Federal Court  Cour fédérale

Date: 20220531

Docket: T-549-20

Citation: 2022 FC 715

Ottawa, Ontario, May 31, 2022

PRESENT: Madam Justice Pallotta

BETWEEN:

JANSSEN INC. AND ACTELION PHARMACEUTICALS LTD

Plaintiffs

and

SANDOZ CANADA INC.

Defendant

PUBLIC JUDGMENT AND REASONS

(Confidential Judgment and Reasons Issued May 12, 2022)

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I. **Introduction**

[1] The plaintiffs, Janssen Inc. (Janssen) and Actelion Pharmaceuticals Ltd (Actelion), bring this patent action against Sandoz Canada Inc. (Sandoz) pursuant to subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [*PMNOC Regulations*], made under the *Patent Act*, RSC 1985, c P-4 [*Patent Act*].

[2] Janssen markets the prescription medication OPSUMIT® in Canada. OPSUMIT® is a film-coated tablet containing 10mg of macitentan as the active ingredient, for the treatment of pulmonary arterial hypertension (PAH). PAH is a serious and incurable condition of high blood pressure in the blood vessels of the lungs, caused by changes to the arteries that transport deoxygenated blood from the heart to the lungs for reoxygenation. If left untreated, the high blood pressure strains the heart, leading to heart failure and death.

[3] OPSUMIT® belongs to a class of drugs known as endothelin receptor antagonists (ERAs). ERAs work by binding to endothelin receptors within the walls of blood vessels, preventing endothelin from binding to these receptors. Endothelin binding is one of the steps in the endothelin pathway, a biological pathway that causes smooth muscle cells in blood vessel walls to constrict and proliferate, forcing the heart to work harder to push blood through the narrowed and thickened arteries. By blocking the endothelin binding step, ERAs disrupt the vasoconstricting and proliferative effects of the endothelin pathway.

[4] OPSUMIT® can be prescribed alone or in combination with another class of drugs known as phosphodiesterase type-5 inhibitors (PDE5-Is). Like ERAs, PDE5-Is affect blood

pressure, but they do so by enhancing the vasorelaxation and anti-proliferative effects of another biological pathway—the nitric oxide (NO) pathway. The vasorelaxation and anti-proliferative effects of the NO pathway are mediated by cyclic guanosine 3',5'-monophosphate (cGMP). PDE5-Is work by blocking the effects of PDE5, an enzyme that breaks down cGMP.

[5] Currently, Janssen is the only company authorized by Health Canada to sell macitentan as a prescription medication. Sandoz seeks Health Canada's approval to sell a generic prescription medication containing 10mg of macitentan as the active ingredient, for use alone or in combination with PDE5-Is. The plaintiffs allege Sandoz will infringe claims 21-31 (Asserted Claims) of Actelion's Canadian Patent No. 2,659,770 titled "Therapeutic Compositions Comprising a Specific Endothelin Receptor Antagonist and a PDE5 Inhibitor" (770 Patent).

[6] The 770 Patent relates to macitentan in combination with a PDE5-I to treat diseases wherein vasoconstriction is involved, including PAH. Claim 21 is an independent claim of the 770 Patent that claims the use of macitentan in combination with a PDE5-I to treat a disease wherein vasoconstriction is involved. The other Asserted Claims depend directly or indirectly on claim 21 and they are narrower in scope. The dependent claims include limitations on the specific PDE5-I, the specific disease, or both.

[7] For the purposes of this proceeding only, Sandoz concedes it would infringe the Asserted Claims if it is authorized to market macitentan tablets in Canada. Sandoz defends the plaintiffs' allegations on the basis that the Asserted Claims are invalid.

[8] Sandoz advances four grounds of invalidity. Sandoz asserts that each Asserted Claim is invalid for one or more of the following reasons: (i) the subject matter of the claim was obvious in view of what was already publicly known; (ii) the inventor had not demonstrated or soundly predicted the utility of the claimed invention; (iii) the claim is overly broad, claiming more than what the inventor actually made or disclosed; and (iv) the 770 Patent specification does not correctly and fully describe how macitentan in combination with a PDE5-I would be used to treat various diseases of vasoconstriction, failing to meet the sufficiency requirements of paragraphs 27(3)(a) and (b) of the *Patent Act*.

[9] For the reasons below, Sandoz has not established that the Asserted Claims are invalid based on the alleged grounds of invalidity. The plaintiffs are entitled to a declaration that Sandoz would infringe the Asserted Claims by making, constructing, or using its macitentan tablets in Canada.

II. **Background**

A. *The Parties and the Nature of this Proceeding*

[10] Janssen is a pharmaceutical company with a head office in Toronto, Ontario. Actelion is a pharmaceutical and biotechnology company with a head office in Allschwil, Switzerland. Janssen is wholly owned by Johnson & Johnson, which acquired Actelion in 2017. Both Janssen and Actelion are members of the Johnson & Johnson group of companies. Janssen is a "first person" within the meaning of subsections 4(1) and 6(1) of the *PMNOC Regulations*. Actelion is the registered owner of the 770 Patent and is a necessary party to this action under subsection 6(2) of the *PMNOC Regulations*.

[11] Sandoz is a pharmaceutical company with a head office in Boucherville, Quebec. Sandoz is a "second person" within the meaning of subsections 5(1) and 6(1) of the *PMNOC Regulations*.

[12] Sandoz filed an Abbreviated New Drug Submission (ANDS) with Health Canada, seeking authorization to market 10mg macitentan tablets based on their equivalent pharmaceutical and bioavailability characteristics, when compared to OPSUMIT®.

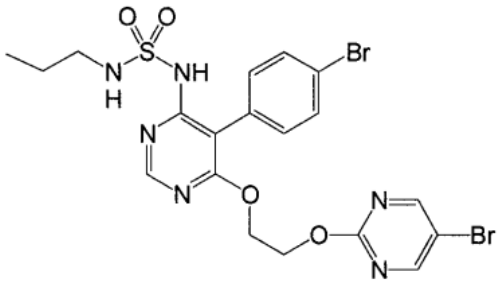
[13] The Minister of Health maintains a list of patents related to drugs that have been authorized for sale under a notice of compliance (NOC). As a condition of obtaining market authorization for its macitentan product, the *PMNOC Regulations* required Sandoz to address the patent list for OPSUMIT®. Sandoz served a Notice of Allegation on April 1, 2020 and the plaintiffs commenced this action in response.

[14] When this action was commenced, three patents were listed in relation to OPSUMIT®: Canadian Patent No. 2,437,675, Canadian Patent No. 2,621,273, and the 770 Patent. Canadian Patent No. 2,437,675 has expired, and Canadian Patent No. 2,621,273 is not at issue in this action. Only the 770 Patent is at issue.

[15] By commencing this action, the plaintiffs triggered a stay that prevents the Minister of Health from issuing an NOC to Sandoz for up to 24 months, that is, before May 14, 2022, in order to allow time for the action to be heard and decided.

B. *The 770 Patent*

[16] The 770 Patent was issued on November 18, 2014. It relates to a specific compound, referred to throughout the patent as "formula (I)", in combination with a PDE5-I to treat diseases wherein vasoconstriction is involved. Formula (I) is identified by the following diagram of its chemical structure:



(I)

[17] There is no dispute that formula (I) is the compound now known as macitentan, the active ingredient in OPSUMIT®, and that formula (I)/macitentan is an ERA.

