. <u>The POSA</u>.

The parties appear to agree on the background and qualifications of the POSA, to whom the Fyfe Patent is directed. That person is a medical doctor who specializes in oncology, specifically medical oncology, with several years of experience in the treatment of cancer. Ex. 2011 ¶ 39–41. The POSA also has access to other physicians and medical professionals such as radiologists and

surgeons who can take diagnostic measures to detect a GI perforation when the oncologist suspects one. *Id.*; *see also* Pet. 18–19 (describing POSA).

ARGUMENT

The Board instituted this trial on three of the eleven Grounds advanced in the Petition:

> -- Ground 1, asserting that the claims of the Fyfe Patent are anticipated by Kabbinavar;
>
> -- Ground 5, asserting that Kabbinavar renders the claims obvious; and
>
> -- Ground 7, asserting the claims are obvious over the 2000 Press Release.

Each of these Grounds is premised on the unreasonable construction Hospira has advanced, or on a serious misreading of the relevant prior art, or both. None satisfies Hospira's burden to show by a preponderance of the evidence that any of the claims of the Fyfe Patent are invalid.

I. HOSPIRA'S PROPOSED CONSTRUCTION OF THE "ASSESSING" LIMITATION IS UNREASONABLY BROAD.

Hospira's anticipation and obviousness challenges largely rise or fall on the construction of "assessing the patient for gastrointestinal perforation during treatment with bevacizumab," a phrase that appears in claim 1 and remains a

limitation of all the dependent claims. The parties are worlds apart on the correct construction.

Genentech construes this phrase to mean "taking diagnostic steps to determine whether a GI perforation exists." This construction squares with the plain language of the claims as well as the prosecution history, and is fully endorsed by Dr. Michael Morse, an oncologist at Duke University Medical Center whose declaration Genentech has submitted as Exhibit 2011. Ex. 2011 ¶¶ 42–51. This construction comports with the POSA's understanding that an assessment "for" a particular medical condition requires a targeted evaluation capable of revealing whether the condition in question did or did not exist, and is performed for that purpose. *Id.* ¶¶ 43–44, 49. In the case of "assess[ments] . . . for [GI perforation," the POSA "would understand that such diagnostic steps include CT scans and radiography, as both techniques are able to confirm the presence of a perforation." *Id.* ¶ 43.

Under Hospira's proposed construction, a doctor practices the claim language whenever "evaluating the patient in any way that may provide information about whether the patient may be experiencing a GI perforation." Pet. 15 (citing Ex. 1002 ¶¶ 91–94). Not surprisingly, the tendered construction dovetails with Hospira's anticipation argument. Hospira contends that reports of earlier bevacizumab clinical trials disclose the invention because the physicians in

those trials performed routine office examinations of their patients. But those reports do not disclose any instances of GI perforation, or that the physicians involved knew of this heightened risk and took particular steps to manage it.

Hospira's construction cannot be correct. It effectively removes all meaning from the concept of "assessing" someone "for" GI perforation in particular. This became clear during the deposition of Hospira's expert, Dr. Alfred Neugut, an oncologist at Columbia University College of Physicians & Surgeons. He testified that an oncologist who does little more than glance at a patient has "assess[ed]" her for a GI perforation, because if the patient appears "happy" and otherwise fine, she is unlikely to have a GI perforation; on the other hand, if the patient had suffered a perforation, she might experience severe abdominal pain that might be visually observable. Ex. 1002 ¶¶ 91–92; Ex. 2013 at 42–43. Dr. Neugut conceded that under this construction, every patient he or his medical students or even his nurse practitioners have ever physically examined has been assessed for GI perforation. Ex. 2013 at 190–93. The proposed construction is so broad that Dr. Neugut actually claimed to have assessed Genentech's counsel for a GI perforation during the course of his deposition. *Id.* at 50–51.

The requirement in this proceeding that claim language receive its "broadest reasonable construction in light of the specification of the patent," 37 C.F.R. § 42.100, does not mean "giving [the] claims a legally incorrect interpretation."

D'Agostino v. MasterCard Int'l Inc., 844 F.3d 945, 948 (Fed. Cir. 2016). Rather, "claims should always be read in light of the specification and teachings in the underlying patent," *id.* (quoting *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010)), and "the Board 'should also consult the patent's prosecution history in proceedings in which the patent has been brought back to the agency for a second review,'" *id.* (quoting *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015)). Unlike Genentech's construction, Hospira's ignores these standards. It conflicts with the prosecution history, is wholly inconsistent with the ordinary meaning of the term to the POSA, and is so broad that it strips the concept of "assessing" of any real meaning.

1. Claim language mirroring the construction Hospira now advances was considered and rejected during prosecution. The application originally claimed a method of treatment with bevacizumab comprising "monitoring the patient for signs or symptoms of gastrointestinal perforation." Ex. 1020 at 90. The Examiner rejected this claim as anticipated by a reference, Gordon (Ex. 1015), reporting on the results of a Phase I bevacizumab clinical study. Ex. 1020 at 94–97, 100–01. The Examiner concluded that Gordon taught "a method for treating cancer in a patient comprising administering rhuMAb VEGF (bevacizumab) and monitoring patients for adverse events during treatment including nausea." *Id.* at 101. She reasoned that "nausea is a sign or symptom of gastrointestinal perforation, hence

the nausea monitored in the method taught by Gordon *et al* is a sign or symptom of gastrointestinal perforation." *Id.*

Genentech responded with an amendment substituting the current "assessing . . . for [GI] perforation" language for the problematic "monitoring . . . for signs or symptoms." *Id.* at 107. Genentech explained:

> [T]he Examiner contends that the nausea monitored in Gordon's method is a sign or symptom of gastrointestinal perforation. Applicants traverse in view of the claim amendments. . . . *Gordon does not teach assessing patients being treated with bevacizumab for gastrointestinal perforation. In fact, gastrointestinal perforation was a newly observed potential adverse event associated with bevacizumab in the clinical trials described in the instant application.* Moreover, the occurrence of gastrointestinal perforation in these patients was unexpected based on the adverse events observed in previous clinical trials using bevacizumab.

