UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOSPIRA, INC.,
Petitioner

v.

GENENTECH, INC.,
Patent Owner

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

Inter Partes Review No. 2016-01771

PETITIONER REPLY

Petitioner, Hospira, Inc., ("Hospira") submits this Petitioner Reply to the Patent Owner Response ("Response") filed by Patent Owner Genentech, Inc. ("Genentech") on June 13, 2017.

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Appendix of Exhibits

(Filed Pursuant to 37 C.F.R. § 42.6)

Hospira Exhibit Number	Description
1001	U.S. Patent No. 7,622,115 to Fyfe et al.
1002	Declaration of Alfred Neugut, M.D., with Exhibits
1003	Genentech Press Release, *Phase III Trial of Avastin Plus Chemotherapy Markedly Extends Survival of Metastatic Colorectal Cancer Patients* (May 19, 2003), http://www.gene.com/media/press-releases/6147/2003-05-19/phase-iii-trial-of-avastin-plus-chemothe
1004	Genentech Press Release, *Anti-VEGF Monoclonal Antibody with Chemotherapy Demonstrates Preliminary Positive Phase II Results in Colorectal Cancer* (May 21, 2000), http://www.gene.com/media/press-releases/4617/2000-05-21/anti-vegf-monoclonal-antibody-with-chemo
1005	Kabbinavar et al., *Phase II, Randomized Trial Comparing Bevacizumab Plus Fluorouracil (FU)/Leucovorin (LV) With FU/LV Alone in Patients With Metastatic Colorectal Cancers*, 21 J. OF CLIN. ONCOLOGY 60-65 (2003)
1006	Margolin et al., *Phase Ib Trial of Intravenous Recombinant Humanized Monoclonal Antibody to Vascular Endothelial Growth Factor in Combination With Chemotherapy in Patients With Advanced Cancer: Pharmacologic and Long-Term Safety Data*, 19 J. OF CLIN. ONCOLOGY 851-856 (2001)
1007	Kennedy & Spence, Chapter 6: *Gastrointestinal Emergencies*, ONCOLOGIC EMERGENCIES, 117-152 (Oxford Univ. Press 2002)
1008	Matsui et al., *Efficacy of Vascular Endothelial Growth Factor in the Treatment of Experimental Gastric Injury*, 66 DIGESTION 99-105 (2002)
1009	Hata et al., *Intestinal Perforation Due to Metastasis of Breast Carcinoma, with Special Reference to Chemotherapy: a Case Report*,

	31 JPN. J. CLIN. ONCOL 162-164 (2001)
1010	Wada et al., *Spontaneous gastrointestinal perforation in patients with lymphoma receiving chemotherapy and steroids*, 66 J. NIPPON MED. SCH. 37-40 (1999)
1011	Reese et al., *A Phase II Trial of Humanized Anti-Vascular Endothelial Growth Factor Antibody for the Treatment of Androgen-Independent Prostate Cancer*, 3 THE PROSTATE JOURNAL, 65-70 (2001)
1012	Mandava et al., *Perforated Colorectal Carcinomas*, 172 THE AMERICAN JOURNAL OF SURGERY 236-238 (1996)
1013	Liaw et al., *Spontaneous Gastrointestinal Perforation in Patients with Cancer Receiving Chemotherapy and Steroids*, 72 CANCER 1382-1385 (1993)
1014	Fata et al., *5-Fluorouracil-Induced Small Bowel Toxicity in Patients with Colorectal Carcinoma*, 86 CANCER 1129-1134 (1999)
1015	Gordon et al., *Phase I Safety and Pharmacokinetic Study of Recombinant Human Anti-Vascular Endothelial Growth Factor in Patients With Advanced Cancer*, 19 JOURNAL OF CLINICAL ONCOLOGY 843-850 (2001)
1016	National Cancer Institute Common Toxicity Criteria Manual Version 2.0, June 1, 1999, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf (last visited August 27, 2016) ("1999 NCI CTC v.2 Manual")
1017	National Cancer Institute Common Toxicity Criteria Version 2.0, April 30, 1999, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf (last visited August 27, 2016) ("1999 NCI CTC v.2")
1018	U.S. Provisional Application No. 60/474,480 filed May 30, 2003 ("'480 Provisional Application")
1019	Excerpts from Certified Prosecution File History of U.S. Application No. 10/857,249 filed May 28, 2004 ("'249 Application Prosecution History Excerpts")