[18] The first paragraph of the 770 Patent specification describes the invention as relating to a product containing a compound of formula (I) in combination with at least one compound having PDE5-inhibitory properties for therapeutic use in the treatment of a disease wherein vasoconstriction in involved. Some of the Asserted Claims do not include a limitation on the disease, while others are limited to: hypertension and pulmonary hypertension (PH), PH specifically, or PAH specifically.

[19] The patent specification defines "compound having PDE5-inhibitory properties" to be a compound that meets or exceeds a threshold measurement of its ability to inhibit PDE5

according to an experimental test protocol described in the patent. Examples of such compounds are sildenafil, vardenafil, tadalafil, and udenafil. Some of the Asserted Claims do not include a limitation on the PDE5-I, and others are limited to: the four example PDE5-Is, sildenafil or tadalafil, sildenafil specifically, or tadalafil specifically.

C. *The Circulatory System and Diseases Involving Vasoconstriction*

[20] Vasoconstriction is the constriction of the vasculature (arteries and veins) of the circulatory system. The vasculature can be divided into two circuits that circulate blood between the body, heart, and lungs. The systemic circuit involves the left side of the heart, which pumps oxygenated blood from the heart to the rest of the body (except the lungs). The pulmonary circuit involves the right side of the heart, which pumps deoxygenated blood from the heart to the lungs for reoxygenation.

[21] The 770 Patent specification lists particular diseases said to involve vasoconstriction: hypertension, PH (including PAH), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris. The following provides a brief description of each disease of vasoconstriction listed in the 770 Patent.

[22] Hypertension is a condition of persistently raised blood pressure in the systemic circulatory system (also known as systemic hypertension and colloquially referred to as “high blood pressure”). Long-term excessive force of the blood against the artery walls can damage the blood vessels and organs.

[23] PH is a general term that describes abnormally high blood pressure in the pulmonary circulatory system. The blood pressure in the pulmonary circulation is far lower than in the systemic circulation. Abnormally high blood pressure in the pulmonary circulation is defined hemodynamically as a mean pulmonary arterial pressure of 25 mmHg or higher.

[24] PAH is one subtype of PH. As noted above, PAH is a progressive and incurable disease where the artery walls of the lungs constrict and thicken, increasing vascular resistance to blood flow and making the right side of the heart work harder to push blood through narrowed arteries. The extra stress causes the right ventricle of the heart to enlarge and dilate. Over time, the changes become unsustainable. The right ventricle weakens, its ability to push blood out of the heart to the lungs is compromised, and eventually, the heart fails.

[25] Diabetic arteriopathy is a vascular disease caused by accelerated atherosclerosis, a condition in which plaque builds up and hardens in the arteries of diabetic patients. Over time this narrows the arteries, which limits the flow of oxygenated blood to the body.

[26] Heart failure is a disorder of cardiac performance where the heart is unable to meet the blood supply needs of the body. Patients with congestive heart failure may be breathless or fatigued during exertion, or even at rest.

[27] Erectile dysfunction is an inability to obtain and maintain a penile erection sufficient for sexual intercourse. Penile erection is dependent upon a balance between vasoconstricting and vasorelaxing forces on cavernosal smooth muscle, which requires adequate levels of cGMP.

Inhibitors of enzymes that degrade cGMP, particularly PDE5-Is, aid in vasodilation and thus erection.

[28] Angina pectoris is a disorder of vascular obstruction (a narrowing or blockage) of arteries that supply the heart muscle itself, which leads to chest pain or discomfort.

III. **Issues and Relevant Dates**

[29] The issues in this action relate to claim construction and validity of the Asserted Claims. Infringement of the Asserted Claims is not an issue that is before the Court. Since Sandoz concedes that it would infringe the Asserted Claims for the purposes of this proceeding, the parties agree that the plaintiffs are not required to establish infringement of the essential elements of any Asserted Claims.

[30] The 11 Asserted Claims of the 770 Patent must be construed—that is, interpreted—before there is an assessment of whether they are valid: *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 43 [*Whirlpool*]. Doing so requires that the claims be read in an informed and purposive way, from the perspective of a notional person of ordinary skill in the art or science to whom the patent is addressed (skilled person): *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 44 [*Free World*].

[31] In this case, the parties and their expert witnesses disagree on the qualifications of the skilled person and the relevant experience and knowledge that person would bring to bear on the issues in the action. The first issue for the Court is to define the skilled person.

[32] The parties' disagreement on the skilled person affects their respective positions on issues of validity, but it does not affect their positions on claim construction. The parties and their experts agree on what the Asserted Claims mean. However, the Court is not required to accept the parties' or the experts' proposed construction. Claim construction is a matter of law for the Court to decide: *Whirlpool* at para 61; *Zero Spill Systems (Int'l) Inc v Heide*, 2015 FCA 115 at para 41 [*Zero Spill*]. The construction of the Asserted Claims is the second issue.

[33] Sandoz alleges that each of the Asserted Claims is invalid. The claims of a patent are presumed to be valid and Sandoz bears the burden of proving invalidity on a balance of probabilities. The parties' joint statement of issues outlines the following validity issues in respect of the 770 Patent:

(i) Obviousness: Are any of the Asserted Claims invalid on the basis of obviousness?

(ii) Utility: Are any of the Asserted Claims invalid for lack of utility (i.e. no demonstration of utility or sound prediction of utility)?

(iii) Overbreadth: Are any of the Asserted Claims invalid for overbreadth (i.e. claiming more than what the inventor made or disclosed)?

(iv) Sufficiency: Does the 770 Patent meet the sufficiency requirements of paragraphs 27(3)(a) and (b) of the *Patent Act*?

[34] The relevant date for construing the claims of a patent is the date the patent application was published. The application for the 770 Patent was published on March 6, 2008.

[35] The same date, March 6, 2008, is the relevant date for determining whether the Asserted Claims are invalid for (iv) failing to meet the sufficiency requirements of paragraphs 27(3)(a) and (b) of the *Patent Act*. For simplicity, I will sometimes refer to the publication date as March 2008 or simply 2008.

[36] The claim date (section 28.1 of the *Patent Act*) is the relevant date for determining whether the Asserted Claims are invalid for (i) obviousness, (ii) lack of demonstrated or soundly predicted utility, and (iii) overbreadth. The application for the 770 Patent was filed in Canada on August 28, 2007, however, the application claimed the benefit of an earlier priority date based on applications that were filed on August 29, 2006 and October 19, 2006 (the October 19, 2006 application differs from the August 29, 2006 application in that it includes additional results from experimental testing on macitentan).

[37] The parties do not allege any differences in the relevant prior art or the common general knowledge of the skilled person as of any of these dates. Consequently, it makes no difference to the result if the earliest priority date is the claim date for the obviousness analysis, and the parties have addressed the question of obviousness as of August 29, 2006. For simplicity, I will sometimes refer to this date as August 2006 or simply 2006.

[38] Similarly, the parties do not allege any material difference in assessing utility or overbreadth as of the priority date or the Canadian filing date. The parties have addressed those issues as of the Canadian filing date (August 28, 2007). For simplicity, I will sometimes refer to this date as 2007.

IV. **Evidence**

[39] The parties agreed on a number of facts. They provided a joint scientific primer and a joint statement of facts.