Id. at 114 (emphasis added).

This amendment leaves little question that Genentech and the Examiner drew a distinction between assessing for GI perforation itself and merely looking for symptoms that could be consistent with this condition. And, critically, this amendment makes clear that the amended claims do not cover routine examinations of patients, in clinical trials or otherwise, as that is all that Gordon

disclosed (and is all that the prior art in the Grounds instituted upon discloses). Ex. 2011 ¶¶ 52–55, 57; Ex. 1005; Ex. 1006. The Examiner agreed that this amendment overcame the § 102 rejection and allowed the claims. Ex. 1020 at 121.

Hospira does not dispute that its proposed construction is functionally identical to the "monitoring" language the Examiner rejected and the applicants replaced through amendment. Dr. Neugut candidly acknowledges that he does not "see that there's a difference between the word 'assessing' and 'monitoring,'" and thus concedes that under his construction, Claim 1 remains anticipated by Gordon even though the Examiner concluded otherwise. Ex. 2013 at 155–57.[4] The very reason evaluations as simple as visual observations or standard physical examinations constitute "assessments" in Dr. Neugut's view is that these evaluations might detect signs or symptoms of GI perforation. *See id.* at 47–50. But such symptom-monitoring is explicitly what applicants *disclaimed*. Indeed, under Dr. Neugut's construction, the claims would have remained anticipated by not only Gordon but at least *four* additional references reporting on bevacizumab

[4] *See also id.* at 158 ("Q. There's nothing in your view about Gordon that would cause it to anticipate the earlier form of the claim language but not anticipate the later form of the claim language, correct? A. I think so.").

clinical trials that were also before the Examiner.[5] *See* Ex. 2011 ¶¶ 48–51; *see also* Ex. 1005; Ex. 1006; Ex. 2015; Ex. 2016. Neither Genentech nor the Examiner understood the "assessing" language to have the definition Hospira now advances, and the POSA reviewing the prosecution history would recognize as much, making Hospira's construction unreasonable.

2. Hospira's construction is likewise unfaithful to the interpretation the POSA would give the claim language. As Dr. Morse explains, oncologists understand that when they "assess" *for* a given disease, event, or condition, they conduct a targeted evaluation of that disease, event, or condition. Ex. 2011 ¶¶ 43–44; *see also id.* ¶¶ 45–49.

Hospira insists that its construction finds support in the specification's statement that "safety was assessed" "from reports of adverse events, laboratory test results, and vital sign measurements." Pet. 17 (quoting Ex. 1001 at 38). Hospira reasons that, just as "[r]eports of adverse events, laboratory test results, and vital signs were part of the evaluation because each may provide information

[5] Kabbinavar (Ex. 1005)—one of Petitioner's alleged invalidating references and the art underlying two of the three grounds for which the Board instituted trial—was not only disclosed to the PTO during examination of the Fyfe Patent, Ex. 1001 at 2, but is directly referenced twice in the specification, *id.* at 16, 37.

that allows the evaluation of safety," any evaluation that might provide information about a GI perforation should be considered "assessing . . . for [GI] perforation." Pet. 17. But this argument merely assumes Hospira's conclusion. Nothing in the cited portion of the specification requires, for example, that the result of any individual laboratory test constitutes an "assessment" of safety merely because it could provide information useful to that conclusion.

Hospira's argument in any event misses the point. The salient question is not whether "assess" could be synonymous with "evaluate"—which is essentially Petitioner's entire argument, *see* Pet. 16—but rather *what* is being assessed or evaluated. When one assesses *for* GI perforations, one is determining if the patient has that specific condition. Ex. 2011 ¶¶ 43–44; *see also id.* ¶¶ 45–49. That requires taking steps to actually confirm the presence of the condition, hence Genentech's proposed construction: "taking diagnostic steps to determine whether a GI perforation exists."

While such diagnostic steps might vary depending on the clinical circumstances, they are techniques well known to the POSA and can include performing or ordering medical imaging (*e.g.*, radiographs and CT scans). *Id.* ¶¶ 31–34, 43. A GI perforation assessment requires the confirmation provided by such measures. *Id.* ¶¶ 31–35. A medical oncologist would not have understood an assessment for GI perforation to have occurred through physical examination

alone, even where the patient exhibited symptoms of a GI perforation. *Id.* ¶¶ 31–35, 43–51. Such symptoms, which may include nausea, fever, abdominal pain, and vomiting, are typical of many conditions, and a medical oncologist would not purport to have assessed a patient "*for* [GI] perforation" solely because an examination observed these symptoms (or their absence). *Id.* ¶¶ 43–47; *see also id.* ¶¶ 80, 81.