1020	Excerpts from Certified Prosecution File History of U.S. Patent No. 7,622,115 filed June 14, 2007 ("'115 Patent Prosecution History Excerpts")
1021	Jones et al., *Gene Therapy for Gastric Ulcers With Single Local Injection of Naked DNA Encoding VEGF and Angiopoietin-1*, 121 GASTROENTEROLOGY 1040-1047 (2001)
1022	Singh et al., *Evolution of imaging for abdominal perforation*, 92 ANN. R. COLL. SURG. ENGL. 182-88 (2010)
1023	Yeung et al., CT evaluation of gastrointestinal tract perforation, 28 J. OF CLIN. IMAGING 329-333 (2004)
1024	Wong et al., *A Phase II Study of Oxaliplatin, Dose-intense Capecitabine, and High-dose Bevacizumab in the Treatment of Metastatic Colorectal Cancer*, 10:3 CLIN. COLORECTAL CANCER 210-16 (2011)
1025	Supplemental Declaration of Alfred Neugut, M.D., with Exhibits
1026	July 21, 2017 Deposition Transcript of Michael A. Morse, MD, FACP, MHS
1027	July 19, 2017 Deposition Transcript of Angel D. Levy, MD
1028	Morse et al., *Supportive Care in the Management of Colon Cancer*, 3:3 SUPPORTIVE CANCER THERAPY, 168-179 (2006)
1029	Therasse et al., *New Guidelines to Evaluate the Response to Treatments in Solid Tumors*, 92:3 J. OF THE NATIONAL CANCER INSTITUTE 205-216 (2000)

Genentech does not dispute in its Response that United States Patent No. 7,622,115 (the "'115 Patent") is invalid under Hospira's proposed claim construction. Rather, Genentech bets the farm on an improperly narrow claim construction for the "assessing" limitation of claim 1 that ignores the plain and ordinary meaning of "assessing" in the medical context, has no support in the intrinsic record, and ultimately fails to rescue the '115 Patent claims from being anticipated by and obvious over the prior art of the instituted grounds.

I. THE EVIDENCE OF RECORD SUPPORTS HOSPIRA'S CONSTRUCTION OVER GENENTECH'S

Hospira proposes construing the claim 1 language "assessing the patient for GI perforation" to mean "evaluating the patient in any way that might provide information about whether the patient might be experiencing a GI perforation." That construction reflects the plain and ordinary meaning of the term "assessing" in the context of GI perforation and is supported by the intrinsic record as explained in Hospira's September 9, 2016 Petition ("Petition") and herein. Genentech's proposed construction—"taking diagnostic steps to determine whether a GI perforation exists"—imports multiple new limitations into claim 1. (Response at 2.) Notably, Genentech identifies ***no*** intrinsic evidence to affirmatively support its construction. Rather, Genentech relies entirely on the opinion of Dr. Michael Morse, an oncologist who has regularly consulted with

Genentech and worked on Genentech clinical trials since the late 1990s.[1] (Ex. 1026 at 8:2-14:20.)

A. Genentech's Construction Improperly Imports Multiple Limitations into Claim 1

Genentech explains that its construction requires "taking steps to actually ***confirm the presence of*** the condition." (Response at 20 (emphasis added)) and that "diagnostic steps" include "CT scans and radiograpy, as both techniques are ***able to confirm the presence of*** a Perforation." (*Id*. at 14 (emphasis added).) Additionally, Genentech explains that its construction requires that the diagnostic steps "must have been performed ***for the purpose of*** determining whether a perforation had occurred." (*Id*. at 21 (emphasis added).) Regarding the "purpose" limitation, Dr. Morse explains "[t]hat diagnostic steps that were performed for some other reason were also potentially *capable of* detecting a GI perforation would not be viewed by the POSA as assessing the patient for GI perforation." (Ex. 2011 at ¶ 54 (emphasis in original).) According to Genentech's construction, a diagnostic step that, in fact, results in detection of signs of GI perforation might or might not constitute "assessing" for GI perforation depending on the physician's mental impression as to its purpose. (*See* Response at 21; Ex. 1026 at 152:3-

[1] Dr. Morse estimated that he earned about $65,000 to $70,000 in 2016 from Genentech work. (Ex. 1026 at 14:5-14:20)

153:9.) As explained below, there is no support in the intrinsic record for these additional limitations.

B. CT Scans and X-Rays Do Not "Confirm" a GI Perforation

Genentech attempts to support and distinguish its construction from Hospira's by asserting that the diagnostic steps it identifies—e.g., CT scans and X-rays—can ***confirm*** the presence of a GI perforation. (Response at 14 and 20.) But as Genentech's expert, Dr. Morse testified, such techniques ***do not*** confirm a GI perforation, but simply serve to provide additional information about its likelihood. (Ex. 1026 at 53:4-58:7.) And Dr. Morse also explained that other methods of evaluating for GI perforation, such as taking a medical history or performing a physical examination, also accomplish the same function. (*Id*. at 93:7-18.) Consequently, Genentech's position that a CT scan or X-ray constitutes "assessing," but a physical examination does not is at best arbitrary and at worst wholly motivated by Genentech's desire to narrow the claims in a failed attempt to avoid the prior art.

