IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EDWARDS LIFESCIENCES CORPORATION,

Petitioner,

v.

ENDOHEART AG

Patent Owner.

IPR2016-00300

U.S. Patent No. 8,182,530

PATENT OWNER’S PRELIMINARY RESPONSE
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I. INTRODUCTION

Endoheart AG ("Patent Owner") submits this Preliminary Response to the Petition filed by Edwards Lifesciences Corporation ("[Edwards Corporation]") or "Petitioner"). Patent Owner demonstrates below that Petitioner has incorrectly construed claims, relied upon redundant references, improperly relied upon a reference that was derived from Dr. Huber, inventor of the '530 Patent, improperly relied upon an antedated reference and failed to state grounds that show or suggest all the elements of the properly construed claims and upon which a trial can be instituted under 37 C.F.R. § 42.108. For at least the foregoing reasons, which are set forth below after a brief discussion of technical background and the '530 Patent, the Petition should be denied.

II. TECHNOLOGICAL BACKGROUND

A. Antegrade and Retrograde

"Antegrade" and "retrograde" are directions that are defined relative to a direction of blood flow. The directions are shown for the aortic and mitral annuli in Schematic A, rendered by Patent Owner, at right. Valve leaflets, which would be present in the different valve annuli, for the purpose of simplicity, are not
shown. In nature, the left ventricular valves alternate opening, so that only the mitral valve is open during filling ("diastole") and only the aortic valve is open during ejection ("systole"), which is driven by contraction of the ventricles.

In an antegrade valve delivery, the valve is delivered in the direction of the blood flow. In a retrograde valve delivery, the valve is delivered opposite the direction of the blood flow. A long instrument, such as a guide wire, that travels along numerous blood vessels, may have antegrade portions and retrograde portions.

**B. Aortic Stenosis**

In aortic stenosis, the aortic valve leaflets become calcified. The maximum valve opening is reduced, as shown here in Schematic B, rendered by Patent Owner. This can interfere with ejection of blood from the left ventricle and thus cause left ventricular systolic pressure to increase significantly. The shape and location of the orifice of a stenosed aortic valve can be irregular. This often makes navigation and through-passage of rigid instrumentation difficult and dangerous.

Mitral valve pathologies generally interfere with ventricular filling during diastole and blood retention during systole. Mitral valve pathologies can therefore lead to decreased left ventricular systolic pressure.
C. **Systolic Pressure In A Normal Heart**

Schematic C, below, is a rendering by the Patent Owner showing normal systolic (ejection) pressures in the different chambers of the heart. Normal systolic atrial pressures are low: 5 and 10 mm Hg for the right and left atria, respectively. Normal systolic right ventricular pressure is higher—25 mm Hg, for pumping blood through the lungs and back to the left atrium. Normal systolic left ventricular pressure is the highest—120 mm Hg, for pumping blood through the rest of the body. Ex. 2007, Giuliani, at 1517.

D. **Systolic Pressure In A Heart With Aortic Stenosis**

Schematic D, below, is a rendering by the Patent Owner showing representative systolic (ejection) pressures in the different chambers of the heart when the aortic valve is stenotic (as indicated by red broken lines...
at aortic annulus). The stenosis leaves the right atrial systolic pressure virtually unchanged at 5 mm Hg. The right ventricular systolic pressure is reduced from 25 to 20 mm Hg. The left atrial systolic pressure is increased from 10 to 15 mm Hg. Ex. 2007, Guiliani, at 1517.

The left ventricular systolic pressure, however, undergoes a dramatic pressure increase from 120 mm Hg to 195. In some aortic stenosis patients, the systolic left ventricular pressure can exceed 200 mm Hg. Id. at 1516.

E. Seldinger, 1952: Introduction Of A "Lead" Into The Circulatory System

Schematic E, below, is a rendering by the Patent Owner that schematically shows Seldinger's approach for introduction of contrast agent—at a distance from the vascular access point—in internal organs by insertion of a catheter into an artery at the access point. This enabled Seldinger to advance the catheter "up" (and therefore against the flow—"retrograde") to various internal organs for delivery of the contrast agent for radiography. Ex. 2001, Seldinger; see esp. id. at 371 ("catheter is usually pushed 'up' the vessel without difficulty…").

Ninety-five percent of Seldinger's reported procedures can be inferred to be retrograde. (Id. at 373 (reporting 40 arterial catheterizations that included 35
aortographies via the femoral artery, 3 subclavian arteriographies by means of puncture of the brachial artery in the antecubital fossa, and 2 catheterizations of the femoral artery in a distal direction).

Seldinger taught, in relevant part, that:

1. The tip of a flexible round-end "metal leader" with increased flexibility of its distal 3 cm is inserted "a very short distance into the lumen of the artery through the needle." (Id. at 370.);

2. The needle is removed, leaving the leader in place; pressure should be placed proximal the puncture site to control bleeding, because the puncture is wider than the leader (Id. at 371.);

3. The catheter is threaded onto the leader;

4. The catheter and the leader are pushed just far enough to ensure that the tip of the catheter is in the lumen of the vessel;

5. The leader is removed and the catheter is "directed" to the level required. The unsupported catheter is "usually pushed up the vessel without difficulty…" (Id.) (emphasis added). Seldinger cautioned that "The leader should not be passed beyond the tip of the catheter." (Id.)

Delivery of contrast agent is facilitated by the use of a catheter having as large a diameter as practicable. Before Seldinger, practitioners placed the catheter in the femoral artery by inserting the catheter through the needle. Id. at 375. This, in
turn, required as large a needle diameter as practicable, but the femoral artery imposed an upper limit on the needle diameter. Seldinger instead used the "metal lead" as a rail over which to place the catheter—free of the needle—in the femoral artery. *Id.* Now the catheter diameter was limited directly by the femoral artery, with no intervening needle.

**F. Transseptal Aortic Heart Valve Delivery**

With developments in peripheral vascular access, catheter-based heart valve delivery, such as transseptal delivery, became viable. Transseptal refers to "through the septum." Schematic F, at right, is a rendering by the Patent Owner that illustrates a transseptal approach that involves puncturing a hole, while the heart is beating, in the thin atrial septum that separates one relatively low pressure atrium from the other. A prosthetic aortic valve is then passed through the hole and then delivered through the left atrium, the left ventricle, and into position of the base of the aorta. The ’530 Patent, on the other hand, provides a method for delivering the prosthetic aortic valve straight through a hole in the left ventricular wall.
III. THE '530 PATENT

A. Overview

The '530 Patent (Ex. 1001) discloses apparatus and methods for providing replacement heart valves, particularly replacement aortic valves. Figure 14 of the '530 patent, at right (Ex. 1001 at 11), shows compressed heart valve 140 being delivered to aortic valve rim 141 through left ventricle 26 by valve delivery device 142. Valve delivery device 142 runs along catheter 66, which extends through aortic valve rim 141 into the aorta. Elements 90, 92, and 94 are embolic protection devices. Element 60 is an access device. Ex. 1001, 14:48-61. Guidewire 66, which is a stiff guidewire for supporting the introduction of valve 140 is emplaced through a guidewire exchange that is initiated by the introduction of a thin and flexible guidewire. Id., 9:10-20. As will be discussed below, the use of the thin and flexible guidewire in the left ventricle is patentable over the use of prior stiff guidewires.

B. Claims

Petitioner challenges claims 1 and 6.
Claim 1 recites, with elements enumerated as set forth by Petitioner:

(a) A method for implanting a heart valve comprising:
(b) accessing a patient's heart by piercing a myocardium with a cannulated needle having a sharp end;
(c) feeding through the cannulated needle an elongated wire configured to conform to a direction of blood flow, the feeding continuing such that the wire follows the blood flow until a length of the wire extends at least from a ventricular apex of the heart through an aortic valve of the heart;
(d) installing an access device in a wall of the heart,
(e) the access device having means for preventing bleeding through the access device;
(f) inserting a valve delivery device through the access device; and
(g) installing the heart valve.

Claim 6 recites, with elements enumerated as set forth by Petitioner:

(a) A method of operating on a patient comprising:
(b) accessing the patient's heart by piercing a myocardium at a ventricular apex of the heart with a cannulated needle having a sharp end;
(c) feeding through the cannulated needle an elongated wire having a length along which the wire is configured to conform to a direction of blood flow, the feeding directed by the blood flow such that the wire follows the blood flow,
the feeding continuing until the length extends at least from the ventricular apex to an aorta;

(d) installing an access device in a wall of the heart,

(e) the access device having means for preventing bleeding through the access device; and

(f) performing a surgical procedure of implanting a heart valve.

Patent Owner sets forth below reasons that petitioner's ground 1 fails to demonstrate a reasonable likelihood that claims 1 and 6 are unpatentable. Patent Owner focuses on Elements 1c and 6c, above, and reserves the right if necessary to provide reasons based on other Elements that petitioner's ground 1 fails to demonstrate a reasonable likelihood that claims 1 and 6 are unpatentable.