[40] The parties introduced expert evidence in support of their respective positions on claim construction and validity. Since Sandoz bears the burden on validity, the parties had agreed that Sandoz would serve its expert reports first and the plaintiffs would serve responding expert reports. Sandoz did not file a reply expert report. The trial evidence followed the same sequence, with Sandoz leading its evidence first.

[41] Sandoz relied on the evidence of one expert witness, Dr. Randall Zusman. The plaintiffs relied on the evidence of two expert witnesses, Dr. Jean-Luc Vachiery and Dr. Murali Chakinala. The plaintiffs also called Dr. Martine Clozel, the sole inventor named in the 770 Patent, as a fact witness.

[42] The following summarizes each expert witness' qualifications and provides an overview of the witnesses' testimony.

A. *Dr. Zusman (Sandoz's Expert Witness)*

[43] Dr. Zusman is a medical doctor specializing in cardiology at the Massachusetts General Hospital (MGH) in Boston, Massachusetts. Dr. Zusman received his M.D. from the Yale University School of Medicine in 1973. He completed his internship, residencies, and chief residency at the MGH. Dr. Zusman has over 42 years of experience as a physician and clinical

researcher. He was board certified in internal medicine in 1976 and cardiovascular diseases in 1983. Since 1982, Dr. Zusman has been the Director of Hypertension at the MGH Cardiac Unit. He is also an Associate Professor in Medicine at Harvard Medical School.

[44] Dr. Zusman's clinical activities include the care of patients with hypertension, PH, PAH, hyperlipidemia, cardiovascular risk factors, and other vascular diseases. Dr. Zusman is active in professional societies including American College of Cardiology, American Heart Association, and American Society of Hypertension. He has been an editor and a member of the editorial board for several scientific journals on the topics of cardiology and hypertension.

[45] At trial, the plaintiffs objected to the admissibility of Dr. Zusman's report and his ability to testify. The plaintiffs first notified Sandoz and the Court that they intended to raise this objection during their opening statement at trial. The plaintiffs' objection could have disqualified Dr. Zusman from testifying at trial, and it should have been raised "as early as possible in the proceeding", instead of the day of his scheduled testimony: Rule 52.5 of the *Federal Courts Rules*, SOR/98-106. Nonetheless, I allowed the plaintiffs to argue their objection following their cross-examination on Dr. Zusman's qualifications. The plaintiffs argued that Dr. Zusman is not properly qualified to provide expert evidence in respect of the issues in this action because he does not have the requisite expertise in PH and PAH, which they contend to be the focus of the 770 Patent. While the plaintiffs presented a second argument, that the expertise as set out in Dr. Zusman's proposed qualifications overreaches, it boiled down to the same concern: according to the plaintiffs, when Dr. Zusman's evidence is properly narrowed to relate only to

his actual expertise, there would be no purpose in having him testify because his opinion would only cover tangential issues.

[46] Sandoz argued that while the commercial embodiment of macitentan is related to PAH, the 770 Patent is broader and does not exclude one disease condition over another. The 770 Patent is about treatment of diseases of vasoconstriction, the skilled person does not change on a claim-by-claim basis, and Dr. Zusman is properly qualified to give expert evidence. He has experience treating patients with the diseases referred to in the 770 Patent, including seeing 300-400 patients a year with PH. While PAH is not the focus of his practice, it is also a rare disease: *Hoffmann-La Roche Limited v Sandoz Canada Inc*, 2021 FC 384 at para 139.

[47] The following morning I issued a ruling that I was satisfied Dr. Zusman had the requisite expertise and qualifications to give expert opinion evidence on the material issues in dispute. I had not yet made any determinations regarding the focus of the 770 Patent and the characteristics of the skilled person to whom the patent is addressed. I stated that the importance of any specific expertise was a question that remained to be determined. I also noted that an expert witness may be in a position to opine on what the skilled person would know or understand, even if their qualifications do not mirror those of a skilled person: *Halford v Seed Hawk Inc*, 2006 FCA 275 at para 17. I held that Dr. Zusman's evidence would be necessary to assist me in deciding material issues in this case and I was satisfied that Dr. Zusman had sufficient experience in the subject matter of his opinion to find that his report and testimony were admissible.

[48] I noted that the extent of Dr. Zusman's experience in the area of PH or PAH or the focus of his research or study were matters that could affect the weight that would be accorded to his evidence, or to parts of it.

[49] Having reviewed the proposed qualifications put forward by Sandoz, I was satisfied that Dr. Zusman was qualified to testify as an expert as follows:

> Dr. Randall M. Zusman is a practicing clinical cardiologist, researcher and professor in medicine with expertise in the diagnosis, management and treatment of hypertension, pulmonary hypertension (including pulmonary arterial hypertension), diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris, and other diseases wherein vasoconstriction is involved.
>
> Dr. Zusman has expertise in the design, conduct and evaluation of clinical trials for therapies including in diseases wherein vasoconstriction is involved. Such expertise encompasses pre-clinical testing, including the use of animal models, and clinical trials of therapies of these diseases.

[50] Dr. Zusman prepared an expert witness report dated July 29, 2021. The report sets out Dr. Zusman's opinions on a number of specific mandates related to the qualifications and knowledge of the skilled person, construction of the Asserted Claims, and the validity of the Asserted Claims.

[51] The plaintiffs contend that a number of factors should negatively affect the weight accorded to Dr. Zusman's opinions. According to the plaintiffs, Dr. Zusman is a relative stranger to ERAs, and has tangential knowledge of PH/PAH as a result of working with colleagues who are the true experts. They say he was evasive under cross-examination and revealed himself to be a professional witness (Dr. Zusman has testified as an expert witness in a number of other cases) and an advocate for Sandoz. The plaintiffs further submit that Sandoz's

counsel provided the documents Dr. Zusman relied on, including 39 references cited as the prior art to support his opinion on obviousness. The plaintiffs allege that, as a physician who was not active in the PAH field at the relevant time, Dr. Zusman can only conduct the obviousness analysis with hindsight, and his opinions in this regard are therefore unreliable. I consider the weight that ought to be accorded to Dr. Zusman's evidence in the context of my analysis below.

B. *Dr. Vachiery (Plaintiffs' Expert Witness)*

[52] Dr. Vachiery is a cardiologist, professor, and researcher. Dr. Vachiery received his M.D. from the Université Libre de Bruxelles in 1985 and became board certified in internal medicine in 1992 and cardiology in 1995. Dr. Vachiery has treated patients with various cardiovascular disorders since 1995 and he has specialized in PH and PAH. Currently, Dr. Vachiery is a Clinical Professor of Cardiology and Director of the Pulmonary Vascular Diseases and Heart Failure Clinic at the Hôpital Erasme – Cliniques Universitaires de Bruxelles, Belgium. He is also a member of the pulmonary vascular disease interdisciplinary network at the International Society for Heart & Lung Transplant.

[53] Dr. Vachiery has been active on a number of councils and working groups related to PH, including by serving as co-chair of the Pulmonary Hypertension Council at the International Heart and Lung Society (2002-2005), chair of the Working Group on Pulmonary Circulation and Right Ventricular Function at the European Society of Cardiology (2006-2008), chair of the Working Group on Heart Failure at the Belgian Society of Cardiology (2008-2009), chair of the Pulmonary Hypertension Council at the International Society for Heart & Lung Transplantation

(2018-2020), and Task Force member and Section Editor of the European Guidelines on Pulmonary Hypertension (2009 and 2015).