C. Genentech's Construction is Incompatible with the Plain and Ordinary Meaning of "Assessing" in the Medical Context

Hospira explained why its construction reflects the plain and ordinary meaning of "assessing" in the context of GI perforation at the time of the alleged invention in its Petition and provides additional evidence in this Reply. (Petition at 16-18.) The plain and ordinary meaning of "assessing" for GI perforation does not

require "confirming" or "diagnosing" or performing any specific method of evaluation as Genentech proposes. (Ex. 1002 at ¶¶ 92-93; Ex. 1025 at ¶¶ 12-17, 20-26.) Rather, "assessing" simply refers to performing an evaluation that provides information about the likelihood of a GI perforation. (Ex. 1002 at ¶ 91; Ex. 1025 at ¶ 13, 18.)

Moreover, the Skilled Artisan would have understood the plain and ordinary meaning of "assessing" for GI perforation to include performing any evaluation that ***is capable*** of identifying signs of a GI perforation. (Ex. 1002 at ¶¶ 91-93, 112, 125; Ex. 1025 at ¶¶ 12, 18-26.) Indeed, the Skilled Artisan would have understood that when evaluations such as physical exams or CT scans capable of identifying signs of GI perforation are performed on patients being treated for cancer, the evaluations are performed for the purpose of identifying any adverse effects the patient is experiencing, including GI perforation. (*Id*.) As Dr. Neugut explains, Genentech's construction ignores that aspect of actual medical practice and results in the paradoxical scenario where patients are diagnosed with a GI perforation without actually having been "assessed" for GI perforation because the "diagnostic step" that led to the diagnosis was not performed for the purpose of determining whether a GI perforation exists. (Ex. 1025 at ¶ 19.) Dr. Neugut explains that the Skilled Artisan would not have understood the plain and ordinary meaning of "assessing" for GI perforation to exclude situations where a patient is actually

diagnosed as having a GI perforation. (Ex. 1025 at ¶ 19.) Dr. Neugut also explains that patients who experience a GI perforation that presents indolently, as Dr. Morse describes, would not be "assessed" under Genentech's construction because a physician would not suspect such patients of having GI perforations and therefore would not request a CT scan or X-ray to determine whether the patient has a GI perforation. (Ex. 1025 at ¶ 16.)

Additionally, the prior art identifies the steps of taking a medical history and performing a physical examination as an "assessment" for GI perforation and therefore supports Hospira's construction over Genentech's. (Ex. 1025 at ¶ 17; Ex. 1007 at 9.) For example, Kennedy & Spence describes how to perform a "clinical assessment" for GI perforation in Section 6.3.1, titled "Clinical Assessment" which includes (1) taking a medical history and (2) performing a physical examination to look for "severe abdominal tenderness and guarding," "abdominal distention," "absent bowel sounds," "elevated temperature," and "hypotension." (*Id*.) There is no mention of CT scans or X-rays in the "Clinical ***Assessment***" section. (*Id*.) Indeed, Kennedy & Spence does not use the term "clinical assessment" to refer to "diagnostic steps" such as CT scans or X-rays. (*Id*.)

Even Dr. Morse recognizes that Genentech's construction is inconsistent with his own use of the term "assessment" in prior clinical publications. For example, in a 2011 bevacizumab clinical study publication, Dr. Morse and his

coauthors reported two cases of GI perforation. (Ex. 1024 at 15.) The "Patient Evaluation" section describes that "toxicity and safety ***assessments*** . . . . included vital signs, ECOG performance status, ***medical history***, ***physical examination***, ..." (*Id*. at 13.) Dr. Morse used the term "assessments" similarly as in Examples 1 and 2 of the '115 Patent to describe the safety evaluation on the study subjects. (Ex. 1001 at 42:18-35, 48:40-47.) When asked about his prior use of that term to describe taking a medical history and physical examinations, Dr. Morse responded:

> You know, again, the terminology of "assessment," I would have probably used a ***different word*** compared to what's the ***meaning of "assessment" for our purposes today***.

(Ex. 1026 at 177:19-22.) But Dr. Morse did not use a different word then and is now performing the claim construction analysis backwards. Instead of relying on the plain and ordinary meaning of "assessing" as evidenced by its use in the relevant art to interpret the claim, Dr. Morse begins with a presumption that Genentech's preferred construction is correct and attempts to explain away the inconsistency with how the term is candidly used in that art.

For these reasons, Genentech's construction is incompatible with the plain and ordinary meaning of "assessing the patient for gastrointestinal perforation."

D. The Intrinsic Evidence Supports Hospira's Construction Over Genentech's

Notably, Genentech and Dr. Morse point to ***no*** intrinsic evidence to affirmatively support Genentech's narrow construction. Indeed, there is no support in the intrinsic record for the limitations that Genentech now wants to import into claim 1—(1) taking diagnostic steps that confirm a GI perforation and (2) having the mental impression that such steps are performed for the specific purpose of determining whether a GI perforation exists. (1025 at ¶ 23.)