Nor would a medical oncologist have understood a GI perforation assessment to have occurred whenever diagnostic steps like a CT scan or radiograph of the patient receiving bevacizumab happened to have been taken for any purpose. *Id.* ¶¶ 42–51. An assessment of a particular condition connotes a targeted investigation of that condition. *Id.* Thus, in order for a CT scan to constitute an assessment for GI perforation, it must have been performed for the purpose of determining whether a perforation had occurred. *Id.* This construction not only conveys the ordinary, purposeful meaning of the term "assess," it also recognizes that there exist substantive differences between diagnostic steps taken in order to determine whether a GI perforation has occurred and the way the same diagnostic tests are done when this purpose is not present. Dr. Levy's testimony underscores the point. *See* Ex. 2012 ¶¶ 21–35. A CT scan undertaken for the purpose of determining whether a patient has suffered a perforation (*e.g.*, an

abdominal CT scan using a lung window) is considerably more likely to identify the presence of free air in the abdominal cavity. *Id.*

II. KABBINAVAR DOES NOT ANTICIPATE THE CLAIMS OF THE FYFE PATENT.

Ground 1 argues that Kabbinavar (Ex. 1005), a 2003 article in the *Journal of Clinical Oncology* reporting the results of a Phase II bevacizumab trial, anticipates all claims of the Fyfe Patent.

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently." *Eli Lilly & Co. v. Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017) (internal quotation marks omitted). "In the context of anticipation, the question is not whether a prior art reference 'suggests' the claimed subject matter[;] . . . [r]ather, the dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference." *Id.*

Kabbinavar does not disclose the second step of the claimed method: "assessing . . . for [GI] perforation." There were no episodes of GI perforation reported in this trial. Thrombosis (blood clotting), not GI perforation, was "the most significant adverse event" observed, with hypertension, proteinuria, and epistaxis (nose bleeds) also seen. Ex. 1005 at 2. Table 5 of Kabbinavar lists more

than a dozen other adverse events or categories of adverse events experienced, but GI perforations are nowhere mentioned. *Id.* at 5. Overall, "[b]evacizumab therapy was associated with fever, headache, rash, epistaxis, and chills," and "these events were generally mild to moderate in severity." *Id.*

Despite this, Hospira contends that Kabbinavar disclosed "assessing . . . for [GI] perforation" by reporting "that the patients underwent 'physical examinations' and 'laboratory tests' and were 'questioned about . . . adverse effects' during treatment with bevacizumab." Pet. 29 (quoting Ex. 1005 at 3). This argument is entirely dependent on Hospira's unreasonably broad construction of "assessing," one that Dr. Neugut agreed meant that he has assessed every patient he has ever examined for GI perforation. Ex. 2013 at 44, 190–91. Kabbinavar nowhere indicates that any patient underwent imaging, laparoscopy, or any other diagnostic procedure to determine whether a GI perforation in fact had occurred. Ex. 2013 at 93–94, 96; Ex. 2011 ¶¶ 52–55. There is no indication in the reference that any physician involved in the trial knew that GI perforation was a particular risk when bevacizumab was administered. Petitioner's position is simply that because patients in the trial were evaluated for *other* adverse events, they necessarily were examined in a way that *might* have provided some information about whether they were experiencing a GI perforation. *See, e.g.*, Pet. 27, 29; Ex. 2013 at 93. This is

not "assessing . . . for GI perforation" as that term is used in the patent and understood by the POSA.

Kabbinavar's statement that three patients treated with bevacizumab suffered GI *hemorrhage* does not affect the analysis. Ex. 2011 ¶ 55. Strangely, Hospira suggests in its claim chart that a GI *hemorrhage* is equivalent to a GI *perforation*, citing the report of these three incidents as a disclosure of GI perforations in the Phase II trial. *See* Pet. 28. This contention is scientifically baseless. Both parties' experts agree that hemorrhage and perforation are separate, unrelated medical events. Ex. 1002 ¶ 90; Ex. 2011 ¶ 55; Ex. 2013 at 35–36. As Dr. Morse explains, "a diagnosis of GI hemorrhage refers to severe bleeding in the GI tract often leading to anemia, while a GI perforation refers to an opening in the GI tract that generally allows stool and other contents to spill in the abdominal cavity." Ex. 2011 ¶ 55; *see also* Ex. 2013 at 114. Hospira's suggestion that disclosure of a GI hemorrhage likewise discloses a GI perforation, at best, fundamentally misapprehends the science at issue.

In sum, it is undisputed that Kabbinavar includes no disclosure of any physician taking diagnostic steps to determine whether a GI perforation exists. Ex. 2013 at 96. This is why Kabbinavar was cited to the PTO and referenced twice in the specification but did not trouble the Examiner during prosecution. *See* Ex. 1001 at 2, 16, 37. Instead, Hospira's anticipation challenge relies entirely upon its

unreasonably broad claim construction, and the Board's institution on this Ground also apparently flowed from its acceptance of that construction at the preliminary stage. For the reasons discussed above, however, Hospira's construction is improper, and there is no basis for the Board to find that Kabbinavar renders any claim of the Fyfe Patent invalid under § 102.

III. NEITHER KABBINAVAR NOR THE 2000 PRESS RELEASE RENDERS ANY CLAIM OBVIOUS.

In Grounds 5 and 7, Petitioner alleges that Kabbinavar and the 2000 Press Release, respectively, would have rendered obvious all claims of the Fyfe Patent.[6] Petitioner's obviousness challenges require it to demonstrate that "the difference between the subject matter [of the claims] and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Since "obviousness must be assessed at the time the invention was made," it is "inappropriate" to rely on the inventors' own path of discovery or other forms of "hindsight analysis." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1073 (Fed. Cir. 2012).