[54] Sandoz did not object to Dr. Vachiery's proposed qualifications. I was satisfied Dr. Vachiery was qualified to provide expert opinion evidence according to the proposed qualifications that were put forward by the plaintiffs:

> Dr. Vachiery is a medical doctor, researcher, and clinical professor of cardiology with expertise in: (i) pulmonary hypertension ("PH") (including pulmonary arterial hypertension ("PAH")); (ii) the development and science of treatment of PH (including PAH); and (iii) the analysis and interpretation of data and results of pre-clinical experimentations, clinical drug trials, case reports and observational studies in the area of pulmonary medicine and cardiology, including the treatment of PAH.

[55] Dr. Vachiery prepared an expert witness report dated October 29, 2021. The report responds to Dr. Zusman's opinions on mandates related to the skilled person, construction of the Asserted Claims, and the validity of the Asserted Claims.

[56] Sandoz contends that a number of factors should negatively impact the weight accorded to Dr. Vachiery's opinion. His assessment of the prior art was close-minded and he was quick to dismiss any teachings that were not backed by randomized, controlled clinical trials. Furthermore, Sandoz points to Dr. Vachiery's ongoing relationship with the plaintiffs for more than 17 years, and states that his career has been and continues to be tied to and funded by the plaintiffs. I consider the weight accorded to Dr. Vachiery's evidence in the context of my analysis below.

C. *Dr. Chakinala (Plaintiffs' Expert Witness)*

[57] Dr. Chakinala is a pulmonologist (referred to as a respirologist in Canada), professor, and researcher. He received his M.D. from Vanderbilt University in 1994 and completed his internship and residency at the University of Texas, Southwestern Medical Center between 1994 and 1997. In 2002, Dr. Chakinala completed fellowships at the Washington University School of Medicine, in Pulmonary and Critical Care Medicine, and General Medical Sciences. He is currently a professor of medicine at the Pulmonary and Critical Care Medicine Division of Washington University School of Medicine, where he is also the director of the Pulmonary Hypertension Care Center.

[58] The focus of Dr. Chakinala's clinical practice and research as a clinician scientist is on pulmonary vascular disorders. He has been a staff physician and pulmonary consultant at Barnes-Jewish Hospital in Missouri since 2002. He is a pulmonary hypertension consultant at Washington University's Pulmonary Fibrosis Foundation Care Center Network since 2016, and the Adult Congenital Heart Disease Center since 2017.

[59] Dr. Chakinala is a member of the American College of Chest Physicians and Pulmonary Hypertension Association, among other professional societies. He has also received awards for his work on pulmonary hypertension.

[60] Sandoz did not object to Dr. Chakinala's proposed qualifications as put forward by the plaintiffs. I was satisfied of Dr. Chakinala's qualifications to testify as an expert as follows:

> Dr. Chakinala is a medical doctor, clinical researcher, and professor of pulmonary and critical care medicine with expertise in (i) pulmonary hypertension ("PH") (including pulmonary arterial hypertension ("PAH")); (ii) the development and science of treatment of PH (including PAH); and (iii) the analysis and interpretation of data and results of pre-clinical experimentation, clinical drug trials, case reports and observational studies in the area of pulmonary medicine, including the treatment of PAH.

[61] Dr. Chakinala prepared an expert witness report dated October 29, 2021. The report responds to Dr. Zusman's opinions on mandates related to the skilled person, construction of the Asserted Claims, and the validity of the Asserted Claims.

[62] Sandoz advances similar criticisms of Dr. Chakinala's evidence as those advanced in respect of Dr. Vachiery and argues that his evidence should be accorded less weight as a result. In addition, Sandoz argues that Dr. Chakinala made statements that were demonstrably false, gave opinions that were outside of his expertise, and opined on documents without reading them. I consider the weight accorded to Dr. Chakinala's evidence in the analysis below.

D. *Dr. Clozel (Plaintiffs' Fact Witness)*

[63] At the material times, Dr. Clozel was responsible for all pre-clinical drug development as Chief Scientific Officer, Head of Pharmacology, and Executive Vice President of Actelion. She is the sole named inventor of the 770 Patent.

[64] Dr. Clozel testified about her role in the conception of the invention of the 770 Patent and the experimental work that was conducted at Actelion prior to the filing date.

[65] Dr. Clozel also testified about her role in the development of macitentan. Her work on ERAs started at Hoffmann-La Roche (Roche) where Dr. Clozel and her team conducted research that led to the discovery of ERAs, including a compound known as bosentan. In 1997, Dr. Clozel and others left Roche to found Actelion and they continued their work in this area, including work on bosentan which was licensed from Roche. In November 2001, Actelion received regulatory approval from the U.S. Food and Drug Administration (FDA) to market bosentan (TRACLEER®) for the treatment of PAH. Bosentan was the first ERA to receive drug regulatory approval.

[66] Actelion developed other compounds with ERA activity. These included the compounds disclosed in now-expired Canadian Patent No. 2,437,675 titled, "Novel Sulfamides and Their Use as Endothelin Receptor Antagonists", one of them being the compound now known as macitentan.

V. **The Skilled Person**

[67] The notional person of ordinary skill in the art or "skilled person" is a legal construct embodying a number of concepts that inform a proper approach to resolving issues in a patent action. The concepts that are relevant to the claim construction and validity issues that arise in this action are set out below.

[68] First, the skilled person possesses a level of skill and knowledge necessary to appreciate the nature and description of the invention at a technical level, and to put it into practice: *Whirlpool* at para 53. This is the ordinary level of skill and knowledge of the particular art or

science to which the patent relates: *Free World* at para 44. Where a patent relates to multiple scientific or technical fields, the skilled person can comprise a team of people: *Amgen Inc v Pfizer Canada ULC*, 2020 FC 522 at para 172. However, the skilled person is not defined on a claim-by-claim basis: *Teva Canada Limited v Janssen Inc*, 2018 FC 754 at para 236, aff'd 2019 FCA 273, leave to appeal to SCC refused, 39007 (7 May 2020). The skilled person embodies the common general knowledge that is generally known and accepted in the field, and they are reasonably diligent in keeping up with advances: *Pfizer Canada Inc v Teva Canada Limited*, 2017 FC 777 at para 185.

[69] Second, the skilled person adopts a fair and objective approach. They have a mind willing to understand and are trying to achieve success, not looking for difficulties or seeking failure: *Les Laboratoires Servier v Apotex Inc*, 2019 FC 616 at para 156, citing *Free World* at para 44. They objectively apply the same standards to all issues, which relate to construction and validity in this case.

[70] Third, the skilled person is not inventive. They pursue reasonable and logical enquiries, and can make deductions based on the information available, but they possess no imagination or inventiveness: *Jay-Lor International Inc v Penta Farms Systems Ltd*, 2007 FC 358 at para 75, citing *Beloit Canada Ltd v Valmet Oy*, [1986] FCJ No 87, 8 CPR (3d) 289 at 294 (FCA) [*Beloit*].

[71] Fourth, the skilled person addresses each issue at the correct point in time. They understand any differences in the relevant skills or knowledge as of each material date, and adopt the proper temporal frame of reference to analyze the issues, without hindsight. As noted above,

in this case the parties do not identify any practical differences in the prior art or the relevant skills and knowledge of the skilled person at any material time between August 29, 2006 and March 6, 2008, which simplifies the analysis. Nonetheless, the Court must guard against an *ex post facto* analysis and the dangers of a backward-looking perspective: *Janssen Inc v Teva Canada Limited*, 2020 FC 593 at para 169.