C. Specification Teaches A Practical Distinction Between Guidewires With Two Distinct Performances

Huber FIGS. 4-6 (Ex. 1001 at 5-6), reproduced below, illustrate exchange of guidewire 44 with guidewire 66.

Guidewire 44 is advanced from the apex into the aorta following the direction of blood flow. Id., 9: 1-2. Huber teaches that guidewire 44 may be further advanced into the arteries. Huber teaches that a wire with a snare loop may be
advanced retrograde to capture guidewire 44. Neither the further advancement, antegrade, of guidewire 44 through the arteries, nor the advancement, retrograde, of the snaring wire is an advancement that "follows" the blood flow. *Id.*, 9: 3-9. What is common between the further advancement of guidewire 44 and the advancement of the snaring wire is that their trajectory—whether antegrade or retrograde—is that both are advancements following the lumen in which they travel. Only the advancement across the ventricle is an advancement "following the blood flow."

Guidewire 44 is then replaced with guidewire 66 by placing catheter 50 over guidewire 44, removing guidewire 44 from catheter, and inserting guidewire 66.

Guidewire 44 is not sturdy enough to support the transportation of surgical tools. *Id.*, 9: 10-13 ("Guidewire 44 may be a relatively thin and flexible guidewire."). Guidewire 66 is capable of bearing the tools. *Id.*, 9:10-13 ("In order to provide sturdier support for the exchange of surgical tools, it may be
Because guidewire 44 is relatively "thin and flexible" and follows the blood flow, and guidewire 66 is sturdier and is not specified to follow the blood flow, Huber illustrates the distinction between a wire that is configured to conform to the blood flow and a wire that is not.

**D. Prosecution History Shows the Differences Between The ‘530 Patent And Lattouf**

New claims including the term "configured to conform to a direction of blood flow" on June 3, 2011 (Reply to Office Action, Ex. 1002 at 112) were added after the Examiner issued rejections over Seguin in combination with Lattouf (Id. at 133). The Examiner sustained the rejections in a June 27, 2011, Office action (Id. at 60). At a September 16, 2011, interview with Examiners Mashack and Woo,
amendments of the claims were agreed upon that led to the allowance of the claims. Issued claims 1 and 6 correspond to prosecuted claims 7 and 1, respectively.

1. **Claims 1 and 6 distinguish, in terms of use, between Huber's guidewire and Lattouf's guidewire**

   As required by the Examiner (Ex. 1002 at 44), a distinction between the claimed guidewire and the Lattouf guidewire was expressed, after amendment, in terms of "method claim phraseology." The amendment thus required that the wire be fed in a way that produced an outcome that reflected the physical properties, viz., "such that the wire follows the blood flow." Prior to the amendment, however, the distinction was not, for the Examiner, at least, articulated sufficiently in a method claim phraseology. That perceived insufficiency was remedied by adding the qualification of the feeding: "such that the wire follows the blood flow."

2. **The Examiner recognized the distinction—and deemed its role in the claimed methods to be nonobvious**

   Applicant first amended claims 1 and 6 to include feeding through a needle wire "configured to conform" to a direction of blood flow in a June 3, 2011 amendment. Ex 1002 at 87. The Examiner stated that Lattouf teaches advancing a guide wire and that "A guide wire is known to be floppy and would be capable of conforming to blood flow." *Id.* at 63. Applicant requested an interview to argue that Seguin and Lattouf do not render obvious the claimed "feeding of a length of
flow-conforming wire from a ventricular apex to an aorta…” *Id.* at 58. At the interview, the Examiner "proposed amending the claims to express allowable subject matter in method claim phraseology." *Id.* at 44. The interview led to an amendment that qualified the claimed feeding "such that the wire follows the blood flow." *Id.* at 36-37. The claimed feeding was thus amended to become a feeding in which the wire follows the blood flow.

Post-interview amendments elucidated the distinction between the performance of the claimed guide wire and the performance of the Lattouf guidewire. *Id.* at 45, e.g. (stating that the claim previously required feeding wire "configured to conform" to a direction of blood flow and that the Lattouf guidewire is configured for advancement "against" the direction of blood flow).

Based on the Examiner's requirement to express the non-obvious claim feature as a method (as opposed to an apparatus qualifier), the applicant amended the claims—in the very language that the Examiner recorded in the Examiner's interview summary (*Id.* at 33)—to qualify the feeding, as a feeding "such that the wire follows the blood flow." The amendment thus expressed the wire performance in terms of an outcome of feeding the guidewire—an outcome that Lattouf's teachings contradicted. *Id.* at 45. The Examiner then allowed claims.
IV. CLAIM CONSTRUCTION

A. "Configured To Conform To A Direction Of Blood Flow" (Claims 1 And 6)

The only term that warrants construction at this time is “configured to conform to a direction of blood flow,” which appears in both Claims 1 and 6. Petitioner did not offer an explicit construction of this term but did implicitly construe the term in its claim charts (Pet. 50, 54) and expert declaration (Ex. 1026, ¶ 79). However, as explained below, Petitioner’s implicit construction is incorrect. The proper construction of the term that the Board should adopt is “having the property or structure for adapting to the direction of blood flow.”

B. Petitioner’s Implicit Construction Is Flawed Because It Incorrectly Reads The Term Out Of The Claims

In its claim charts and declaration, Petitioner improperly equates the term “configured to conform to a direction of blood flow” with “antegrade direction.” In its ’300 Petition claim charts, Petitioner literally equates (using “i.e.” = “that is”) “guidewires conforming configured to a direction of blood flow” with “antegrade direction.” Pet. 42, 45. This portion of the claim chart in the ‘300 Petition refers to paragraph 76 of the Garrett Declaration, which posits that “the guidewire must necessarily conform to the direction of blood flow” merely because “access [is] being made from the apex of the left ventricle to the aortic annulus.” Ex. 1026, ¶ 76 (emphasis added).
Petitioner’s implicit construction is incorrect, however, because it ignores and gives no effect to the language “configured to conform.” A rigid, inflexible stick could be advanced in the “antegrade direction” but the stick is not “configured to conform” to a direction of blood flow. Moreover, other language in Claims 1 and 6 already requires the wire to extend “from a ventricular apex of the heart through an aortic valve of the heart,” which is an antegrade direction. This other language in the claim would be superfluous if, under Petitioner’s implied construction, “configured to conform to a direction of blood flow” simply means an “antegrade direction.”

C. Patent Owner’s Proposed Construction Is Correct

Patent Owner’s proposed construction is correct because it is consistent with the plain and ordinary language of the words in the claims, as confirmed by the specification and prosecution history. The ordinary meaning of “configured” is having a property or structure for achieving something. The ordinary meaning of “conform to” is adapting to.

The specification explains that guidewire 44 is “relatively thin and flexible,” which is an example of a property and structure that enables the wire to adapt to the direction of blood flow, i.e., “following the direction of blood flow”. Ex. 1001, 8:67-9:2; 9:10-11. Guidewire 44, however, is not sturdy enough to support the transportation of surgical tools. By contrast, guidewire 66 is “stiffer” and
“sturdier” and thus capable of bearing surgical tools. *Id.*, 9:10-13 (“In order to provide sturdier support for the exchange of surgical tools, it may be desirable to replace guidewire 44 with a stiffer guidewire.”); 9: 51-52 (“Next, a dilator (not shown) may be advanced over stiffer guidewire 66 (FIG. 6”); 12: 51-53 (“Valve delivery device 142 is advanced along guidewire 66.”).

The prosecution history likewise confirms that this phrase means having the property or structure for adapting to the direction of blood flow. As the Examiner recognized in the June 27, 2011 Office Action in rejecting the claims over the prior art: “A guide wire is known to be floppy and would be capable of conforming to blood flow.” Ex. 1002 at 63. Consistent with the Examiner’s statement, Dr. Huber demonstrated at the October 12, 2011 Interview that a soft guidewire is configured to conform to the direction of blood flow, in contrast to a stiff guidewire, which does not conform to the direction of blood flow. Dr. Huber showed the Examiners a video of the behavior of both types of guidewires when placed in a fluid stream. Ex. 1002 at 44. The soft guidewire adapted to the direction of the flow by bending in the direction of the flow, whereas the stiff guidewire did not. Dr. Huber also showed the Examiners a second video in which a soft guidewire followed the blood flow in the heart from the left ventricle into the aorta. After seeing these videos, the Examiners noted that the claims of the ‘530 patent would be patentable over the prior art if limitations were added concerning “the wire follows the blood
flow.” Ex. 1002 at 33. The Examiners’ proposed language was added to Claim 1 and to Claim 6 (id. at 36-37), and those claim were allowed. Id. at 14.