The only disclosure related to GI perforation in the specification is that eight subjects who received bevacizumab experienced a GI perforation, two of whom died, and that GI perforation is a "new potential adverse effect" associated with bevacizumab. (Ex. 1001 at 46:18-27; 50:49-54; 47:6-22.) But the specification does not describe how the eight GI perforations were detected as Dr. Morse admitted. (Ex. 1026 at 153:10-154:3.) In particular, the specification does not disclose whether the perforations were identified through diagnostic steps taken to determine whether a GI perforation exists. (1025 at ¶ 22.) Indeed, Dr. Morse revealed that in the cases of the two deceased subjects, the perforations might have been identified by autopsy. (Ex. 1026 at 154:4-155:8.) Because the specification does not teach how the reported GI perforations were identified, the mere fact of their occurrence does not support Genentech's narrow construction. In contrast,

Hospira's construction is consistent with the limited disclosure because it does not require any specific method of evaluation or mental impression.

On the other hand, the disclosures in the specification regarding safety assessments in Examples 1 and 2 and the identification of those specific disclosures by Genentech during prosecution as supporting the "assessing" limitation is informative, if not, determinative. In response to the new matter rejection described below, Genentech replaced the existing language with the "assessing" limitation and argued that there is support for the limitation because "the instant application describes ***generally*** how safety was assessed in patients being treated with bevacizumab in the clinical trial described in Examples 1 and 2." (Ex. 1020 at 111.) Genentech's statement to the examiner is inconsistent with Genentech's narrow construction, which requires particular diagnostic tests and those performing them to have specific mental impressions as to their purpose.

In particular, Genentech identified passages in Examples 1 and 2 under the heading "Assessments," which describe how safety was assessed, as providing support. (*Id*. at 111-112.) Those passages do not identify any particular diagnostic test capable of confirming GI perforation or any particular sign or symptom of GI perforation and make no reference regarding a physician's mental impressions. Rather, those passages teach performing general medical evaluations such as measuring vital signs and performing laboratory testing. (Ex. 1025 at ¶ 21.) In

contrast, Hospira's construction, which does not require any particular method of evaluation, reflects the general nature of that disclosure as understood and argued by Genentech during prosecution.

Additionally, Genentech's construction is inconsistent with the reason the "assessing" limitation was added. The examiner had rejected amended claim 47 under 35 U.S.C. § 112 because the new limitation "monitoring the patient for signs or symptoms of gastrointestinal perforation during treatment with the anti-VEGF antibody" constituted ***new matter without proper written description in the specification***. (Ex. 1020 at 94-95 (emphasis added).) The examiner argued that the cited support for the new claim "***does not disclose any signs or symptoms*** of gastrointestinal perforation, or ***methods comprising monitoring patients for signs or symptoms*** of gastrointestinal perforation." (*Id*. at 96-97 (emphasis added).) Genentech replaced "monitoring for signs or symptoms" with the "assessing" limitation. Therefore, Genentech and the examiner understood that the "assessing" limitation is not limited to performing any particular method of evaluation or evaluating for any particular symptom or sign. But now Genentech is inconsistently advocating for a narrow construction that requires specific diagnostic tests (i.e., ***methods***) that detect specific ***signs*** of GI perforation—i.e., air in the peritoneum. In contrast, Hospira's construction, which is not so limited, reflects that understanding.

Moreover, under Genentech's construction, claim 1 would be invalid under 35 U.S.C. § 112 for lack of written description because there is no description in the specification or the original claims of "taking diagnostic steps to determine whether a GI perforation exists." As explained above, Dr. Morse testified that the patent does not say specifically how the eight GI perforations were identified. (Ex. 1026 at 153:23-154:3.) In fact, Dr. Morse even testified that the patent does not "specifically say people were assessed for perforation" (*id*. at 153:10-20) and could not recall whether the phrase "assessing for GI perforation" appears in the patent. (*Id*. at 118:22-119:21.) Clearly, the Board should not adopt a construction resulting in a claim for which there is no written description support.

Because Genentech's narrow construction imports multiple limitations that have no support in the intrinsic evidence and is inconsistent with the prosecution history, it cannot be the broadest reasonable construction in view of the specification. In contrast, Hospira's construction reflects the broad level of disclosure in the specification relating to GI perforation and safety assessments. For the reasons explained in the Petition and herein, the Board should adopt Hospira's construction.

II. CLAIMS 1 TO 5 ARE INVALID PURSUANT TO THE INSTITUTED GROUNDS

Kabbinavar anticipates claims 1 to 5 of the '115 Patent pursuant to Instituted Ground 1, and Kabbinavar and the 2000 Press Release each renders claims 1 to 5

obvious pursuant to Instituted Grounds 5 and 7 under either Hospira's or Genentech's construction.