[72] Expert witnesses assist the Court by opining on the qualifications, relevant experience, and knowledge of the notional skilled person, and by providing expert evidence so as to put the Court in the position of the skilled person at the relevant time: *Tetra Tech EBA Inc v Georgetown Rail Equipment Company*, 2019 FCA 203 at para 88, citing *Free World* at para 51.

[73] In this case, the parties and their experts disagree on how to define the skilled person in respect of the 770 Patent. This disagreement only affects issues of validity, and particularly the interpretation of the relevant prior art for assessing whether any of the Asserted Claims were obvious. As noted above, the parties agree on the construction of the Asserted Claims.

[74] Sandoz's expert witness, Dr. Zusman, opines that the 770 Patent relates to the use of macitentan administered to a patient in combination with at least one PDE5-I for the treatment of a disease wherein vasoconstriction is involved. Consequently, the skilled person is a clinician, that is, a specialist physician who would treat such diseases. Where the disease is one that involves the systemic circulation, the specialist would be a cardiologist, endocrinologist, or nephrologist, with expertise in vascular medicine. Where the disease is one that involves the pulmonary circulation, the specialist would be a cardiologist, pulmonologist, or critical care

physician. According to Dr. Zusman, pulmonologists focus on pulmonary circulation, but cardiology presents an overlap because cardiologists focus on both the systemic circulation and pulmonary circulation. The clinician would have a good knowledge of the drugs and therapies to treat these diseases, including monotherapy and combination therapy, and would keep up to date with the research conducted in the field.

[75] Since the 770 Patent describes tests for PDE5 inhibitory activity and experiments of the combined effects of macitentan and certain PDE5-Is in animal models, Dr. Zusman further states that the skilled team would include a clinical or pre-clinical pharmacologist who might be a medical doctor and/or hold a Ph.D. in medicinal chemistry, pharmaceutics, or a related discipline, and have a few years of experience in the pharmaceutical industry.

[76] The plaintiffs assert that Dr. Zusman's opinion on the skilled person ignores the 770 Patent's focus on the treatment of PH and PAH, and is belied by his own near-immediate focus on PH and PAH in his expert report. According to the plaintiffs, Dr. Zusman broadly defines the skilled person as having expertise with diseases wherein vasoconstriction is involved because he lacks a sufficient level of expertise in PH and PAH, and his qualifications do not align with those of the skilled person.

[77] The plaintiffs' expert witnesses, Drs. Chakinala and Vachiery opine that the skilled person for the 770 Patent would have a narrower focus. The skilled person would be a clinician—a cardiologist or pulmonologist—or a researcher who focuses their clinical and/or research interests on the treatment of patients with PH, and more specifically PAH, and who is

knowledgeable about the treatment options. The skilled person would understand that the focus of the 770 Patent is on the use of an ERA (being macitentan) in combination with a PDE5-I for treating PAH. The 770 Patent specification explicitly states that the disease intended to be treated according to the invention is "more preferably" selected from hypertension and PH, in particular PH, and notably PAH.

[78] Drs. Vachiery and Chakinala state that a physician who does not have a particular focus on PH or PAH would not be a part of the skilled team because this would not be reflective of how PH or PAH is treated. In 2008 (and today) it was rare for a general cardiologist to treat PH or PAH patients—such patients were and still are referred to physicians who specialize in PH and PAH. The PH/PAH specialist would be familiar with ERAs, and understand their role in treating PH, and particularly PAH, as of the relevant dates.

[79] Also, Dr. Vachiery notes that the clinician would be part of a larger team that would include a pharmacologist, biologist or biochemist in the field of drug development who is interested in studying compounds in different animal models as part of pre-clinical development.

[80] Sandoz asserts that Drs. Vachiery and Chakinala improperly adopted a claim-by-claim approach to defining the skilled person, rather than considering the 770 Patent as a whole. Dr. Chakinala's and Dr. Vachiery's definitions of the skilled person are problematic because they focus solely on PH/PAH and none of the other diseases to which the 770 Patent relates.

[81] I find that the definition of the skilled person would not be limited to PH/PAH specialists. The 770 Patent is not limited to the treatment of PH and PAH. It describes the invention as being related to the treatment of a disease wherein vasoconstriction is involved. The experimental results included in the disclosure are not specific to PH/PAH. While PH and particularly PAH are a focus of the patent, I disagree the skilled team consists solely of PH/PAH specialists. A number of claims are restricted to PAH, but as Sandoz correctly points out, the attributes of the skilled person do not change on a claim-by-claim basis.

[82] Dr. Zusman acknowledges that the skilled person team includes a physician who would have a good knowledge of the drugs and therapies for treating PH and PAH, and would keep up to date with the research conducted in the field. As a rare and potentially fatal disease largely treated by specialists, I find that a physician who treats patients with PH or PAH would have a fairly high level of knowledge of these conditions and their treatments. In my view, while the skilled team is not limited to those who focus on PH or PAH, the skilled person's specialized knowledge in the area of PH and PAH is important to the issues in this action. ERAs were, at the material times, only being used to treat patients with PAH, and the majority of the prior art references relate to PH or PAH.

[83] In summary, I find the skilled person would be a specialist physician or researcher, who would have knowledge of systemic and pulmonary hypertension, the physiologic pathways involved in these diseases, and the drugs and therapies to treat them. The skilled person would have an understanding of the pre-clinical and clinical research and experiments used to develop drugs for systemic and pulmonary hypertension. In my view, a specialist physician who treats

systemic and pulmonary hypertension or researcher would have sufficient expertise in other diseases of vasoconstriction and the skilled person team does not need to include specialists for those diseases.

VI. **Claim Construction**

[84] An analysis of the skilled person's common general knowledge (CGK) would normally precede claim construction; however, the parties agree on claim construction. Their disagreements on CGK do not affect their positions on claim construction, but they are central to the validity issues, and especially to obviousness. My analysis of CGK is in the section that addresses the issue of obviousness.

[85] Claims are to be read in an informed and purposive way through the eyes of a skilled person, having regard to the CGK: *Free World* at para 44. As noted above, the skilled person possesses the ordinary skill and knowledge of the art to which the patent relates, and approaches the construction of the patent claims with a mind willing to understand. The application for the 770 Patent was published on March 6, 2008, which is the relevant date for construing the claims: *Free World* at paras 53-54.

[86] In actions where infringement is an issue, a purposive construction will determine whether claim elements are essential or non-essential: *Free World* at para 50; *Tearlab Corporation v I-MED Pharma Inc*, 2019 FCA 179 at para 31 [*Tearlab*]. There will be no infringement if an essential element of a claim is different or omitted: *Free World* at para 31. In

view of Sandoz's concession on infringement, the parties agree that the plaintiffs are not required to establish infringement of the essential elements for any of the Asserted Claims.