[6] These references both report results from the same Phase II bevacizumab trial, *see* Ex. 2013 at 122–23, and Petitioner's arguments in Grounds 5 and 7 are nearly identical, *see* Pet. 45–52. As such, Genentech responds to these Grounds together.

Hospira offers four reasons why it would have been obvious for the POSA to "assess" any patient treated with Avastin® for GI perforation. None are persuasive.

A. The Standard of Care was to Observe the General Health of Cancer Patients, Not to Assess Cancer Patients for GI Perforations.

Hospira asserts that "the standard of care at the time of the alleged invention was to observe the health of cancer patients undergoing cancer therapy and, in particular, to assess whether the patients were experiencing any adverse events caused by the therapy, including GI perforation." Pet. 45; *see also id.* at 52. Hospira and Dr. Neugut rely on the National Cancer Institute's 1999 Common Toxicity Criteria v.2 (Ex. 1017) as their sole evidence of this "standard of care." Pet. 45–46; Ex. 1002 ¶¶ 20–22, 108, 112, 118, 125, 138.

The NCI CTC does not support Hospira's argument. It is a set of guidelines clinicians used to grade adverse events that may be observed during clinical trials. Ex. 2011 ¶¶ 59–62; Ex. 1016 at 9. Grades are assigned using a scale of 0 to 5, with 0 meaning that no adverse event has occurred or relevant measurements are within normal limits and 5 representing an adverse event-related death. Ex. 1016 at 4. According to Hospira, this confirms that "[a]s a matter of routine medical practice, cancer patients receiving therapy underwent regular evaluations that would have identified any adverse events the patient may have been experiencing, including GI perforation." Pet. 45.

This is no more than a restatement of Hospira's flawed anticipation challenge. It is hardly controversial to allege that an oncologist would have "evaluat[ed]" a cancer patient during treatment. That would be true whether or not the NCI CTC existed or instructed that "cancer patients receiving therapy" should undergo "regular evaluations." But that is not the meaning the POSA would ascribe to the phrase "assessing the patient for [GI] perforation," and any teaching by the NCI CTC that cancer patients should be generally evaluated is irrelevant. *See* Section I *supra*.

Rather, the POSA would understand the claim language to require taking diagnostic steps to determine whether a GI perforation exists, Ex. 2011 ¶¶ 42–51, and none of the art teaches such steps. Kabbinavar and the 2000 Press Release themselves do not suggest any potential association between bevacizumab and GI perforations that might lead the POSA to so assess a patient. To the contrary, they teach that bevacizumab was "generally well tolerated," Ex. 1004 at 2, that no perforations were encountered during the relevant Phase II trial, *see* Ex. 1005 at 2, and that instead the "most significant" toxicity experienced was thrombosis, *id.*; *see also* Ex. 1004 at 3.

The NCI CTC adds nothing to this. It does not encourage oncologists prescribing bevacizumab to take diagnostic steps to determine whether a GI perforation exists. It is true, as Hospira points out, that the NCI CTC uses GI

perforations as one of its grading markers for a handful of adverse events. Pet. 46. But this is far different from teaching assessment for GI perforation—the NCI CTC guidelines just inform medical professionals how to characterize or grade an adverse event *after it is observed*. Ex. 2011 ¶ 61; Ex. 2021 at 2.

Common sense alone refutes any suggestion that the publication establishes a standard of care or that its listed adverse events or grading criteria represent medical problems assessed in every cancer patient. The NCI CTC contains more than 200 separate adverse events and many more grading markers. Ex. 1016 at 8; Ex. 1017. As Dr. Neugut conceded in his deposition, the POSA would not and could not have ordered diagnostic steps to confirm the presence of hundreds of medical problems in each cancer patient:

> Q. But it would not be correct in your view to say that for purposes of this case that the fact that an adverse event is listed on the common toxicity criteria means that the person of ordinary skill would necessarily assess patients for that adverse event?
>
> A. It would take him two hours on every patient to fill out a form if that's what he was doing. I mean . . .
>
> Q. So in your view, that's not what he would be doing?
>
> A. I don't think so. Now, of course, the general question, "How are you doing?" may in some general, nonspecific way review every possibility, and then every now and then you get a patient who can

> have 40 complaints and then you can end up going through all of these. But for the most part, most clinical encounters are targeted and focal on what's relevant to the patient at hand.

Ex. 2013 at 79. This is particularly true given the abbreviated time an oncologist typically spends with each patient, Ex. 2011 ¶ 62; Ex. 2013 at 17 (explaining that, in his clinical practice, Dr. Neugut spends an average of fifteen to twenty minutes with each patient), and the fact that confirmation of many of the grading criteria in the CTC—including the presence of GI perforation—requires the use of specialized equipment unavailable in a typical oncologist's office, Ex. 2011 ¶ 62; Ex. 2013 at 77 (Dr. Neugut conceded that he cannot diagnose a GI perforation from a physical examination performed in his office, explaining that "a GI perforation requires testing and evaluation in the emergency room to make . . . the diagnosis"); *see also* Ex. 2013 at 75–78.

Dr. Neugut's own experience with these guidelines proves the point. He does not keep the CTC with him while writing patient notes, Ex. 2013 at 69, does not know the listed events "in depth," *id.*, and was not even aware that newer versions of the CTC have been published since the 1999 version referenced by Petitioner, *id.* at 74. (In fact, the NCI has since published two additional versions, one in 2006 and one in 2009. Ex. 2011 ¶ 61.)