The dictionary definition of “configured” confirms that Patent Owner’s construction is correct: “To design or adapt to form a specific configuration or for some specific purpose.” Ex. 2010 (emphasis supplied). Here, the wire becomes shaped by the blood flow to achieve the anatomical curvature (a specific configuration) necessary to accomplish the goal of entering the aorta (a specific purpose). That goal requires a material shaping of the wire by the blood flow.

D. Other Claim Terms In The Petition Are Not Material At This Time

Because Petitioner’s proposed grounds of rejection fail even under Petitioner’s proposed constructions set forth in the Petition, Patent Owner does not find it necessary at this time to comment on Petitioner's proposed constructions and reserves the right to do so if necessitated at a later date.

V. GROUND 1 FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD OF UNPATENTABILITY

A. Petitioner Has Not Addressed How The Prior Art Meets Elements 1c And 6c Beyond Merely Disclosing An Antegrade Approach

Petitioner has failed to articulate how the limitation “configured to conform to a direction of blood flow” in Elements 1c and 6c, properly construed above, is present in the prior art, beyond merely disclosing an antegrade approach. As explained above regarding the construction of this term, Petitioner incorrectly
equates this term with “antegrade.” Instead, the correct construction requires the wire to possess a property or structure for adapting to the direction of blood flow, which none of Cribier (Ex. 1009), Neish (Ex. 1016) or Lattouf (Ex. 1015) disclose, either expressly or inherently.1

1. **Cribier does not expressly disclose elements 1c and 6c**

Schematic G, rendered by Patent Owner, below, is Patent Owner's interpretation of Cribier. Cribier describes his method as follows

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1 Petitioner cites, repeatedly, to Patent Owner’s Markman brief for a purported admission regarding what the prior art discloses. Those statements are confusingly taken out of context. The issue of what the prior art discloses, including Lattouf, goes to the second step of an anticipation or obviousness analysis—after the claims are first properly construed. The second step was not at issue in the Markman briefing, and in any event, Patent Owner made clear that "nothing was said [during prosecution] about the structure of the [Lattouf] guidewire itself.” Ex. 1027 at 6.
"After standard transseptal catheterization ["A"], a straight 0.035-inch guidewire ["B"] was advanced across the stenotic aortic valve ["C"] through a balloon flotation catheter ["D"]. After advancement of the balloon catheter into the descending aorta ["E"], the guidewire was exchanged for a stiff 260-cm long guidewire..." Ex. 1009 at 3007. Petitioner argued that the Cribier's guidewire and catheter are configured to conform to the direction of blood flow. Pet. 36 (emphasis added).

Cribier does not describe the wire or how it is deployed, other than that the wire was advanced across the aortic valve "through" the balloon floatation catheter. Id. Cribier does not describe the trajectory of the wire and does not discuss when, where, or if the wire is extended beyond the balloon catheter such that it could be inferred from the wire's behavior whether the wire were configured to conform to the direction of blood flow. (At "B," the wire (black, broken line) inside the balloon catheter (yellow, broken line) is rendered in broken line, because of the missing information.)

Even, assuming arguendo, that Cribier provides a wire configured to conform to the blood flow, which it does not, Cribier does not teach a wire that extends at least from a ventricular apex to an aorta. In fact, Petitioner does not even assert that Cribier does teach a wire that extends from a ventricular apex to an aorta. Even more importantly, nowhere does Cribier disclose the characteristics of the
first wire, which is why Petitioner is forced to speculate (incorrectly, as discussed below) that the first wire "would have been" a "floppy" guidewire. Pet. 41, 45.

Dr. Garrett baldly asserted that Cribier discloses the first successful human implantation of a percutaneously implanted heart valve (PHV), via an antegrade, transseptal catheter-based approach, in which the guidewire and catheter were configured to conform to the direction of blood flow. Ex. 1026, ¶ 63 citing Ex. 1009, abstract [Sic], 3008. Emphasis bold italic in original. Underline added. In fact, the Cribier Abstract does not mention a guidewire at all. The guidewire mentioned on page 3008 is a "long guidewire exiting the left femoral artery [that] provided excellent support for tracking the device." Neither provides any support for Dr. Garrett's conclusion.

2. Cribier himself never disclosed a “transapical” approach until after Huber’s filing date and Scottsdale presentation.

Further confirming that transseptal and transapical approaches are not “fairly interchangeable,” Dr. Cribier himself did not disclose a “transapical” approach until May 27, 2005, when Dr. Cribier filed a continuation-in-part (“CIP”) application that added a “transapical” approach as "new matter" relative to his earlier patent applications. Ex. 2038 (Pre-Grant Publication No. 20050251251 of U.S. App. No. 11/139,356 filed May 27, 2005); Ex. 2039 (Pre-Grant Publication No. 20030014104 of U.S. App. No. 10/139,741 filed May 2, 2002). A redline comparison of the text of Dr. Cribier’s applications shows that newly-added
paragraph [0194] in the CIP application—the only paragraph that discloses “transapical” and/or “antegrade”—is new relative to Dr. Cribier’s earlier 2002 application. Ex. 2040 (redline comparison). Importantly, Dr. Cribier’s CIP application was filed after Dr. Huber’s applications were filed (in Oct. 2, 2004 and Dec. 28, 2004), and after Dr. Huber’s presentation in February 2004 in Scottsdale, Arizona, disclosed the transapical technique. Ex. 2015.

Therefore, if a POSA such as Dr. Cribier had truly viewed transseptal and transapical approaches as “fairly interchangeable,” one would think that Dr. Cribier would have at least mentioned “transapical” somewhere among the 182 paragraphs of his earlier application filed in 2002. Instead, Dr. Cribier only mentioned this technique in 2005, after Dr. Huber showed the world it was possible.

3. **Neish does not expressly disclose elements 1c and 6c**

Neish’s FIG. 3 (Ex. 1016 at 808) is reproduced below. Neish reported open-chest transapical valvuloplasty on neonates in the first week of life. *Id.* at 809.

Neish FIG. 3 shows that Neish inserted a balloon catheter into a stab incision on the exposed apex and advanced the balloon
catheter across the aortic valve. Neish does not teach a guidewire in connection with apical access.

4. **Lattouf does not expressly disclose Elements 1c and 6c**

The relevant portion of Lattouf FIG. 10 (Ex. 1005, at 5) is shown at below. Guidewire 53 is advanced, against the direction of blood flow, from the apex into left ventricle 12, passing mitral valve leaflets 14 and 15, into left atrium 11. Grasping device 40, which includes elongated shaft 41 and jaws 42, is slidably advanced over the guide wire through the valve 30 and into the left atrium through mitral valve 13. *Id., ¶ 57.*

Schematic H is a rendering by Patent Owner showing Petitioner's proposed application of Lattouf to the claims. "Lattouf following Lattouf Figures" shows a guidewire leading from the apex to the mitral valve, as shown by Lattouf FIG. 10. The guidewire must be able to overcome the oncoming blood flow from the mitral
valve. "Lattouf following Petitioner’s position" shows the guidewire disposed in the aortic valve.

Lattouf, however, does not teach a separate and different guidewire in connection with the single sentence in Lattouf that touches on aortic procedures. Ex. 1005, ¶ 8 ("Other procedures which may be performed include…aortic stenting for aortic dissections and aneurysm therapy…"). Instead, it is the same guidewire that is stiff enough to advance against blood flow and carry Lattouf's hardware.

Thus, nothing about "Lattouf Antegrade" suggests a wire that is "configured to conform to a direction of blood flow," even though the wire is aligned with the blood flow. Petitioner implicitly recognized this: "In summary, Lattouf describes a method for treating the aorta with stent devices and repairing heart valves via access from the apex of the heart, from both the antegrade and retrograde directions." Pet. 53 (emphasis added). That is, the procedure of Lattouf can be performed in both directions—using the same guidewire, which logically must be a stiff guidewire if it is to be used retrograde. Thus, nothing in Lattouf expressly discloses a loose or floppy guidewire used in aortic procedures in the antegrade direction.

B. **Elements 1c and 6c are not necessarily present in the prior art to meet the high standard for inherency**

Petitioner appears to rely on the doctrine of inherency to meet the limitation “configured to conform to a direction of blood flow” in Elements 1c and 6c. See
Pet. 42, 45 (asserting for Elements 1c and 6c that the "techniques employed by Cribier and Lattouf were known to result in the guidewires conforming to a direction of blood flow") (emphases added). However, Petitioner has not met the "high standard" that is required "in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis." Par Pharm., Inc. v. TWi Pharms., Inc., 773 F.3d 1186, 1195-1196 (Fed. Cir. 2014). As the Federal Circuit has explained, “the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” Id. (emphases added).

As explained below, Petitioner’s own cited references show that the prior art guidewires on which Petitioner relies would not necessarily have conformed to a direction of blood flow.