[87] The Asserted Claims read as follows:

> 21. A use of the compound of formula (I) as defined in claim 1 [i.e., macitentan], or a pharmaceutically acceptable salt of said compound of formula (I), in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable sale thereof, for treating a disease wherein vasoconstriction is involved.
>
> 22. The use according to claim 21, wherein the compound having PDE5-inhibitory properties is sildenafil, vardenafil, tadalafil or udenafil.
>
> 23. The use according to claim 22, wherein the compound having PDE5-inhibitory properties is sildenafil or tadalafil.
>
> 24. The use according to claim 23, wherein the compound having PDE5-inhibitory properties is sildenafil.
>
> 25. The use according to claim 23, wherein the compound having PDE5-inhibitory properties is tadalafil.
>
> 26. The use according to claim 21, wherein the disease is selected from hypertension and pulmonary hypertension.
>
> 27. The use according to claim 26, wherein the disease is pulmonary hypertension.
>
> 28. The use according to claim 27, wherein the disease is pulmonary arterial hypertension.
>
> 29. The use according to claim 28, wherein the compound having PDE5-inhibitory properties is sildenafil or tadalafil.
>
> 30. The use according to claim 28, wherein the compound having PDE5-inhibitory properties is sildenafil.
>
> 31. The use according to claim 28, wherein the compound having PDE5-inhibitory properties is tadalafil.

[88] The parties introduced a joint claim chart for the Asserted Claims that is attached as Schedule A to these Reasons. As noted above, although the parties and their experts agree on the proper construction of the Asserted Claims, claim construction remains a question of law for the Court to decide: *Whirlpool* at para 61; *Zero Spill* at para 41.

[89] The construction of the Asserted Claims is straightforward based on the claim language, and I accept the construction proposed by the parties. For the purposes of determining the issues in this action, the following summarizes the key elements and definitions:

> ***Claim 21*** relates to the *use* of macitentan in combination with at least one *PDE5-I* for treating a *disease wherein vasoconstriction is involved*.
>
> - *use* means the administration of the compounds together, without limitation as to timing or route of administration;
>
> - *PDE5-I* is a compound that will inhibit the activity of the PDE5 enzyme by 50% at concentrations less than or equal to 1μM, measured according to the experimental protocol described in the 770 Patent;
>
> - *disease wherein vasoconstriction is involved* is a disorder of increased resistance to blood flow in the systemic or pulmonary circulation; the 770 Patent specification lists particular diseases said to involve vasoconstriction: hypertension, PH (including PAH), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris; the term *disease wherein vasoconstriction is involved* includes but is not limited to hypertension, PH (including PAH), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris.
>
> ***Claims 22-25*** depend, directly or indirectly, on claim 21 and add limitations with respect to the specific PDE5-I: sildenafil,

vardenafil, tadalafil or udenafil (claim 22); sildenafil or tadalafil (claim 23); sildenafil (claim 24); tadalafil (claim 25).

Claims 26 depends on claim 21 and adds a limitation that the disease is *hypertension* or *pulmonary hypertension*.

- *hypertension* is elevated blood pressure in the systemic circulation;

- *pulmonary hypertension* (PH) is elevated blood pressure in the pulmonary circulation.

Claim 27 depends on claim 26 and limits the disease to PH.

Claim 28 depends on claim 27 and limits the disease to *pulmonary arterial hypertension*.

- *pulmonary arterial hypertension* (PAH) is a form of PH where the walls of the pulmonary arteries constrict and stiffen, straining the right side of the heart by requiring it to work harder to push blood through narrowed arteries.

Claims 29-31 depend, directly or indirectly, on claim 28 and are limited specifically to the use of macitentan in combination with sildenafil (claim 30), tadalafil (claim 31), or both (claim 29) for treating PAH.

VII. **Validity**

[90] The 770 Patent is presumed to be valid: *Patent Act*, s 43(2). Sandoz bears the onus of establishing invalidity on a balance of probabilities.

[91] Each claim is assessed independently for its validity: *Patent Act*, s 58.

[92] Sandoz alleges that each of the Asserted Claims is invalid for obviousness, lack of utility, overbreadth, and insufficiency.

[93] In the analysis of the validity issues, prior art references are identified using a short-form title. Schedule B to these Reasons is a table that includes full titles of the prior art references referred to in the analysis.

A. *Obviousness*

(1) The Test for Obviousness

[94] The subject matter that is defined by a patent claim must be subject matter that would not have been obvious on the claim date to a person skilled in the art or science to which it pertains, having regard to the relevant prior art: *Patent Act*, s 28.3.

[95] As the Federal Court of Appeal stated in *Beloit* (page 294), the test for obviousness is not to ask what competent inventors did or would have done. Inventors are by definition inventive. The question to be asked is whether the skilled person, having no inventiveness, in light of the state of the art and the CGK as at the material date, would have come directly and without difficulty to the solution taught by the patent.

[96] *Sanofi-Synthelabo Canada Inc v Apotex Inc*, 2008 SCC 61 (paragraph 67) [*Sanofi*] sets out a four-step framework for determining whether the subject matter of a claim is obvious:

> (1) (a) Identify the notional "person skilled in the art";
> (b) Identify the relevant common general knowledge of that person;
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept;
> (4) Determine whether, when viewed without any knowledge of the alleged invention as claimed, those differences would have

> been obvious to the person skilled in the art, or whether they require any degree of invention.

[97] This framework contemplates a flexible approach that must be applied contextually to the facts and circumstances of each claim: *Allergan Inc v Sandoz Canada Inc*, 2020 FC 1189 at para 154 [*Allergan*], citing *Amgen Inc v Pfizer Canada ULC*, 2020 FCA 188 at para 5. It is applied to the combination of the elements defining the invention, rather than to each of its discrete elements: *Allergan* at para 154, citing *Teva Canada Limited v Janssen Inc*, 2018 FC 754 at para 86.

[98] Under step 4, it may be appropriate to consider whether the alleged invention would have been "obvious to try" in fields where advances often occur through experimentation. Relevant considerations for an "obvious to try" inquiry can include (*Sanofi* at paras 67-69):

> (1) Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?
>
> (2) What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?
>
> (3) Is there a motive provided in the prior art to find the solution the patent addresses?

[99] These considerations are not exhaustive. Other factors that might be considered include the actual course of conduct that culminated in the making of the invention: *Sanofi* at para 70.

[100] Obvious to try does not mean "worth a try" (*Sanofi* at para 65):

> Mere possible inclusion of something within a research programme on the basis you will find out more and something might turn up is

> not enough. If it were otherwise there would be few inventions that were patentable. The only research which would be worthwhile (because of the prospect of protection) would be into areas totally devoid of prospect. The "obvious to try" test really only works where it is more-or-less self-evident that what is being tested ought to work.

(2) Introduction to Obviousness Analysis and Overview of the Parties' Positions

[101] As part of his mandate, Dr. Zusman was asked to review 39 prior art documents provided by Sandoz's counsel. Eight of the publications are patents or patent applications. Dr. Zusman states that patent documents may not have been reviewed by a clinician of ordinary skill on a frequent basis, but advances in the field, including those described in patents and patent applications, formed part of poster presentations or publications and the skilled person would know how to find patent documents in a reasonably diligent online search.

[102] In addition to these references, Dr. Zusman relies on review articles that relate to PAH or to ERAs as therapy in cardiovascular disease. One review article was published in September 2006 and therefore post-dates the material claim date, but Dr. Zusman opines that it reflects information that was known as of August 2006. Dr. Zusman also relies on references that are relevant to the experiments conducted at Actelion and described in the 770 Patent.