Finally, even if the POSA could have assessed all cancer patients for the adverse events listed in the NCI CTC, the version of those guidelines in the prior art notably did not list GI perforation as an adverse event. Ex 1017 at 10–13. It was simply identified as a marker, a guidepost for grading the severity of the adverse events actually listed.[7]

B. That a Small Percentage of Colorectal Cancer Patients Experienced GI Perforations Does Not Render The Invention Obvious.

Hospira next argues that because Kabbinavar and the 2000 Press Release reported on a bevacizumab clinical trial in colorectal cancer patients, and because

[7] Hospira is also mistaken in its assertion that "[t]he fact that the patients in the two clinical trials described in the [Fyfe] Patent were assessed for GI perforation by their physicians provides additional evidence that assessing cancer patients receiving bevacizumab therapy for adverse events including GI perforation was the standard of care at the time of the invention." Pet. 46–47. Even if the conduct of these physicians in the clinical trial were good evidence of the standard of care, Hospira's premise is flawed—the Fyfe Patent nowhere indicates that any of these incidents of GI perforation were identified through an assessment for GI perforation, *i.e.*, a doctor taking diagnostic steps to determine whether a patient was experiencing a GI perforation. Ex. 1001 at 34–40.

prior art publications reported that some colorectal cancer patients were known to experience GI perforations, the POSA would have found it obvious to perform the claimed assessment. Once again, this argument conflicts with standard oncology practice including Dr. Neugut's own experience.

The Petition cites two references for the proposition that there exists some association between GI cancer and GI perforations. Ex. 1002 ¶¶ 96–97. The first—Kennedy & Spence—discloses only that GI perforation is among the "most common [GI] *emergencies* in cancer patients." Ex. 1007 at 3 (emphasis added). This publication provides no information about the actual percentage of GI cancer patients who suffer perforations, whether GI cancer patients experience perforations at a higher than average rate, or whether GI cancer patients should be assessed for GI perforation, Ex. 2011 ¶ 65. The second reference—Mandava—reports on a retrospective analysis of colorectal cancer patients that found 3.3% of such patients presented with a GI perforation. Ex. 1012 at 2; Ex. 2011 ¶ 65. From these publications, Dr. Neugut concludes that "it would have also been obvious to the POSA to assess patients receiving bevacizumab therapy for GI perforation because it was known at the time that GI-related cancers (GI cancer or other cancer types that have metastasized to the GI) were associated with GI perforation." Ex. 1002 ¶ 139.

This argument is wrong, first of all, because it depends on Dr. Neugut's proposed construction of "assessing . . . for [GI] perforation." For the reasons already discussed, that construction is incorrect.

But the argument is wrong even under Genentech's proposed construction, for it assumes that infrequent occurrences of GI perforations in GI cancer patients would drive the POSA to assess this population for perforations. Dr. Neugut himself agreed that such an assumption would be inaccurate, Ex. 2013 at 229, and Dr. Morse concurs, Ex. 2011 ¶ 63–69. Asked whether he takes diagnostic steps to determine whether his own GI cancer patients have suffered perforations, Dr. Neugut revealed that the mere fact that these patients have GI cancer does not cause him to take such action:

> Q. [E]arlier I had understood you to say you assess all of your patients for GI perforation, correct?
>
> A. Whenever I see them, yes.
>
> Q. Right. That assessment does not include for each of your patients sending them for a CT scan or an x-ray?
>
> A. That's correct.

Ex. 2013 at 229. Nor does he assess GI cancer patients for other serious medical emergencies that may occur in this population—*e.g.*, pancreatitis—without some

further indication the emergency in question has occurred. *See id.* at 220–22; Ex. 2011 ¶ 67; Ex. 2018 at 20–21.

Nor is Dr. Neugut (or the POSA) medically reckless for not undertaking such an assessment in light of these references. Ex. 2011 ¶¶ 63–69. Most GI cancers are lengthy in duration. *id.* ¶ 67; *see also* Ex. 2013 at 217–18. The average colorectal cancer patient, for example, will live with the disease for many years. Ex. 2011 ¶ 7; *see also* Ex. 2013 at 217–18 (explaining that "most people have cancer for decades before they present"). That a small percentage of them might experience a perforation at some point over these years would not motivate the POSA to assess such patients for GI perforations absent additional signs of a problem, which had not been reported for bevacizumab in the prior art. Ex. 2011 ¶ 67, 69; *see also id.* ¶ 57. Given the duration of these cancers, any continuous or regular perforation assessments would need to occur over a number of years, and these assessments are too costly—both in terms of resources and the burden to patients of undergoing medically unnecessary procedures—to perform over an extended period and as a matter of course on GI cancer patients. The rate of GI cancer patients suffering perforations is just not high enough to warrant these costs of continuous GI perforation assessments over the lifetime of the cancer. *See, e.g.*, *id.* ¶ 64 (citing Ex. 2017 at 3–19 (omitting GI perforations from discussion of the "more important syndromes and problems of [cancer] management" afflicting the

alimentary system); Ex. 2009 at 1 ("The incidence [of free perforation of gastric carcinoma] is less than 1% . . . and only two publications have appeared in the English literature over last 20 yr.")).

The circumstances of a patient receiving bevacizumab are entirely different. Ex. 2011 ¶ 67. As the inventors discovered, approximately 2% of bevacizumab patients experience GI perforations while on therapy. Ex. 2014 at 1. This was, in the contemporaneous words of the NCI, "unexpected." Ex. 2021 at 1. This elevated risk exists in a short window compared to the duration of a GI cancer. Ex. 2011 ¶ 67. Given the severity of GI perforations and the short course of treatment, knowledge that approximately 2% of bevacizumab patients experience a perforation could well lead a medical oncologist to practice the claimed method of administering bevacizumab and assessing a patient for GI perforation during treatment, rather than administering bevacizumab without taking this additional step. *Id.* This is particularly true in light of the fact that "[t]he majority of [GI perforation] cases occur[] within the first 50 days of initiation of Avastin." Ex. 2014 at 5.