1. Cribier does not necessarily include a guidewire that is configured to conform to a direction of blood flow—even between the mitral valve and the aortic valve

Cribier does not state whether or not the guide wire was ever extended beyond the balloon catheter. Ex 1009 at 3007 (reporting, "After standard transseptal catheterization, a straight 0.035-inch guidewire was advanced across the stenotic aortic valve through a balloon flotation catheter. After advancement of the balloon catheter into the descending aorta, the guidewire was exchanged for a stiff 260-cm-long guidewire.").
Petitioner deduces from the Cribier’s wire exchange that Cribier's first wire "would have been" a "floppy" guidewire, because it was exchanged for a stiff guidewire. Pet. 41. This is not necessarily true, however. For example, if Cribier advanced the balloon catheter from the left atrium into the aorta such that the curvature of the balloon catheter were constrained by anatomy after floating into the aorta, and then advanced a wire through the balloon catheter, the wire would not need to be a wire configured to conform to the direction of the blood flow.

It is therefore not inherent in Cribier that a wire conforming to the direction of blood flow was used. Indeed, Petitioner's expert, Dr. Garrett, discusses Cribier's wire, but did not proffer a deduction from Cribier's wire exchange. The deduction is therefore merely attorney argument that is conclusory and entitled to little weight. See In re Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (attorney arguments and conclusory statements that are unsupported by factual evidence are entitled to little probative value).

2. **Semple and Seldinger diametrically oppose Dr. Garrett's position**

In support of its assertion that the “techniques employed by Cribier and Lattouf were known to result” in guidewires conforming to a direction of blood flow, Petitioner cites the 1968 article by Semple (Ex. 1024). Notably, Petitioner does not suggest to modify Cribier and Lattouf’s techniques by substituting any one of their guidewires for Semple’s guidewire. Rather, Petitioner cites Semple as
evidence to prove that the “techniques employed by Cribier and Lattouf were known to result” in the guidewires conforming the blood flow. Pet. 42, 45.

However, this assertion is merely attorney argument because, as will be discussed below, nowhere in Petitioner’s expert declaration is Semple even mentioned, much less discussed with specificity.

Semple performed pressure measurements based on modifications of the teachings of Levy and Lillihei (1964) (Ex. 2003). Semple replaced the Levy and Lillihei needle with a narrower needle, over which a soft teflon catheter was snugly fit. Ex. 1024 at 402. The catheter, with needle acting as trocar, was inserted through the ventricular wall. Upon detection of blood pressure through the needle, the catheter was advanced beyond the needle and the needle was withdrawn, leaving the teflon catheter alone in the left ventricle. As the Petitioner stated, quoting Semple, "In most cases, further gentle advancement of the soft teflon catheter takes it into the aorta along with the blood flow." Pet. 42, 46 (quoting Ex. 1024 at 402). (Emphasis in Petition.)

Petitioner omits the fact that Semple, like Lattouf, teaches a wire sufficiently stiff for retrograde advancement. This can be seen from Semple's application of Seldinger. Specifically, Semple teaches that "left atrial catheterization [a retrograde approach] may be attempted through the mitral valve” (Ex. 1024 at 402) using the soft catheter and the "Seldinger guidewire," which would have to have
been stiff enough for the retrograde procedure. Thus, although Petitioner analogizes from Seldinger to Lattouf and Cribier to show that both Lattouf and Cribier would have been known to conform to the blood flow, the opposite is true of the Semple/Seldinger approach: the Semple/Seldinger wire was configured to not conform to the blood flow.

3. **Dr. Garrett improperly derived from Seldinger that Lattouf necessarily conforms to the direction of blood flow**

Petitioner’s expert, Dr. Garrett, reasons that merely because Lattouf implements the Seldinger technique, the Lattouf guidewire “must necessarily” conform to the direction of blood flow. Ex. 1026, ¶ 76. Seldinger advanced a wire against the blood flow. And Semple demonstrated that, like Lattouf, a stiff wire is required to traverse the mitral valve in the retrograde direction. Dr. Garrett thus fails to explain why implementing the Seldinger technique means that a guidewire “must necessarily” conform to the blood flow.

Further compounding Dr. Garrett’s lack of explanatory rigor above, Dr. Garrett does not even cite to an actual Seldinger reference to support the declaration’s reliance on the "renowned Seldinger technique." Ex. 1026, ¶ 71. Instead, Dr. Garrett cites to a single slide in an undated online presentation by an individual named Sarbesh Tiwari, PGT. Ex. 1026, ¶ 71 n.69 (citing Tiwari, Ex. 1041). Without a publication date, this online student presentation has not been shown to be prior art and thus cannot be used as evidence in support of obviousness.
4. Petitioner’s reliance on Semple is mere attorney argument

Petitioner argues that the techniques of Cribier and Lattouf were “known to result in the guidewires conforming to a direction of blood flow.” Pet. 42, 45-46 (emphasis added). Petitioner attempts to support this statement with citations to Semple (Ex. 1024 at 402) and the declaration of its expert Dr. Garret (Ex. 1026). But nowhere in Dr. Garrett’s declaration is Semple even mentioned, much less explained in any detail. Therefore, Petitioner's position that Semple somehow confirms that the guidewires of Cribier and Lattouf were "known to result” in the guidewires conforming to a direction of blood flow is merely attorney argument. That argument is also conclusory, because it does not explain how the Semple guidewire is in any way related to or is the same as the guidewires of Cribier and Lattouf (which, as Patent Owner has explained above, were relatively stiff wires used in retrograde techniques). See In re Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (attorney arguments and conclusory statements that are unsupported by factual evidence are entitled to little probative value).

C. Even if all claim elements were present across disparate references, Petitioner has failed to demonstrate interchangeability and predictability of transseptal and transapical approaches to establish obviousness

As the Supreme Court has explained, “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” KSR Int'l Co. v. Teleflex Inc., 550 U.S. 28
In an obviousness analysis, conclusory and unsupported assertions are insufficient to establish a reasonable likelihood of obviousness in *inter partes* review. See IPR2015-01774 (Paper 15); IPR2015-01696; IPR2013-054 (Paper 12); IPR2014-00347 (Paper 9); Office Patent Trial Practice Guide, 77 Fed. Reg. 48, 756, 48,763 (“Affidavits expressing an opinion of an expert must disclose the underlying facts or data upon which the opinion is based.”). Further, the references cited by Petitioner and Dr. Garrett do not deal with the risk associated with increased left ventricular pressure caused by arterial stenosis, as discussed below.

1. **Petitioner's evidence does not demonstrate interchangeability or a reasonable expectation of success**
   
a. **Petitioner improperly relies on Dr. Garrett to assert that the apex is an "obvious alternative" to the septum for ventricular access**

   Petitioner boldly asserts: "The prior art makes plain that piercing the heart at the apex, as opposed to the septum, is an obvious alternative for accessing the left ventricle depending on the limitations and risks presented by the anatomy of the given patient.” Pet. at 38-39 (citing Ex. 1026, ¶¶ 77-79). The cited portions of Dr. Garrett’s declaration, however, do not explain how or why the alleged obviousness of the alternative depends on the “limitations and risks.” Indeed, Dr. Garrett does not provide any qualitative or quantitative data or sources that characterize the “limitations and risks,” whether with respect to type or degree. See Trial Guide at
30,763 (“Affidavits expressing an opinion of an expert must disclose the underlying facts or data upon which the opinion is based.”)

While Dr. Garrett does mention risk trade-offs for elderly patients, at least qualitatively (Ex. 1026, ¶ 23), Dr. Garrett does so only in connection with the balance of risk between non-intervention and conventional surgery, rather than in connection with different non-surgical access sites to the heart, whether transseptal, apical, or otherwise. Moreover, Petitioner does not explain the relevance of risk-balancing to the obviousness determination.

b. Dr. Garrett failed to mention the surgical trauma caused by Neish

The Neish approach involved gaining access to the apex by exposing the heart through a midline sternotomy (Ex. 1016). Neish then accessed the left ventricle by making a "stab wound" at the apex. A balloon catheter was then inserted into the ventricle and advance across the aortic valve. "Proper position of the balloon catheter [in the aortic valve] was confirmed by the surgeon by palpation at and above the aortic valve annulus.” Id. at 809. Dr. Garrett failed to mention that Neish performed midline sternotomy to gain access to the apex.

c. The petitioner incorrectly relied upon Wong and Dr. Garrett to show that Cribier could be modified to use transapical approach

Petitioner asserts that "it was well known prior to the filing of the '530 patent that the transapical approach was a workable alternative for left ventricular
catheterization when other common approaches, including the transseptal, were precluded." Pet. 36-37 (citing Ex. 1013, Wong, at 426-429 and Ex. 1026, Garrett ¶¶ 36, 66, 68 and 77). Petitioner relied upon Wong and the Declaration of Dr. Garrett. As explained below, Petitioner’s assertion is incorrect.

Wong reported a "seldom required" apical puncture procedure for delivery of contrast agent. He stated that such procedures have numerous "potential hazards," haemopericardium, pneumothorax, haemothorax, laceration of a coronary artery, embolisation and cardiac arrhythmias (Ex. 1013 at 431).