[103] Sandoz takes the position that the prior art documents (including the patent references) would have formed part of the skilled person's CGK; the skilled person knew how to find a patent. Alternatively, Sandoz states all of the prior art documents would have formed part of the state of the art.

[104] The plaintiffs submit that by providing the prior art references to Dr. Zusman, Sandoz created the danger of hindsight analysis—there was a "selection" of references without evidence that the skilled person would have focused on these references in particular. I do not see this criticism as important to this case. The plaintiffs had the opportunity to challenge Sandoz's evidence on the basis that it does not reflect the state of the art, and their experts provided additional references, omitted by Dr. Zusman, that they allege to be relevant to a proper understanding of the state of the art and/or CGK. The plaintiffs do not allege that any of Sandoz's references are not "citable" as prior art, or that they would not have been located by a reasonably diligent search. They do allege that not all the references would have formed part of the CGK, and a key difference between the parties and their experts in this case relates to how the skilled person would have interpreted and understood the information in the references at the relevant time.

[105] Sandoz argues that the relevant prior art included numerous disclosures of the combination of an ERA with a PDE5-I to treat a disease involving vasoconstriction, including PH and PAH. Accordingly, Sandoz asserts that the only difference between the CGK or state of the art and the subject matter of the Asserted Claims is that the Asserted Claims are limited to macitentan. This single difference applies equally to independent claim 21 and the dependent claims 22-31, because Sandoz asserts there was nothing inventive in limiting the disease or in limiting the PDE5-I.

[106] The starting point for Sandoz's obviousness allegation is that macitentan was not a new compound. Sandoz states that Actelion admitted, on page 1 of the 770 Patent, that macitentan

was disclosed in its earlier patent application WO 02/053557 (WO 557) that was published on July 11, 2002. WO 557 disclosed a group of compounds useful for treating diseases involving vasoconstriction due to their ERA activity. It also disclosed that the compounds could be used in combination with vasodilators or other therapeutics that treat high blood pressure or cardiac disorders, and macitentan is listed among 78 "preferred compounds". In Canada, WO 557 issued to Canadian Patent No. 2,431,675 (675 Patent).

[107] Sandoz relies on Dr. Zusman's opinion that all the Asserted Claims are obvious because it was already known by 2006 that the combination of an ERA and PDE5-I would be useful to treat a disease that involves vasoconstriction. Sandoz contends the skilled person would have expected, based on prior art disclosures of ERAs and PDE5-Is used in combination and the known "class effects" of ERA and PDE5-I drugs, that the combination of any ERA with a PDE5-I would be useful for treating diseases involving vasoconstriction, including PAH. Sandoz maintains that the 770 Patent is not a "selection patent" in that it does not disclose or claim any particular advantage of macitentan as a selection over the ERAs that were disclosed in WO 557 and the 675 Patent. As such, advantages of macitentan itself, such as a level of safety or efficacy, must not inflate the claimed invention in order to widen the gap between the invention and the prior art.

[108] Furthermore, Sandoz argues that it would have been obvious to try macitentan in combination with a PDE5-I. The skilled person would be steered toward combining an ERA with a PDE5-I, which are orally administered medications, as opposed to combinations of compounds from other drug classes. For example, epoprostenol has a short half-life and requires

continuous infusion into the pulmonary circulation by an intravenous catheter and pump, and so it was often reserved for patients with the most severe functional impairment.

[109] The skilled person would also be steered toward macitentan as the particular ERA to combine with a PDE5-I. Sandoz states there were a finite number of identified, predictable solutions because there were only three known pathways, a very limited number of PDE5-Is, a very limited number of ERAs, and macitentan was known to be the next generation ERA. The possible combinations of these therapies were "incredibly limited", and the skilled person would have been led to macitentan. Sandoz argues that in view of the CGK and the state of the art, it was self-evident to try the combination of macitentan and a PDE5-I to treat diseases involving vasoconstriction, and the skilled person would have expected that combination to be useful.

[110] The plaintiffs argue that Sandoz's position on obviousness is an exercise in hindsight. The skilled person would not have expected that the combination of any ERA with a PDE5-I would be useful, and furthermore the skilled person would not have been led "directly and without difficulty" to the specific combination of macitentan with a PDE5-I: *Beloit* at 294.

[111] In my view, there is a tension between Sandoz's arguments that, on the one hand, the skilled person would expect any combination of an ERA and PDE5-I to be useful based on known class effects, and on the other hand, the combination of macitentan with a PDE5-I would have been obvious to try. If the skilled person would expect any combination of an ERA and PDE5-I to work, there would be no need to identify macitentan from the numerous possible ERA candidates and test it in combination with a PDE5-I. According to this argument, specifying

macitentan as the ERA to be combined with a PDE5-I can be thought of as an artificial limitation of the Asserted Claims because any ERA would be expected to work, and the Asserted Claims would be no more than an uninventive extension of Actelion's monopoly under the 675 Patent (which included claims covering macitentan, among other compounds). It seems to me that this argument and the obvious to try argument should have been presented as alternatives. As one aspect of my analysis, I have considered them as alternative arguments.

[112] A large part of the evidence and argument was devoted to the CGK, the state of the art, and how the skilled person would have understood the relevant prior art references as of 2006. While I have considered all of the evidence and arguments in detail, I have focused on the key points in these Reasons. There is some repetition because of the overlapping nature of the parties' arguments. The parties did not clearly differentiate between CGK and the state of the art, which results in repetition in the analyses under steps 1 and 3 of the obviousness framework. The bulk of the analysis of the prior art references is found in the section that addresses CGK, under step 1 of the obviousness framework.

[113] I also note that, although claim 21 is not limited to any particular disease wherein vasoconstriction is involved, Sandoz's obviousness argument and a majority of the prior art references in this case relate to PH, and particularly PAH. For this reason, my analysis focuses on PAH and the CGK or state of the art in that field.

(3) *Step 1*: The Skilled Person and their Common General Knowledge (CGK)

[114] The first step in the obviousness analysis is to identify the skilled person and their CGK.

[115] I have identified the skilled person above. The skilled person would be a specialist physician or researcher, who would have knowledge of systemic and pulmonary hypertension, the physiologic pathways involved in these diseases, and the drugs and therapies to treat them. The skilled person would have an understanding of the pre-clinical and clinical research and experiments used to develop drugs for systemic and pulmonary hypertension.

[116] The CGK consists of what the skilled person would generally know and accept at the relevant time, which is August 29, 2006 in this case: *Sanofi* at para 37; *Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc*, 2016 FCA 119 at para 24 [*Mylan*]; *Bell Helicopter Textron Canada Limitée v Eurocopter*, 2013 FCA 219 at paras 64-65 [*Eurocopter*]. Information only migrates into the CGK if a skilled person would become aware of it and accept it as a good basis for further action: *Mylan* at para 24.

[117] As noted above, the CGK that is most relevant to the obviousness inquiry relates to the field of PH and notably PAH. I will begin with a summary from the joint scientific primer provided by the parties. The parties agree that this information formed part of the skilled person's CGK. I will then address aspects of the CGK where there is disagreement between the parties and the experts.

(a) *PH/PAH and Biological Pathways*

[118] *The disease:* Pulmonary hypertension (PH) is a general term that describes abnormally high blood pressure in the pulmonary circulatory system. PAH is a subtype of PH where the constricted walls of the arteries of the lungs increase vascular resistance to blood flow. If left

untreated, the increased pressure strains the right side of the heart, which is responsible for pumping blood to the lungs, leading to heart failure.