A. Genentech Does Not Dispute the Invalidity of the '115 Patent Claims Under Hospira's Construction

Genentech does not dispute the invalidity of the '115 Patent claims according to any of the Instituted Grounds under Hospira's construction for the "assessing" limitation. In fact, Genentech and its expert Dr. Morse expressly admit that at least claim 1 is anticipated by Kabbinavar under Hospira's construction. (Response at 18-19; Ex. 2011 at ¶51.) Moreover, Genentech does not assert that there are other limitations in claim 1 or dependent claims 2 to 5 that are not described in Kabbinavar or that render claims 1 to 5 nonobvious in view of Kabbinavar or the 2000 Press Release under Hospira's construction. Thus, under Hospira's construction, Kabbinavar anticipates claims 1 to 5 pursuant to Ground 1 and Kabbinavar and the 2000 Press Release each render claims 1 to 5 obvious pursuant to Instituted Grounds 5 and 7, respectively, for the undisputed reasons explained in Hospira's Petition.

B. Kabbinavar Anticipates Claims 1 to 5 Under Genentech's Construction

The only limitation in any of the '115 Patent claims that Genentech disputes is found in Kabbinavar under Genentech's construction is the "assessing" limitation. (*See* Response at 22.) Genentech asserts that "it is undisputed that

Kabbinavar includes no disclosure of any physician taking diagnostic steps to determine whether a GI perforation exists." (*Id*. at 24.) Genentech is wrong because Kabbinavar teaches that the subjects receiving bevacizumab underwent regular CT scans that the Skilled Artisan would have understood (1) were performed to determine whether the subjects were experiencing any GI injury including GI perforation and (2) would have detected signs of GI perforation.

Kabbinavar teaches that the study subjects underwent regular "chest x-ray, abdominal and pelvis computed tomography scans" during the course of the study as part of their tumor evaluation. (Ex. 1005 at 3-4.) "[A]bdominal and pelvis computed tomography scans" are CT scans that image the abdomen and pelvis, respectively, and are the types of CT scans that a physician looking to determine whether a GI perforation exists would have performed at the time. (Ex. 1025 at ¶ 26.) Genentech's expert, Dr. Morse confirmed that Kabbinavar reports that all the subjects received the abdominal and pelvis CT scans. (Ex. 1026 at 39:6-16.)

The Skilled Artisan would have understood that the CT scans described in Kabbinavar were performed for the purpose of determining whether the subjects were experiencing any GI abnormality such as GI perforation. (Ex. 1025 at ¶¶ 27-29.) It was the standard of care at the time of the alleged invention to perform regular abdominal and pelvis CT scans as described in Kabbinavar for all colorectal cancer patients receiving therapy. (*Id*. at ¶ 27.) Such CT scans were

performed to evaluate the progress of any tumors and to evaluate the GI tract and other organs for any signs of abnormalities that the patient might be experiencing including GI perforation. (*Id*.) For example, Dr. Neugut explains that the abdominal and pelvic CT scans that he requested for his colorectal cancer patients receiving therapy in 2003 served both purposes, and that he expected the radiologist reviewing the CT scans to identify and report any GI abnormalities. (*Id*. at ¶ 29.)

Indeed, a radiologist reviewing a cancer patient's CT scan at the time would have been actively evaluating tumor progression, but also purposefully looking for any signs of GI abnormalities. For example, Genentech's expert Dr. Levy testified that she reports on everything that she sees in a CT scan—"***For every CT scan*** we report – regardless of whether it's [a] clinical trial, ***we report on everything we see***." (Ex. 1027 at 49:3-20 (emphasis added).) Similarly, Dr. Neugut explained that when he confers with a radiologist about CT findings for one of his colorectal cancer patients, the radiologist provides findings regarding the patient's tumors as well as any signs of GI abnormalities. (Ex. 1025 at ¶ 29.) Genentech's expert, Dr. Morse confirmed that radiologists report abnormalities detected in the CT scan regardless of why the scan was ordered (ex. 1026 at 61:18-62:1) and provided an example where one of his patients underwent a CT scan and the radiologist detected an abnormality that Dr. Morse believed was likely due to a GI perforation.

(*Id*. at 62:2-63:14.) Moreover, Dr. Morse admitted that there are instances where a CT scan performed for reasons other than to determine whether a GI perforation exists detects free air. (*Id*. at 63:24-64:7.) Therefore, the Skilled Artisan would have understood at the time of the alleged invention that the abdominal and pelvis CT scans described in Kabbinavar were performed to evaluate tumor progression ***and*** the GI tract for any abnormality, including signs of GI perforation and thus, were performed for the purpose of determining whether a GI perforation exists. (Ex. 1025 at ¶¶ 27-29.)