Wong noted the high rates of complications observed by previous workers—18% and 21%. Wong explained that despite Wong's use of a catheter having a diameter (6-7.5 Fr) about 30% greater (Ex. 2025, French catheter scale and Ex. 2026, Needle gauge comparison chart) than the needle (18-21 ga) used by previous workers, Wong's complication rate was "no higher" than theirs. Wong, therefore, recognized an increase in hazard for apical punctures of greater diameter. Wong was concerned about the diameter even though 14 of Wong's 15 subjects had conditions, such as mitral valve regurgitation and compromised left ventricular function, which would lead to reduced ventricular pressure. (Patient No. 15 had, inter alia, aortic stenosis, which would lead to higher ventricular pressure). Ex. 1013 at 428. In contrast, Cribier's prosthetic heart valve required a 24 Fr introducer sheath (Ex. 1009 at 3)—three to four times greater in diameter that
Wong's catheter, and creating a puncture an order of magnitude greater in area. See Ex. 2025.

Thus, in asserting that it would be obvious to modify Cribier's transseptal approach, which traverses from one low pressure atrium to another, with Wong's transapical access, Dr. Garrett failed to consider: (a) the hazards associated with apical access; (b) the pressure differences between hearts with compromised left ventricles (low) and aortic stenosis (high); (c) and the areal differences between Wong's fluid delivery catheter and Cribier's prosthesis-delivering sheath.

d. Dr. Garrett glosses over the serious, publicized risks of apical access

In a single paragraph of his declaration (Ex. 1026, ¶ 69), Dr. Garrett purports to review three other references relating to ventricular access: Golding (Ex. 1012), Morgan (Ex. 1043) and Cata (Ex. 1044). However, Dr. Garrett fails to explain those references in any detail, including what specific patient “situations” required deviating from the preferred transseptal approach, or the associated risks or limitations of doing so.

Golding FIG. 1, right, shows aortic cannulation from the apex using a large diameter cannula (20 Fr). Ex. 2012 at 626 (aortic valve, obscured, at base of aorta).
Golding cautioned, "Obviously, such a technique is not practical for patients with calcific aortic stenosis, in whom the cannula could then completely occlude the aortic orifice…". \textit{Id. at 627.})  Golding, therefore, is an example of the use of a large catheter in the apex, similar to the size required to introduce a heart valve (Cribier used a 24 Fr catheter, Ex. 1009 at 3007), but not for a case of aortic stenosis, and thus not at elevated ventricular pressure. Golding thus is not an obvious alternative access approach for Cribier.

Morgan reported about left ventricular puncture that "in our series a possible relationship between death and direct LV [(left ventricular)] puncture could be found in only one patient, but \textit{even then} severe aortic stenosis was the likely cause of death." Ex. 1043 at 89. (Emphasis added.) Morgan thus experienced a fatality only when treating aortic stenosis. Morgan, therefore, is not an obvious alternative to transseptal access.

Cata reported, for haemodynamic measurement, left ventricular puncture with a small diameter (4 Fr) catheter, which was 85\% smaller in diameter and 36 times smaller in puncture hole area than Cribier’s sheath. Ex. 1044 at 253 Ex. 2025. Cata praised Cata’s approach, echoing Wong’s concern about the hazard of large holes, when Cata reported, "The advantage over previous techniques is the smaller hole made in the left ventricular myocardium." \textit{Id.} at 254-255. Dr. Garrett failed to consider Cata’s comment and its implicit admonition about large access holes.
This is especially important in view of Cribier’s statement, in the following section, that the size of a whole needed for valve replacement was 24 F.

e. Cribier articulated that the Cribier method is a viable approach even in the face of peripheral artery disease

Dr. Garrett states, in relation to Cribier, that "the transapical approach was a common, workable alternative for left ventricular catheterization to the transseptal and transfemoral approaches when stenosis due to severe peripheral artery disease, … precluded access through the septum or femoral artery." Ex. 1026, ¶ 66. However, Cribier himself stated that the Cribier antegrade approach was "necessary because of severe peripheral artery disease…” ² Ex. 1009 at 3008 (stating that "The 24F sheath could be inserted percutaneously into the right femoral vein…"); Cribier 2004, at 702 ("However, in patients with undiseased femoral arteries of suitable size for insertion of a 24-F sheath, the more familiar retrograde aortic approach might be faster and easier to manage for some interventional operators.") (emphasis added). It would thus seem more logical to conclude from Cribier 2002 (Ex. 1009) or 2004 (Ex. 2028) that the Cribier

² Petitioners claim chart (Petition at 50) misquotes Cribier as stating, "severe peripheral artery disease severe peripheral vascular disease." The quote should read "severe peripheral artery disease."
antegrade technique itself was the way to obtain vascular access in the face of severe peripheral artery disease. Cribier also highlighted the advantages of the Cribier antegrade approach over a retrograde approach. Ex. 1009 at 3008.

2. Patent owner's evidence of Cribier's failure and known risk of apical access contradict Petitioner's assertions

a. Petitioner publicly acknowledged Cribier’s morbidity issues and reassured stockholders based on the safety of retrograde approach, not transapical approach

Unmentioned by Petitioner or Dr. Garrett is the fact that after Petitioner acquired the Cribier technology (and after the '530 patent filing date), Petitioner withdrew the Cribier antegrade technique from use because of morbidity outcomes. Ex. 2029 (“Edwards Lifesciences Corporation … , the world leader in heart valve technologies, announced today that it is delaying enrollment in its percutaneous aortic heart valve clinical feasibility trials…” because the antegrade technique showed "a greater degree of clinical complexity and adverse outcomes when compared to results of a Canadian [retrograde] study.") (emphasis added).

Instead of turning to the supposedly "fairly interchangeable" apical approach, the Petitioner turned back to the retrograde approach that Cribier had disparaged. Id., ("We [Edwards Lifescience Corporation] recently have completed a number of procedural refinements, including the development of a simpler and more direct retrograde delivery approach, which has led to more favorable clinical success
rates and fewer complications," said Stanton J. Rowe, Edwards' corporate vice president, Percutaneous Valve Interventions. "Until we gain regulatory approval to allow this option in our trials, we have temporarily suspended U.S. patient enrollment."); see also Ex. 2028, Cribier 2004 at 702 ("special attention must be given at each step of the [Cribier antegrade] procedure to maintain a large guide wire loop ["B," in schematic C] so as to avoid traction on the anterior mitral valve leaflet with subsequent severe mitral regurgitation and hemodynamic collapse. This complication occurred in two patients of this series when the wire was incidentally straightened from the mitral valve to the aortic valve.") and Ex. 2030 at 1555 (The Society of Thoracic Surgeons, the American Associate for Thoracic Surgery, and the Society for Cardiovascular Angiography and Interventions reporting in their consensus statement that "significant paravalvular regurgitation and early mortality characterize the experience [of percutaneous aortic valve insertion] thus far" (citing Ex. 2028, Cribier 2004, and articulating the views of an April 22, 2004 workshop that included representatives of Edwards Lifesciences, "LLP." (Ex. 2030, Appendix 2 at 1559)).)

b. Petitioner Reportedly Engaged in "Unparalleled Efforts," Requiring Unprecedented Collaboration Between Surgeons and Interventional Cardiologists to Develop its Own Transapical Approach

If the transseptal antegrade and transapical antegrade approaches were truly "fairly interchangeable" as Petitioner asserts, then Cribier's morbidity outcomes
beg the question—why did Petitioner not immediately switch to the transapical approach?

Indeed, Petitioner only first started developing its own transapical approach for heart valve replacement in November 2004—nearly a full year after Cribier's 2004 paper (Ex. 2028) announcing the "complexity" of his method was accepted for publication, petitioner began developing its own “fairly interchangeable” transapical approach for heart valve replacement in November 2004. Ex. 2031 at 175 ("[U]nparalleled joint efforts between cardiac surgeons and cardiologists” were applied to further develop therapeutic options for high-risk patients, because of "the awareness that a retrograde transfemoral approach may not be suitable in some patients… an antegrade approach from the left ventricular apex might be feasible…” Drs. Mack and Mohr "started an initiative at Edwards Lifesciences to work on transapical antegrade access...Initial experimental experience was gathered in November and December 2004…[I]nitial clinical implantations were done in two patients in Leipzig in December 2004” However, due to the lack of a 26 mm prosthesis, severe paravalvular leakage occurred. “Towards the end of 2005, a 26 mm SAPIEN prosthesis became available, together with a clear concept of using oversizing. The clinical use of TA AVI was restarted successfully in February 2006…with the support of Professor Cribier.").
Neither petitioner nor the medical community immediately adopted the transapical approach

One year later, a full year after the '530 patent was filed, Drs. Mack and Mohr concluded that the apical approach is "now an additional option." Ex. 2032 (Edwards Lifescience Corporation "announced today the successful completion of the first minimal-access, beating-heart surgical procedure for replacing a patient's aortic heart valve. Edwards is planning on developing the Ascendra aortic heart valve replacement system as an additional option for valve surgery…[The system] is not yet commercially available, and the company plans to continue to evaluate its feasibility in…2006.")