Finally, Hospira's art on this point reflects the rates of cancer patients who *present with a perforation*—that is, patients who are diagnosed with GI cancer having already suffered a perforation. Ex. 2013 at 216–18. In those cases, the cancer is likely to have been present for years already, *id.* at 18, and, in its

advanced state, is far more likely to have interfered with the integrity of the wall of the GI tract, Ex. 2011 ¶ 68. This is entirely different from a patient under treatment with bevacizumab for previously diagnosed GI cancer. In the latter group of patients, not only is the cancer not necessarily so advanced, but, in the cases of metastatic colorectal cancer in particular, the primary tumor is likely to have been removed, erasing the danger of perforation through tumor interference with the GI tract wall. Ex. 2011 ¶ 68. The POSA would not view the rates at which patients present with perforations to be revealing of perforation rates in GI cancer patients under treatment. *Id.* ¶¶ 68–69.

C. That Some Chemotherapy Patients Experienced GI Perforations Does Not Render The Invention Obvious.

Hospira makes a similar argument based on the "well-known [fact] that GI perforation was associated with systemic chemotherapy due to the weakening of the GI wall." Pet. 48 (citing Ex 1002 ¶¶ 79, 139–40). It is deficient for many of the same reasons.

Again, to begin with, the argument relies on the same flawed, overbroad construction of "assessing."

Under a proper construction of "assessing" (Genentech's), the supposed link with chemotherapy would not have made it obvious for the POSA to assess bevacizumab patients for GI perforations. Chemotherapy-related perforations were

understood to be uncommon, and given the rarity of these events, the POSA would not have gone so far as to take diagnostic steps to determine whether a patient receiving bevacizumab and chemotherapy had experienced a perforation. Ex. 2011 ¶¶ 70–74. As in the case of the GI cancer-perforation association, the costs of these assessments outweigh the potential benefits. *Id.*

The proof, once again, is in what Dr. Neugut does in practice instead of what he says as a litigation expert. With his own chemotherapy patients he does not take such diagnostic steps, *see* Ex. 2013 at 229–30, nor does he even warn these patients they are at risk for GI perforation just because they are on chemotherapy, *see id.* at 31. With the benefit of Genentech's invention, he now *does* deliver that warning when he puts them on Avastin®. *Id.* at 26.

Dr. Neugut's declaration also overstates the relationship between chemotherapy and GI perforations. As Dr. Neugut conceded at his deposition, GI perforations were not understood to be a common side effect of chemotherapy in 2003. *Id.* at 169–70. Literature on the subject was consistent with this view. *See* Ex. 2006 at 2 (failing to list GI perforations as one of the "commonest GI complications of chemotherapy" or one of the underlying causes of those complications). And the handful of prior art references that Dr. Neugut draws upon only reinforce this point. Most—Hata (Ex. 1009), Wada (Ex. 1010), Liaw (Ex. 1013), and Fata (Ex. 1014)—are case reports disclosing incidents in which

chemotherapy was thought to have led to a GI perforation. But the very purpose of such case reports is to flag a *rare* event for attention in the relevant medical community. Ex. 2013 at 176. There would be no need for such reports were it true, as Hospira suggests, that chemotherapy-induced perforations were so widespread and well known that the POSA would have assessed all chemotherapy patients for that condition.[8]

Finally, the history of the Avastin® clinical trials, and in particular, the reaction of FDA to the discovery of the link between bevacizumab and GI perforation, underscores the nonobviousness of "assessing . . . for [GI] perforation" patients receiving chemotherapy. Ex. 2011 ¶¶ 75–76. When the inventors learned that patients receiving bevacizumab were at risk for GI perforations, there were a number of bevacizumab clinical trials in progress, most of which involved combination therapy with chemotherapeutic agents. *See id.* The discovery of the bevacizumab-GI perforation association provoked rapid changes in the conduct of these studies. *See id.* As noted above, the NCI promptly warned investigators of

[8] The remaining reference is Kennedy & Spence, a publication provided to Dr. Neugut by Petitioner's counsel, Ex. 2013 at 196, focusing on one particular class of chemotherapeutic agents (taxanes) that were suspected to have some association with GI perforations. Ex. 1007 at 9.

this "unexpected" side effect and required investigators to submit proposed amendments to their clinical trial protocols and patient informed-consent forms within thirty days, so as to alert physicians and trial subjects to the danger of GI perforation. Ex. 2021 at 1–2; *see also* Ex. 2011 ¶¶ 75–76. And, as Dr. Neugut acknowledges, once the inventors discovered the link between bevacizumab and this dangerous adverse event, patients with a history of GI perforation were excluded from the Avastin® clinical trials. *See, e.g.*, Ex. 2013 at 36–38; *see also* Ex. 2004 at 1.

None of this makes sense if, as Hospira suggests, a method of "assessing the patient for [GI] perforation" been obvious for all patients receiving chemotherapy . There would have been no need for the NCI's Action Letter and the subsequent changes to the clinical trial protocols and informed consent forms—the various protocols and forms *already* would have warned of such a risk because the same patients receiving bevacizumab also received chemotherapy. Had the claimed method been so obvious, patients with a history of GI perforations *already* would have been excluded from the trials. Hospira's obviousness challenge rests upon an untenable assumption that the leading clinical investigators across the country should have known of the danger of perforations in chemotherapy patients but for years inexplicably failed to warn clinical trial participants or exclude those at particular risk.