The Skilled Artisan would have also understood that the CT scans described in Kabbinavar would have detected signs of GI perforation**.** (Ex. 1025 at ¶¶ 30-31.) Genentech attempts to fend off the teachings of abdominal and pelvis CT scans in Kabbinavar by asserting that radiologists typically analyze CT scans using a "lung window" to determine whether a GI perforation exists instead of a "soft-tissue window", which is typically used to assess tumor progression, thereby suggesting that a radiologist might miss a GI perforation if using a "soft-tissue window". (Response at 9.) Genentech's argument fails, however, because it ignores how abdominal and pelvis CT scans such as those described in Kabbinavar are actually performed and misrepresents the ability of a radiologist to detect signs of GI perforation in a CT scan.

A radiologist reviewing the CT scans described in Kabbinavar would have performed a systematic examination of the scans for any sign of GI injury or abnormalities such as free air in the peritoneum, which is a sign of GI perforation. For example, Genentech's expert Dr. Levy testified that lung and soft-tissue windows are both used with abdominal CT scans (Ex. 2012 at 33:19-34:10) and that she utilizes a specific routine like all radiologists do when reviewing a CT scan which involves altering the windows and other settings[2]:

> Q. When you have a CT scan of a patient, do you typically as you are starting to read it have an initial setting in mind that you are going to use as far as windows?
>
> A. I have a ***specific routine***, mental checklist, and order of which I read a scan, ***which every radiologist does***, and ***you alter the window and level settings as you go through your routine***.
>
> Q. And as you go through your routine, do you alter the window based in part on what you are seeing in the scan?
>
> A. Yes.

(*Id*. at 35:22-36:4.) In fact, it was recommended practice at the time for a radiologist to switch through various windows when reviewing an abdominal or pelvis CT scan performed on GI cancer patients during therapy in order to obtain a

[2] Dr. Levy explained that the window settings can be adjusted in the analytical software and that it is not difficult to switch between lung and soft-tissue windows. (*See* Ex. 1027 at 34:22-35:1.)

complete picture of the patient's clinical condition. For example, Therasse et al.[3] describes guidelines for evaluating tumor progression in cancer patients receiving therapy. (Ex. 1029.) Therasse et al. instructs regarding the use of CT scans:

> All images from each examination should be included and not "selected" images of the apparent lesion. This distinction is intended to ensure that, if a review is undertaken, ***the reviewer can satisfy himself/herself that no other abnormalities coexist***. ***All window settings should be included***, particularly in the thorax, where the lung and soft-tissue windows should be considered.

(Ex. 1029 at 13 (emphasis added).) Because it was standard radiological practice to review CT scans such as those described in Kabbinavar using multiple windows and settings, Genentech's suggestion that a radiologist might miss a GI perforation if using a soft-tissue window is unconvincing.

Additionally, GI perforation is, in fact, readily detectable using both soft-tissue and lung windows. For example, Singh et al. (ex. 1022) and Yeung et al. (ex. 1023) report the use of CT scans for detecting signs of GI perforation. The publications teach that signs of GI perforation in a CT scan include the presence of free air, segmental bowel wall thickening, bowel wall discontinuity, stranding of mesenteric fat, and abscess formation. (Ex. 1022 at 5; Ex. 1023 at 6.) Genentech's expert, Dr. Levy agreed that those are signs of GI perforation (Ex. 1027 at

[3] Therasse et al., *New Guidelines to Evaluate the Response to Treatment in Solid Tumors*, 92:3 J. OF THE NATIONAL CANCER INSTITUTE, 205-216 (2000).

56:23:57:4) and testified that some of the signs are preferably identified using a soft-tissue window setting. (*Id*. at 55:1-56:12.)

Moreover, Dr. Levy testified that free air in the peritoneum can be seen using a soft-tissue window setting. For example, Dr. Levy testified that free air in the peritoneum can be seen in figures 4-5 and 9 in Singh et al. and figures 2 and 3 in Yeung et al. which Dr. Levy testified show CT scan images captured using a soft-tissue window. (*Id*. at 56:23-59:5; 67:15-68:10.) Similarly, Dr. Levy also testified that free air in the peritoneum can be seen in the soft-tissue window in the two sets of images included in her declaration. (*Id*. at 41:22-44:17.) Indeed, it is telling that Genentech has not provided one example where free air is detectable in a lung window, but not in a soft-tissue window. Thus, the Skilled Artisan would have understood that the abdominal and pelvis CT scans described in Kabbinavar would have detected signs of a GI perforation.

Because Kabbinavar teaches performing abdominal and pelvis CT scans on cancer patients receiving bevacizumab, it discloses "taking diagnostic steps to determine whether a GI perforation exists." And because the "assessing" limitation is the only limitation of claims 1 to 5 of the '115 Patent that Genentech argues is not disclosed by Kabbinavar under its construction, Kabbinavar anticipates claims 1 to 5 of the '115 Patent under Genentech's construction.