The surgical community was slow to rely upon transcatheter aortic valve procedures. Dr. Mohr, associated with Petitioner, urged the surgical community to adopt transcatheter approaches, in particular transapical approaches, citing four papers naming Huber as author. Ex. 2033, Walther and Mohr Editorial ("Aortic Valve Surgery: Time to be open-minded and to rethink"). Other authors associated with Petitioner reported that "[S]ome skepticism [about the transapical approach] remains within the surgical and cardiological communities. Therefore, prospective randomized studies should be performed, comparing transapical as well as transfemoral transcatheter valve implantation techniques, to the gold standard of conventional [surgical] aortic valve replacement surgery. Future protocols are being developed at present." Ex. 2034, Walther et al. at 15, naming as co-authors
other Petitioner associates: Greinecker, Mack and Mohr, and citing Huber et al., Ex. 2035.

The Petitioner's wobbly route, from the failure of Cribier prior to the '530 filing date to the skepticism after the filing date, better support the propositions that (1) the movement to transapical was based not on peripheral artery disease, but on Cribier's shortcomings; and (2) two years after Petitioner's first experiments on animals, Petitioner acknowledged ambivalence about the viability of the transapical approach, and that therefore the Cribier antegrade approach and the transapical antegrade approach are not fairly interchangeable.

Furthermore, along that wobbly route, Petitioner validated Huber's approach. Ex. 2036, Dewey, at 111 ([AK1])("Previous reports have described the use of the left ventricular apex as a reproducible route for minimally invasively accessing the aortic annulus.") citing Huber et al., Ex. 2035 (authors Drs. Mohr, Mack, Dewey, Doss, and Wimmer-Greinecker being associated with Petitioner).

3. Garrett failed to consider evidence that today left ventricular puncture remains risky

Pitta (Ex. 2002) reported retrospectively, in 2010, on numerous cases of left ventricular puncture ("LVAP"), a "rarely used procedure," including those of Morgan (Ex. 1043, discussed above) and Semple (Ex. 1024). Ex. 2002 at 994-995. Pitta, FIG 4 (Id. at 996), reproduced here, shows the frequency distribution of access-related complications occurring during LVAP. Pitta concluded: "Apical
access site related complications were higher in patients requiring LVAP for intervention that for diagnostic purposes (25% vs. 12.5%)." Id. at 993. Pitta also concluded that "LVAP is associated with a significant incidence of access-related complications, particularly in patients requiring LVAP for interventional [not merely diagnostic] purposes." Id. at 996.

VI. GROUND 2 FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT CLAIMS 1 AND 6 ARE UNPATENTABLE

A. Petitioner Has Failed, Even Under Petitioner's Own Construction, To Show How the Prior Art Meets Element 6c

In claim 6 (Element 6c), Petitioner proposes to construe the term "the feeding directed by the blood flow such that the wire follows the blood flow" to mean "feeding or advancing a guidewire that is in some way controlled by blood flow, whether it be by being dragged by a floatation balloon attached to a distal tip of the guidewire, or by being fed through a balloon floatation catheter." Pet. 34 (emphasis added). However, in its claim chart and associated discussion for Ground 2, Petitioner never addresses how the prior art meets Element 6c under its construction, which requires the guidewire to be “controlled by blood flow.” Pet.
57-58. In fact, Petitioner’s claim chart for Ground 2 is literally identical regarding the application of Lattouf to both Elements 1c and 6c. Compare Pet. 54-55 (Element 1c) with Pet. 58 (Element 6c). However, Petitioner’s construction of Element 6c is more specific than its construction of Element 1c: the former requires the guidewire to be “controlled by blood flow” whereas in the latter the guidewire “merely follows” the direction of blood flow. Pet. 33-34. Petitioner fails to explain how Lattouf’s guidewire is “controlled by blood flow” for purposes of Element 6c, beyond “merely follow[ing]” the direction of blood flow for purposes of Element 1c. The three cited paragraphs of Dr. Garrett’s declaration (Ex. 1026, ¶¶ 73, 76, 80) that are cited in the claim chart also are silent in this regard. Therefore, because Petitioner has failed to submit evidence as to why Lattouf’s guidewire is “controlled by blood flow,” and the Garrett declaration is silent on this point, Ground 2 should be denied for this reason alone with respect to claim 6.

B. Petitioner Has Not Addressed How The Prior Art Meets Elements 1c And 6c Beyond Merely Disclosing An Antegrade Approach

Petitioner has failed to articulate how the limitation “configured to conform to a direction of blood flow” in Elements 1c and 6c, properly construed, is present in the prior art, beyond merely disclosing an antegrade approach. As explained above regarding the construction of this term, Petitioner incorrectly equates this term with “antegrade.” Instead, the correct construction requires the wire to possess a
property or structure for adapting to the direction of blood flow, which neither Lattouf (Ex. 1005) nor Spenser (Ex. 1010) disclose, either expressly or inherently.

1. **Lattouf does not expressly disclose elements 1c and 6c**

   For the same reasons explained above regarding Ground 1, Lattouf does not expressly or inherently disclose a wire that is "configured to conform to a direction of blood flow."

2. **Spenser does not expressly disclose elements 1c and 6c**

   Spenser (Ex. 1010) teaches balloon-deployed replacement aortic valves for retrograde delivery through the aorta into the aortic valve annulus. (As Petitioner has noted, Spenser mentions antegrade deployment of the valves, but the Spenser figures do not show antegrade embodiments. Pet. 51.) Spenser FIG. 4 (Ex. 1010 at 4) is shown at left. FIG. 4 shows balloon 52 at target location 54, the aortic valve position (Id., ¶ 114). Support stent 50 supports an implantable valve (Id., ¶ 175). Balloon 52 is suspended from an unnamed and undescribed element in aorta 56. (Id., ¶ 176).
Spenser FIG. 16c (Id. at 19) is shown here. FIG. 16c shows the aorta curving up and to the left from the left ventricle. This view is presumably a posterior view, in contrast to the anterior views shown in the Schematic drawings. FIG. 16c shows two inflatable chambers: a large unnumbered balloon, in the top of the left ventricle (Id., ¶ 189), and balloon 305. The large balloon is expanded in the left ventricle and then the whole device is pulled slightly backwards, to position the stent device, by an unnamed and undescribed element that is shown in the aorta (Id.).

Spenser FIG. 17b (Ex. 1010 at 20) is shown here. FIG. 17b shows proximal stent 300, prior to balloon dilation, in the natural aortic valve position. (Id., ¶ 200) Deployable stent 320 is positioned by an unnamed, undescribed element that is shown in the aorta.

C. Petitioner Has Not Established That Elements 1c And 6c Are Necessarily Present In The Prior Art To Meet The High Standard For Inherency

To the extent Petitioner relies on the doctrine of inherency to meet the limitation “configured to conform to a direction of blood flow…such that the guidewire follows the blood flow until a length of the guidewire extends at least
from a ventricular apex of the heart through an aortic valve of the heart" in Elements 1c and 6c, Petitioner has not met the “high standard” that is required “in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis.” *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1195-1196 (Fed. Cir. 2014). As the Federal Circuit has explained, “the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art.” *Id.* (emphases added).

Here, Petitioner’s own cited references show that the prior art guidewires on which Petitioner relies would not necessarily have conformed to a direction of blood flow.

1. **The Lattouf provisional application does not necessarily teach that Lattouf's aortic procedure required apical access**

   Petitioner reached to the Lattouf Provisional Application (Ex 1025) to show an example of an aortic procedure. Pet. 14, 51. The sole explicit Lattouf teaching about the aorta is the single sentence, "Other procedures which may be performed include…aortic stenting for aortic dissections and aneurysm therapy…” (Ex. 1005, ¶ 8). Lattouf shows no drawings of aortic valve therapy. The sole provisional application drawing is shown in part below. The provisional application does not show or describe a guidewire.
Lattouf’s provisional application does not discuss how or where Lattouf’s catheter enters the heart. The provisional application identifies the catheter as an "endoventricular and endoarterial interventional catheter," suggesting the possibility of arterial access, not apical access.

Dr. Huber testified as follows about different possibilities for the introduction of the Lattouf provisional application the heart:

**A.** How this catheter came to lie here might as well be that it came all the way from the groin, retrograde fashion, and then piercing out of the apex from within what has been performed.

**Q.** Have you ever heard of something --

**A.** Of course.

**Q.** -- like that happening before?

**A.** Yes, of course.

Ex. 2005, 1/27/16 Huber Dep. Tr., 176:3-11
Q. And looking at [the apparatus shown in the provisional], you think…think it's more likely that they went retrograde than antegrade…?