The effect of the inventors' discovery on the bevacizumab trials also serves as objective indicia of the nonobviousness of the claimed methods. "Objective indicia of nonobviousness play a critical role in the obviousness analysis." *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Any objective evidence that tends to establish nonobviousness at the time of invention can be considered. *Cyclobenzaprine*, 676 F.3d at 1079. The actions of relevant government agencies can be considered for this purpose. *See Leo Pharm.*, 726 F.3d at 1358 (FDA decisions "can be relevant in evaluating the objective indicia of nonobviousness"). Here, the NCI's response to the discovery of the bevacizumab-GI perforation link and the changes to the clinical trials provide unbiased, contemporaneous evidence of nonobviousness. Ex. 2011 ¶ 77. Such objective evidence should play a "critical" role in the Board's assessment of this Petition, *Leo*, 726 F.3d at 1358, and demonstrates that the patentability of the claims should be confirmed.

D. That Some Bevacizumab Patients Exhibited "Symptoms" Associated with GI Perforations Does Not Render The Invention Obvious.

Finally, Hospira argues that Kabbinavar and the 2000 Press Release teach "that some of the patients receiving bevacizumab experienced symptoms that were known at the time to be associated with GI perforation,"— in particular, "acute severe abdominal pain, nausea, diarrhea, GI hemorrhaging, and fever" in

Kabbinavar,[9] *id.* at 48, and "fever and chills" in the 2000 Press Release, *id.* at 52—and so the POSA would have found it obvious to assess bevacizumab patients for GI perforation in light of those symptoms. Pet. 48–49; *see also id.* at 51–52.

If Hospira is suggesting the occurrence of any one of these adverse events in the Avastin® clinical trials would lead the POSA to assess for GI perforations in bevacizumab patients, that ignores that such toxicities are widely observed in cancer patients receiving chemotherapy, Ex. 2011 ¶¶ 78, 80–81; *see also* Ex. 2013 at 52, yet medical oncologists do not routinely take diagnostic steps to check patients receiving other cancer drugs for perforations without some further motivation, Ex. 2011 ¶¶ 78, 80–81; Ex. 2013 at 229–30. 5-Fluorouracil, for example—a common cytotoxic agent—is associated with GI hemorrhage, diarrhea, and nausea, Ex. 2011 ¶ 80, but Dr. Neugut does not take diagnostic steps to determine whether his patients receiving this treatment have experienced a GI perforation absent some additional sign that a perforation has occurred, *see* Ex. 2013 at 229–30; *see also id.* at 31. The POSA would not have been driven to assess for GI perforation simply because a handful of symptoms characteristic of any number of medical problems or treatments surfaced in the bevacizumab

[9] Dr. Neugut notably does not view diarrhea as a symptom of GI perforation. Ex. 2013 at 119.

clinical trials.[10] If anything, Kabbinavar and the 2000 Press Release would have led the POSA in the opposite direction, *see* Ex. 2011 ¶¶ 78, 80–81, as they omitted GI perforations entirely from their lists of adverse events observed, *id.* ¶¶ 53, 57; Ex. 2013 at 93, 124; Ex. 1004; Ex. 1005, and Kabbinavar was explicit that the "most significant" of these events was thrombosis, Ex. 1005 at 2.

If Hospira is suggesting that these two references would motivate the POSA to assess bevacizumab patients for GI perforations because *multiple* symptoms of GI perforations were observed in the Phase II trial, that argument misreads those references. Ex. 2011 ¶ 78–79. Neither Kabbinavar nor the 2000 Press Release discloses that any particular patient experienced more than one of the supposed GI perforation symptoms listed in the Petition. *Id.* Faced with a single patient suffering from "acute severe abdominal pain, nausea, diarrhea, GI hemorrhaging, and fever," the POSA might well assess for GI perforation, but no such patient is disclosed in Kabbinavar or the 2000 Press Release. Ex. 2011 ¶ 78–79; Ex. 2013 at 113–14.

[10] *See, e.g.*, Ex. 2013 at 52 ("Q. And so what does observing or hearing that the patient . . . has nausea contribute to an assessment of whether they have a GI perforation? A. Of itself, very little. . . .").

E. The POSA Would Not Have Found It Obvious to Assess Patients Receiving Bevacizumab for GI Perforation In View of Matsui.

Although Matsui does not form the basis for Petitioner's challenges under Grounds 5 or 7, the Board's Institution Decision noted that "Petitioner's expert Dr. Neugut relies upon the teachings of [Matsui] to support relevant statements made in his declaration" and explained that the Board therefore would consider Matsui as relevant "background art." Paper 7 at 5, n.8. As an initial matter, Genentech respectfully disagrees that Matsui is relied upon by Dr. Neugut to support any relevant statement in his Declaration. In the only paragraph of his declaration that mentions Matsui and is cited by the Board as discussing relevant background art, Dr. Neugut argues the POSA would have appreciated that there might exist a connection between GI perforation and bevacizumab itself. Ex. 1002 ¶ 104. This argument does not appear in any of the Grounds on which trial has been instituted.