C. Kabbinavar and the 2000 Press Release Each Renders Claims 1 to 5 Obvious Under Genentech's Construction

Each claim of the '115 Patent would have been obvious to the Skilled Artisan at the time of the invention over either Kabbinavar or the 2000 Press Release in view of the knowledge of the Skilled Artisan. It is undisputed that Kabbinavar and the 2000 Press Release each describes "[a] method for treating cancer in a patient comprising administering an effective amount of bevacizumab." (Petition at 26-27, 29, 35-36, 38, 45, and 50; Ex. 1002 at ¶¶ 110-111, 122-124, and 135-136.) The additional step of "assessing the patient for GI perforation during treatment with bevacizumab" was also known and adds nothing novel or unobvious to claim 1 because it simply recites the standard of care at the time as explained in Hospira's Petition and in this Reply. (Petition at 2; Ex. 1002 at ¶ 11; Ex. 1025 at ¶¶ 34-37.)

Claim 1 ***does not*** require the actor-physician performing the "assessing" step to do ***anything*** beyond simply practice the standard of care at the time with respect to assessing for GI perforation. For example, claim 1 does not require the actor-physician to do anything differently for a patient receiving bevacizumab than for a patient not receiving bevacizumab with respect to the "assessing" limitation. Indeed, claim 1 does not require the actor-physician to assess the patient for GI perforation under circumstances that he would not have if the patient were not receiving bevacizumab. (Ex. 1025 at ¶¶ 35-36.) In fact, claim 1 does not even

require the physician to consider bevacizumab therapy as a factor in determining whether or how to assess the patient for GI perforation. (*Id*.) Because claim 1 does not require the actor-physician to do anything different with respect to assessing patients receiving bevacizumab for GI perforation than he would have done by practicing the standard of care at the time, there is nothing novel or nonobvious about the claimed subject matter.

Genentech and Dr. Morse, have ***not*** identified ***anything*** that claim 1 requires the actor-physician to do beyond merely practice the standard of care at the time. Genentech cannot do so because there is no disclosure in the specification for treating or managing a patient receiving bevacizumab with respect to GI perforation differently from the standard of care. (Ex. 1025 at ¶ 37.) In fact, as explained above there is no disclosure of how to assess any patient for GI perforation in the '115 Patent. For example, Dr. Morse admitted that the '115 Patent does not teach that the study protocols for Examples 1 and 2 required the physicians to assess the subjects for GI perforation (ex. 1026 at 114:12-19) and teaches that the reported GI perforations were identified using the standard of care at the time. (*Id*. at 114:12-115:2.) Thus, to the extent that Genentech observed a new and unexpected association between bevacizumab and GI perforation as it asserts, Genentech failed to draft claims that incorporate that observation in a way

that renders claims 1 to 5 novel and nonobvious over the prior art of the instituted grounds. (Ex. 1025 at ¶ 37.)

All the experts in this proceeding have testified that they do nothing differently for their cancer patients receiving bevacizumab versus those not receiving bevacizumab and that their practice is essentially the same now as it was back in 2003 with respect to assessing patients for GI perforation. For example, Dr. Neugut explained that his medical practice back in 2003 regarding patients who were not on bevacizumab is the same as for patients today receiving bevacizumab. (Ex. 1002 at ¶¶ 105-107; Ex. 1025 at ¶ 38.) Genentech's expert, Dr. Morse similarly testified that the process of determining whether or not to assess a patient for GI perforation is the same now as it was in 2003 and throughout his entire career:

> Q. In paragraph 33 you indicate that "When a physician suspects that a patient has experienced a GI perforation, he typically will request that diagnostic steps be taken to confirm the presence and ideally the location of the perforation." Is that right?
>
> A. Yes.
>
> Q. Has that always been the practice?
>
> A. I mean, so you're saying "always" predating the 2003 and since the 2003?
>
> Q. Yeah. Throughout your career.
>
> A. Yes.

Q. Has that practice changed at all through your career?

A. No. Essentially, in general, it's the same procedure.

(Ex. 1026 at 43:7-25.) Dr. Morse also testified that he assesses patients for GI perforation the same way regardless of whether they are receiving bevacizumab therapy. (*Id*. at 70:9-71:7.) Similarly, Dr. Morse explained in a 2006 scientific article that in colon cancer patients receiving bevacizumab, "[t]he rare, catastrophic events, including . . . bowel perforation (1.5%) . . . are managed ***in the same manner*** as they would be if not associated with bevacizumab." (Ex. 1028 at 14 (emphasis added).) Genentech's expert, Dr. Levy also testified that it has never been her practice to tailor a CT scan or X-ray based on the medication or therapy that a patient is receiving:

> Q. So if a patient presents with some symptom that justifies an abdominal X-ray, you will tailor that abdominal X-ray to the patient's condition, but not to their cancer therapy?
>
> A. Correct.
>
> Q. Now, do you sometimes do CT scans of cancer patients for reasons other than simply assessing tumor progression?
>
> A. Yes.
>
> Q. And when you do CT scans of cancer patients receiving cancer therapy, do you do those scans by tailoring them to the patient's condition and not their cancer therapy?
>
> A. Yes.