A. "…how he got to install the device here, I don't know. But what I can tell you is that the way the prosthesis was delivered that makes the largest part of the illustration, that was certainly a retrograde fashion, because otherwise it wouldn't work from what I see here.

Q. And how do you know it wouldn't work…?"

…

Q. And what is it?

A. "…in order to open that [deploy the prosthesis for endoaortic stenting], you need a delivery system, and the sheath on the delivery system has to be pulled back in order to open at the distal portion first, and then opens, close it, close it, close it.

So, the way this prosthesis has been implanted implied that there was a back movement coming from the aorta back to the left ventricle to the operator.

Q. "…wouldn't it make sense that the device went up, and then it was pulled back as it was released?

A. I agree with you that the device on this drawing has come from the apical side to be positioned here, and then released retrograde. But how the beginning of the procedure was performed to get the catheter into here, this cannot be concluded from this.

Q. I understand. It could equally be either way?

A. Yes.
Q. So, it could have gone up and come back, or it could have gone retrograde from femoral, as you're saying?

A. Yes.


Lattouf's provisional application catheter, therefore, may have operated from the apical side of the aortic valve, but it did not necessarily enter apically. It also does not show or describe a guidewire and, therefore did not necessarily require a guidewire extending from the apex to the aorta.

2. **Petitioner erroneously relied upon Semple and Dr. Garrett to show that the Lattouf device inherently follows the blood flow such that the guidewire follows the blood flow until a length of the guidewire extends at least from a ventricular apex of the heart through an aortic valve of the heart**

Petitioner argued that the Lattouf technique "was known to result in the guidewire following the blood flow such that the guidewire follows the blood flow until a length of the guidewire extends at least from a ventricular apex of the heart through an aortic valve of the heart" See Pet. 42, 46, 55, 58. Petitioner erroneously relied upon Semple (Ex. 1024) and Garret (Ex. 1026, ¶ 76) for support.

3. **The teachings of Semple et al., 1968, and the teachings of Seldinger diametrically oppose Dr. Garrett's position**

Petitioner erroneously posits that the Lattouf guidewire is configured to conform to the blood flow just like a Seldinger wire is configured to conform to the blood flow.
Semple placed a completely soft Teflon catheter snugly over a narrow needle. Ex. 1024 at 402, 405. The catheter did not extend to the needle tip. The needle was inserted through the ventricular wall. Upon detection of blood pressure through the needle, the catheter was advanced beyond the needle and the needle was withdrawn, leaving the Teflon catheter alone in the left ventricle.

The Teflon catheter was so soft that it was necessary to advance the Teflon catheter an inch or two into the ventricle before withdrawing the needle to "prevent the soft catheter from entering the pericardium (see Schematic A) and looping outside the heart as happened in two of our early patients." Id. at 405. As Petitioner noted, "In most cases, further gentle advancement of the soft teflon catheter takes it into the aorta along with the blood flow." Id. at 402.

When the completely flexible Teflon catheter did not go along with the blood, "a Seldinger guide wire is introduced and this usually passes easily into the aorta, the Teflon catheter following." Pet. at 55, 58.

Petitioner posits that the Lattouf guidewire is configured to conform to the blood flow just like the Seldinger wire is configured to conform to the blood flow. However, as set forth above, Seldinger taught primarily a retrograde procedure—one in which the wire is advanced against blood flow. It is evident that Semple understood this, because Semple used the Seldinger wire and the completely flexible catheter reach the left atrium retrograde—against the blood flow. The
Seldinger guidewire, therefore, was stiff enough for the retrograde procedure.

Thus, although petitioner analogizes from Seldinger to Lattouf to show that Lattouf would have been known to conform to the blood flow, the opposite is true: the Seldinger wire was configured to \textit{not} conform to the blood flow.

\textbf{4. Dr. Garrett improperly derived from Seldinger that Lattouf necessarily conforms to the direction of blood flow}

Petitioner's Declaration of John R. Garrett, M.D., reasons that because Lattouf implements the Seldinger technique, the Lattouf guidewire must necessarily conform to the direction of blood flow. Ex. 1026, ¶ 76. As set forth above, Seldinger advanced a wire against the blood flow. And Semple demonstrated that, like Lattouf, a stiff wire is required to traverse the mitral valve retrograde. The Declaration thus fails to explain why implementation of Seldinger means that the Lattouf guidewire necessarily conforms to the blood flow.

\textbf{5. Garrett failed to cite Semple, so the application of Semple principles to Lattouf is mere attorney argument}

Although Dr. Garret attempted to derive principles from Seldinger, Dr. Garrett did not cite Semple. Petitioner's position based on Semple that the Lattouf technique "was known to result in the guidewire following the blood flow such that the guidewire follows the blood flow until a length of the guidewire extends at least from a ventricular apex of the heart through an aortic valve of the heart" (Pet. 42, 46) is therefore no more than attorney argument.
D. Petitioner Has Failed To Demonstrate Interchangeability And Predictability Of Transseptal And Transapical Approaches To Establish Obviousness

Conclusory and unsupported assertions, as the Board has often held, are insufficient to establish a reasonable likelihood of obviousness. See IPR2015-01774 (Paper 15); IPR2015-01696; IPR2013-054 (Paper 12); IPR2014-00347 (Paper 9); Office Patent Trial Practice Guide, 77 Fed. Reg. 48, 756, 48,763 ("Affidavits expressing an opinion of an expert must disclose the underlying facts or data upon which the opinion is based.").

1. Petitioner and Dr. Garrett ignored that Lattouf's apical access is not for high ventricular pressures associated with aortic stenosis

The Petitioner asserted that Lattouf's transapical approach was a "workable alternative" and an "obvious alternative" for left ventricular catheterization—that Spenser's aortic valve could be executed, like Lattouf, from the apex. Pet. 52. The Petitioner also alleged that it would be obvious to modify the apparatus of the Lattouf provisional or nonprovisional applications with the Spenser valve. Id.

Reference cited by Petitioner (e.g., Wong (Ex. 1013) and Cata (Ex. 1044)) show that successful performance of left ventricular puncture is associated with small puncture diameter. Lattouf delivers small diameter “dry” instrumentation that, while it may be larger than the Wong and Cata catheters, would be understood by a POSA to be smaller than a prosthetic valve having “wet” tissue leaflets that
are not compressible. It is logical that this would be especially true when aortic stenosis is present. The only aortic indications that Lattouf treats are aortic dissections and aneurysm therapy…” Ex. 1005, ¶ 8. Lattouf does not mention aortic stenosis in either his provisional application or his nonprovisional application. It would have been logical for Lattouf to omit aortic stenosis because of increased morbidity risk caused by the higher pressure associated with aortic stenosis. Also, it is sensible that Spenser would have accepted the complexity of the retrograde approach for treating aortic stenosis based on the likely increased morbidity of an apical approach. Only Huber overcame the well-known resistance to dilating an access hole in the apex wide enough to admit a heart valve.

2. **Dr. Garrett implied that apical access carries acceptable risk, but failed to explain the relevant risks or how to evaluate them**

Patent Owner points out that Garrett "reasons" that apical access is an "obvious alternative" "depending on the limitations and risks" presented by the anatomy of a given patient. Pet. 52. Garrett, however, does not state how or why the alleged obviousness of the alternative depends on the limitations and risks. Garrett does not provide any qualitative or quantitative data or sources that characterize the risk, whether with respect to type or degree.

Garrett does mention risk trade-offs, at least qualitatively, but only in connection with the balance of risk between non-intervention and conventional
surgery, and not in connection with different non-surgical access sites to the heart, whether transseptal, apical or otherwise. Ex. 1026, ¶ 23.

Petitioner does not explain the relevance of risk-balancing to the obviousness determination. To what extent, if at all, does a countervailing exigency undercut a teaching away?

3. In reaching his conclusion that apical access is an "obvious alternative," Garrett failed to frankly discuss publicized risks that he attempted to neutralize in his conclusory statements.

Garrett (Ex. 1026, ¶ 69) also reviewed ventricular access references other than Neish, including Golding (Ex. 1012), Morgan (Ex. 1043) and Cata (Ex. 1044)

Golding FIG. 1, shown here, shows aortic cannulation from the apex using a large diameter cannula (20 Fr). Ex. 2012 at 626 (aortic valve, obscured, at base of aorta). Golding cautioned, "Obviously, such a technique is not practical for patients with calcific aortic stenosis, in whom the cannula could then completely occlude the aortic orifice…". Id. at 627.

Morgan reported about left ventricular that "in our series a possible relationship between death and direct LV [(left ventricular)] puncture could be found in only
one patient, but even then severe aortic stenosis was the likely cause of death." Ex. 1043 at 89.