Even if Matsui were relevant to Grounds 5 or 7, however, it still should not be considered by the Board, as it is nonanalogous art. "To qualify as prior art for an obviousness analysis, a reference must qualify as 'analogous art, *i.e.*, it must satisfy one of the following conditions: (1) the reference must be from the same field of endeavor; or (2) the reference must be reasonably pertinent to the particular problem with which the inventor is involved." *K-TEC, Inc. v. Vita-Mix Corp.*, 696

F.3d 1364, 1375 (Fed. Cir. 2012). Neither hurdle is cleared in this case. Ex. 2011 ¶ 86.

As Dr. Neugut acknowledges with his definition of the POSA, the relevant field of endeavor here is medical oncology. Matsui, on the other hand, is an article in the gastroenterology journal *Digestion*. Both parties' experts are in express agreement: this gastroenterology journal is not a publication the POSA, a medical oncologist, would have consulted.[11] Ex. 2011 ¶ 86; Ex. 2013 at 223.

Nor is Matsui "reasonably pertinent to the particular problem with which the inventor is involved." "A reference is reasonably pertinent if it, as a result of its subject matter, logically would have commended itself to an inventor's attention in considering his problem." *K-TEC, Inc.*, 696 F.3d at 1375 (internal quotation marks omitted). The relevant prior art problem here was accomplishing the safe use of bevacizumab, *i.e.*, the avoidance and mitigation of drug toxicities. Matsui, on the other hand, was concerned with what role VEGF could play in *healing* gastric

[11] Even if *Digestion* were a journal that *Dr. Neugut* would have consulted at the time, his experience in the area of gastroenterology is not representative of the experience of the POSA, a medical oncologist with no particular gastrointestinal focus. Ex. 2013 at 122, 214 (identifying himself as a *gastrointestinal* oncologist).

mucosal injury.[12] Ex. 2011 ¶¶ 82–86. Matsui says nothing whatsoever about whether an anti-VEGF agent would *cause* gastrointestinal injury even in rats, let alone in humans on bevacizumab. Ex. 1008; *see also* Ex. 2011 ¶¶ 86–87. Petitioner offers no explanation as to why the POSA would have considered Masui, given that it was directed to an entirely separate problem. *In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992). ("If [a reference] is directed to a different purpose, the inventor would accordingly have had less motivation or occasion to consider it.").

Finally, even were the Board to consider Matsui in evaluating Grounds 5 and 7, this reference adds nothing to Petitioner's obviousness challenge. Ex. 2011 ¶¶

[12] Matsui reported the results of an animal study regarding the effects of VEGF following acute gastric injury. Specifically, the researchers inflicted gastric damage on rats through administration of pure ethanol and then evaluated the effect of administering recombinant human VEGF or an anti-angiogenic rabbit anti-human VEGF antibody. Matsui reported "an increase in gastric damage in animals treated with anti-VEGF" and that "administration of VEGF after the onset of injury reduced the severity of experimentally induced gastric mucosal injury." Ex. 1008 at 8. The article concluded that "VEGF appears to be an important endogenous mediator of the healing process for gastric injury." *Id.* at 10.

82–85, 87. Matsui disclosed that rabbit anti human-VEGF antibody might impair gastric wound healing and that VEGF might reduce the severity of gastric injury. According to Dr. Neugut, bevacizumab was known to be a VEGF–neutralizing antibody, and "Matsui et al. would have provided the motivation for the POSA to perform the known step of assessing for GI perforation in patients receiving bevacizumab in order to provide safe and effective treatment." Ex. 1002 ¶ 147. But there are several holes in Dr. Neugut's logic that Matsui is incapable of filling.

Specifically, Matsui never explained (i) whether the anti-angiogenic agent used in the study was remotely comparable to bevacizumab, (ii) whether the results of the study could be extrapolated to humans, (iii) whether the gastric injury created in the study was relevant to naturally occurring gastric injury, (iv) whether other angiogenic factors in humans might counter the effect of VEGF inhibition, or (v) whether the impaired wound *healing* caused by VEGF inhibition was at all revealing of the potential for *causing* a gastric injury (like a GI perforation). *See* Ex. 2011 ¶ 87. Dr. Neugut does not explain how the POSA would have made each of these at least five logical leaps to reach his conclusion. *Id.*

Further, if the POSA would have "understood from Matsui et al. that treatment with bevacizumab might exacerbate any existing GI tissue damage or even promote new GI tissue damage," patients with a history of GI perforation issues would never have been enrolled in trials for this drug. In reality, their

exclusion did not occur until after the inventors made their discovery. Ex. 2013 at 36–38; *see also* Ex. 2004 at 1.

It is only through hindsight that Dr. Neugut can make this argument now. Where, as here, "hindsight provides the only discernable reason to combine the prior art references" so as to arrive at the claimed invention, the invention is nonobvious. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc*., 688 F.3d 1342, 1369 (Fed. Cir. 2012).

CONCLUSION

For the foregoing reasons, the Board should reject Hospira's challenges to claims 1–5 of the Fyfe Patent.

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CERTIFICATION OF WORD COUNT
(37 C.F.R. § 42.24(d))

In accordance with 37 C.F.R. § 42.24, as amended, the undersigned certifies that this Patent Owner Response complies with the applicable type-volume limitations of 37 CFR §§ 42.24(a)(i) and 42.24(b)(2). Exclusive of the portions exempted by 37 CFR 42.24(a), this Patent Owner Response contains 10,031 words as counted by the word processing program used for its preparation (Microsoft Word 2013).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the above-captioned *Patent Owner Response* and all Exhibits and other documents filed together with this *Patent Owner Response* were served on June 13, 2017 by filing these documents through the Patent Review Processing System as well as delivering a copy via electronic mail upon the following attorneys of record for the Petitioner:

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