Q. And has that always been your practice?

A. Yes.

(Ex. 1027 at 18:19-19:9.)

Furthermore, Dr. Morse confirmed that the Avastin prescribing information does not require physicians to assess patients receiving bevacizumab for GI perforation. (Ex. 1026 at 66:19-69:3.) Indeed, there is nothing in the Avastin label suggesting that physicians should manage patients receiving bevacizumab any differently than patients not receiving bevacizumab with respect to assessing for GI perforation. (Ex. 1025 at ¶ 38.) Thus, the standard of care today with respect to assessing patients for GI perforation is the same regardless of whether a patient is receiving bevacizumab or not and is the same as the standard of care in 2003. (*Id*.)

Claim 1 would have also been obvious to the Skilled Artisan in view of Kabbinavar or the 2000 Press Release because the Skilled Artisan at the time would have been particularly concerned with the possibility of GI perforation occurring in the subjects of the reported clinical study. As explained in Hospira's Petition, the Skilled Artisan would have known that colorectal cancer is associated with a higher risk of GI perforation because GI tumors growing within the gut wall damage the wall. (Petition at 48; Ex. 1002 at ¶¶ 96-97, 100; Ex. 1025 at ¶ 39.) Dr. Morse testified that the rate of GI perforation in GI cancers is around 1-3%. (1025 at 88:2-89:8.) Dr. Morse also explained that "tumors can themselves perforate through the wall of the intestine." (*Id*. at 97:5-16.) Similarly, Dr. Levy confirmed

that GI tumors affect the integrity of the GI wall, and that she has witnessed GI perforations in GI cancer patients caused by GI tumors. (Ex. 1027 at 64:1-24.) The Skilled Artisan would have also known that chemotherapy further weakens the gut wall by killing the tumor cells and effectively eroding away the tumor as well as by killing the epithelial cells that line the gut wall. (Petition at 48; Exhibit 1002 at ¶¶ 98-101; Ex. 1025 at ¶ 39; Ex. 1009 at 5; Ex. 1010 at 3; Ex. 1013 at 2.) Indeed, Dr. Morse confirmed that chemotherapy can actually cause GI perforation. (Ex. 1026 at 95:18-96:17.)

Moreover, the Skilled Artisan would have been aware that bevacizumab's mechanism of action could potentially contribute to the risk of GI perforation. In particular, it had been reported that VEGF-neutralizing antibodies such as bevacizumab impair the ability of VEGF to promote GI injury repair. (Petition at 25, 56-57; Ex. 1002 at ¶ 25, 82; Ex. 1025 at ¶ 39; Ex. 1008 at 3, 8-9; Ex. 1021 at 1.) The Skilled Artisan would have understood from those studies that bevacizumab could interfere with the repair of GI wall damage that occurs in GI cancer patients. (Ex. 1025 at ¶ 39). For example, the February 13, 2003 Action Letter from the NIH reporting incidents of GI perforation on patients treated with bevacizumab, which Genentech cites to in its Response, recognized that "partial delay in wound healing has been demonstrated in animal models treated with anti-VEGF antibodies and it is possible that bevacizumab may delay or compromise

wound healing in patients." (Exhibit 2021 at 1.) Thus, the Skilled Artisan would have understood that normal repair of the GI tract damage from GI tumors and chemotherapy would likely be impaired by bevacizumab, thereby increasing the risk of GI perforation.

For these reasons, the combination of administering an effective amount of bevacizumab to cancer patients and assessing the patients for GI perforation would have been obvious over either Kabbinavar or the 2000 Press Release in view of the knowledge of the Skilled Artisan. And because it is undisputed that Kabbinavar and the 2000 Press Release each discloses all the additional limitations in claims 1 to 5 of the '115 Patent, the recited inventions in those claims would have been obvious to the Skilled Artisan at the time of the alleged invention over either Kabbinavar or the 2000 Press Release in view of the knowledge of the Skilled Artisan.

III. CONCLUSION

For the reasons set forth in Hospira's Petition and in this Reply, claims 1 to 5 of the '115 Patent are anticipated by Kabbinavar according to Instituted Ground 1 and are obvious over either Kabbinavar or the 2000 Press Release in view of the knowledge of the Skilled Artisan according to Instituted Grounds 5 and 7, respectively.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this *Petitioner Reply* complies with the word count limitation of 37 C.F.R. § 42.24(c)(1) because the Reply contains 5,593 words, excluding the cover page, signature block, and the parts of the Reply exempted by 37 C.F.R. § 42.24(a).

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CERTIFICATE OF SERVICE

The undersigned certifies that a complete copy of this *Petitioner Reply* and all Exhibits and other documents filed together with this *Petitioner Reply* were served on September 5, 2017 via electronic mail upon the following attorneys of record for the Patent Owner:

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