Cata reported, for haemodynamic measurement, left ventricular puncture with a small diameter (4 Fr) catheter. Ex 1044 at 253. Cata praised the approach, reporting, "The advantage over previous techniques is the smaller hole made in the left ventricular myocardium [define myocardium; define left ventricular puncture]." *Id.* at 254-255.

4. **Garrett failed to consider evidence that today left ventricular puncture remains risky**

Pitta (Ex. 2002) reported retrospectively, in 2010, on numerous cases of left ventricular puncture ("LVAP"), a "rarely used procedure," including those of Morgan (Ex. 1043, discussed above) and Semple (Ex. 1024). Ex. 2002 at 994-995. Pitta, FIG 4 (*Id.* at 996), reproduced here, shows the frequency distribution of access-related complications occurring during LVAP. Pitta concluded: "Apical access site related complications were higher in patients requiring LVAP for intervention that for diagnostic purposes (25% vs. 12.5%)." *Id.* at 993. Pitta also concluded that "LVAP is associated with a significant incidence
of access-related complications, particularly in patients requiring LVAP for interventional [not merely diagnostic] purposes." *Id.* at 996.

5. Garrett concluded that transseptal and transapical approaches are "fairly interchangeable," but failed to explain what that means or how he arrived at that conclusion despite abundant evidence that the two are not plainly "interchangeable"

The Garrett Declaration states also that "the transseptal and transapical approaches were 'fairly interchangeable,' as both followed the antegrade direction." Ex. 1026, ¶ 44. Petitioner notes that, as shown in the schematics, "antegrade direction" is a direction relative to the blood flow. The fact that two different procedures involve "antegrade" delivery at the aortic valve do not make them interchangeable or even "fairly interchangeable." Does that mean that in Dr. Garrett's view it would be fair to trade one for the other? Does that mean that in Dr. Garrett's view they are *somewhat* interchangeable? It would appear that perhaps neither of those is correct.

Furthermore, Garrett did not tie "fairly interchangeable" to any of the principles that Garret articulated as being relevant to the determination of obviousness, such as predictability of a combination or a modification. See *id.*, ¶¶ 13-14.

a. *Petitioner reportedly engaged in "unparalleled efforts," requiring unprecedented collaboration between surgeons and*
interventional cardiologists to develop its own transapical approach

In 2005, Petitioner began developing its own "fairly interchangeable" transapical approach for heart valve replacement in November, 2004. Ex. 2031 at 175 ("[U]nparalleled joint efforts between cardiac surgeons and cardiologists” were applied to further develop therapeutic options for high-risk patients, because of "the awareness that a retrograde transfemoral approach may not be suitable in some patients… an antegrade approach from the left ventricular apex might be feasible…” Drs. Mack and Mohr "started an initiative at Edwards Lifesciences to work on transapical antegrad access...Initial experimental experience was gathered in November and December 2004…[I]nitial clinical implantations were done in two patients in Leipzig in December 2004” However, due to the lack of a 26 mm prosthesis, severe paravalvular leakage occurred. “Towards the end of 2005, a 26 mm SAPIEN prosthesis became available, together with a clear concept of using oversizing. The clinical use of TA AVI was restarted successfully in February 2006…with the support of Professor Cribier.").

b. Neither petitioner nor the medical community immediately adopted the transapical approach

i. Petitioner

A full year after the '530 patent was filed, Drs. Mack and Mohr concluded that the apical approach is "now an additional option." Ex. 2032 (Edwards
Lifescience Corporation "announced today the successful completion of the first minimal-access, beating-heart surgical procedure for replacing a patient's aortic heart valve. Edwards is planning on developing the Ascendra aortic heart valve replacement system as an additional option for valve surgery…[The system] is not yet commercially available, and the company plans to continue to evaluate its feasibility in…2006.")

ii. The Surgical Community

The surgical community was slow to rely upon transcatheter aortic valve procedures. Dr. Mohr, associated with Petitioner, urged the surgical community to adopt transcatheter approaches, in particular transapical approaches, citing four papers naming Huber as author. Ex. 2033, Walther and Mohr Editorial (“Aortic Valve Surgery: Time to be open-minded and to rethink”). Other authors associated with Petitioner reported that “[S]ome skepticism [about the transapical approach] remains within the surgical and cardiological communities. Therefore, prospective randomized studies should be performed, comparing transapical as well as transfemoral transcatheter valve implantation techniques, to the gold standard of conventional [surgical] aortic valve replacement surgery. Future protocols are being developed at present.” Ex. 2034, Walther et al. at 15, naming as co-authors other Petitioner associates: Greinecker, Mack and Mohr, and citing Huber et al., Ex. 2035.
The Petitioner's wobbly route, from the failure of Cribier prior to the '530 filing date to the skepticism after the filing date better, support the propositions that (1) the movement to transapical was based not on peripheral artery disease, but on Cribier's shortcomings; and (2) two years after Petitioner's first experiments on animals, Petitioner acknowledged ambivalence about the viability of the transapical approach, and that therefore the Cribier antegrade approach and the transapical antegrade approach are not fairly interchangeable.

Furthermore, along that wobbly route, Petitioner validated Huber's approach. Ex. 2036, Dewey, at 111 [AK2]("Previous reports have described the use of the left ventricular apex as a reproducible route for minimally invasively accessing the aortic annulus.") citing Huber et al., Ex. 2035 (authors Drs. Mohr, Mack, Dewey, Doss, and Wimmer-Greinecker being associated with Petitioner).

6. The American College of Cardiology, represented in part by two Edwards Lifesciences Corporation consultants, points out that percutaneous heart valve transplant ("phvt") requires valve-specific skill

The American College of Cardiology sought to provide a consensus-based framework for clinical research directed at further testing of PHVT. The College articulated the views of an April 212, 2004 workshop that included representatives of Edwards Lifesciences, "LLP." Ex. 2030. Those views included General Guidelines Regarding Clinical Trial Design for PHVT ("Use of PHVT requires skill sets independent of the operator's base discipline, and specific training should
be required before engaging in any percutaneous valve procedure.") *Id.* at 1555. Furthermore, "[T]he surgeon's valve experience should be specific for the device under consideration (i.e., a surgeon with a large volume of aortic valve replacement and minimal mitral valve repair would only qualify for an aortic device study.)"

**VII. THE PETITION SHOULD BE DENIED BECAUSE SUBSTANTIALLY THE SAME PRIOR ART AND ARGUMENT WERE PREVIOUSLY CONSIDERED**

Both of Petitioner’s two grounds rely on Lattouf (Ex. 1004). Ground 1 asserts “Cribier in view of Neish and Lattouf,” and Ground 2 asserts “Lattouf in view of Spenser.” However, Lattouf was cited repeatedly by the Examiner during prosecution, in at least four Office Action rejections (see table below), which ultimately were overcome. In addition, Spenser is an application publication issued as a patent (U.S. 6,730,118), which likewise was cited during prosecution and is thus listed on the face of the ’530 patent. Only Neish and Cribier were not cited during prosecution.

Particularly in light of the rejections that relied on Lattouf, Petitioner has not explained what Cribier, Neish and Spenser disclose that make them better references than the references that the Examiner tried to combine with Lattouf (namely, Seguin ’060, Seguin ’304, and Garrison).
Because none of Petitioner’s references are “more specific than” or “differ materially from” those previously considered during prosecution (which Petitioner has not attempted to distinguish whatsoever), the Board should deny institution under 35 U.S.C. § 325(d). Sanofi-Aventis U.S. LLC v. Genentech, Inc., IPR2015-01624, at 24 (PTAB Feb. 5, 2016); Ube Maxell Co. v. Celgard LLC, IPR2015-01511 at 9 (PTAB Jan. 7, 2016) (denying institution under § 325(d)).

VIII. GROUND 1 IS CUMULATIVE WITH GROUND 2

Petitioner has not explained why two separate grounds, each of which relies in part on Lattouf, are needed in this proceeding. As the moving party, Petitioner bears the burden of proving it is entitled to the requested relief, namely, institution on two grounds. See 37 C.F.R. § 42.22(c). In its petition, Petitioner “did not provide a meaningful distinction between the different, redundant rejections,” and therefore the Board should “not authorize[e] what appear[s] to be redundant challenges because an inter partes review had been instituted on the same factual basis.” Illumina, Inc. v. Trustees of Columbia University, IPR2012-00006 at 12 (PTAB May 10, 2013) (denying some grounds as cumulative of other grounds in the same petition); see Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co., CBM-2012-00003 at 2 (PTAB Oct. 25, 2012) (denying redundant grounds in absence of meaningful distinction).
IX. CONCLUSION

For the foregoing reasons, Patent Owners respectfully request that the Board
deny the Petition for Inter Partes Review of the ‘530 Patent.

Date: March 15, 2016

Respectfully submitted,

/s/ Edward M. Arons
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Lead Counsel for Patent Owner
CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the PATENT OWNER’S

PRELIMINARY RESPONSE was served on March 15, 2016, via FEDEX

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