[119] There are three major biological pathways that affect blood pressure in the pulmonary vasculature, mainly by controlling the contraction and proliferation of smooth muscle cells in the pulmonary arteries.

[120] *Prostacyclin pathway*: Prostacyclin released by endothelial cells in the pulmonary arteries acts as a potent vasodilator. In patients with PAH, prostacyclin production is reduced and this contributes to vasoconstriction, blood clotting, and cell proliferation in the pulmonary arteries. Therapeutic use of prostacyclin analogues enables relaxation of the pulmonary arterial vasculature by targeting this pathway.

[121] *Nitric oxide (NO) pathway*: NO is a potent vasodilator that relaxes vascular smooth muscle by stimulating the production of cGMP, which results in vasodilation. Phosphodiesterase (PDE) enzymes, particularly PDE5, break down cGMP. In PH and PAH patients, NO levels are reduced and PDE5 levels are increased, which reduces cGMP levels and limits vasodilation in the pulmonary arteries. Therapeutic use of PDE5-Is targets the NO pathway by inhibiting PDE5, preventing the breakdown of intracellular cGMP and enhancing NO-mediated vasodilation.

[122] *Endothelin pathway*: Endothelin is a potent vasoconstrictor synthesized and released by the endothelial cells lining the blood vessels. Vascular endothelial cells line the entire circulatory system. There are three endothelin isoforms (variants) in humans, with ET-1 being

the most important isoform in the cardiovascular system. ET-1 is a long-acting, potent vasoconstrictor that acts by binding to endothelin receptors. PAH patients have elevated levels of ET-1, which results in increased vasoconstriction and pulmonary arterial blood pressure.

[123] There are two endothelin receptor subtypes, ET_A and ET_B. ET_A receptors are relatively selective for ET-1 and mediate a vasoconstrictive effect. ET_B receptors play a role in clearing circulating ET-1. ET_B receptors mediate local vasodilation by stimulating the release of NO and prostacyclin.

[124] ERAs bind to and block ET_A and/or ET_B receptors, preventing them from being activated by ET-1. Two types of ERAs were known and either approved or under development for therapeutic use by 2006: (i) dual ERAs that target both ET_A and ET_B receptors; and (ii) ERAs that preferentially or selectively bind to ET_A.

[125] The prostacyclin, NO, and endothelin pathways are illustrated in the diagram attached as Schedule C to these Reasons.

(b) *Treatment of PAH*

[126] *WHO-FC*: Physicians assess the severity of PAH by rating a patient's degree of physical impairment, using a table developed by the New York Heart Association/World Health Organization that describes four functional classes. Class I reflects the lowest degree of impairment. Each class is described by functional limitations that reflect the severity of the

disease. The WHO-FC classes influence the choice of treatment, and help a physician to monitor disease progression.

[127] The WHO-FC classes as they stood in August 2006 are set out in the table below:

WHO-FC	**Description**
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or pre-syncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

[128] *Approved drugs*: As of 2006, drugs having a mechanism of action involving each of the three biological pathways had been approved. The prostacyclin analogues epoprostenol, treprostinil, and iloprost were approved in the mid-1990s, 2002, and 2004, respectively. One PDE5-I was approved to treat PAH (in 2005)—sildenafil. Tadalafil had been approved to treat erectile dysfunction and was sometimes prescribed "off label" for PAH. Bosentan, a dual ERA, was the first ERA to be approved for PAH, in 2001. Sitaxsentan, a selective ET_A inhibitor, was the second ERA to be approved. It was approved in Europe in 2006 but it was not approved in Canada until in May 2007. Ambrisentan was approved in the U.S. in 2007, and approved in Canada and Europe after March 2008.

(c) *CGK – Opinion of Sandoz's Expert Witness (Dr. Zusman)*

[129] Dr. Zusman describes the climate in the field as one that was focused on the three biological pathways noted above. He opines that in 2006, the skilled person was motivated to look for new drugs within the three known drug classes and furthermore, the concept of using combination therapy to target abnormalities in multiple pathways of a disease was well understood in medicine. It was recognized that there may be important interactions between the NO, endothelin, and prostacyclin pathways—for example, prostanoids and NO had been shown to inhibit the release of endothelin—and as new therapies targeting each pathway emerged, there was a general interest in testing combinations of drugs for synergistic or additive effects.

[130] In diseases wherein vasoconstriction is involved, combination therapy aimed at targeting multiple pathways that control vascular tone and growth had already been suggested as a means to improve patients' functional capacity, and possibly survival. The skilled person would, and did, test combinations of drugs from the different drug classes. According to Dr. Zusman, there was a preference to test combinations of orally administered ERAs and PDE5-Is, in view of their ease of administration, different mechanisms of action, and acceptable tolerability.

[131] Dr. Zusman opines that the following formed part of the skilled person's CGK as of August 2006 (and as of March 2008):

a. The prostacyclin pathway had been a focus of research for treating cardiovascular disease and was assumed to be useful in PAH very early. Epoprostenol was introduced as a PAH therapy in the early 1990s. While effective, epoprostenol has a short half-life at room temperature and must be continually administered using an intravenous catheter and pump. More stable prostacyclin analogues were

developed; however, all forms of prostanoids were associated with similar limitations and side effects that restricted their use.

b. Researchers studied the potential for ERAs in vascular medicine throughout the 1990s and 2000s. In 2001, the FDA approved bosentan for the treatment of PAH in WHO-FC III or IV patients. Bosentan's mechanism of action was well understood—it is a sulfonamide ERA that antagonizes both ET_A and ET_B receptors, with only slightly higher affinity for the ET_A receptor. Bosentan was considered a significant addition to the treatment armamentarium against PAH as an orally active drug with a different mechanism of action than epoprostenol.
c. By the mid-2000s, several lines of evidence had demonstrated a strong relationship between endothelin system dysfunction and PAH, and antagonism of endothelin receptors was firmly established as a therapeutic target. Elucidation of the role of endothelin in the progression of pulmonary vascular disease, the demonstrated efficacy of ERAs, and long-term outcome data placed ERAs at the forefront of the treatment armamentarium against PAH, as a cornerstone therapy.
d. In 2004, the beneficial hemodynamic effects of combination therapy with bosentan and epoprostenol for PAH were shown in the BREATHE-2 clinical trial.
e. In the early 1990s, inhaled NO was viewed as one of the more effective therapies for treating PH and PAH, but it was inadequate as a long-term therapy due to its short half-life. It was known that: increased activity of cGMP-degrading PDEs in vascular smooth muscle cells causes vascular dysfunction, characterized by an increased vasoconstrictor response and reduced NO-dependant vasodilation; inhibiting PDE5 activity maintains high levels of cGMP, enhancing the relaxation cycle and vasodilating effects of endogenous NO; PDE5 is the main PDE expressed in the pulmonary vasculature.
f. Between the late-1990s and mid-2000s, three PDE5-Is—sildenafil, tadalafil, and vardenafil—were approved and shown to be highly effective for erectile dysfunction. It was known that they had similar affinities for PDE5 but varied in the pharmacokinetics and selectivity toward other PDEs. There was an expectation that PDE5-Is shared a common class effect on vasodilation due to their activity on PDE5 (Ghofrani et al (2004)). Throughout the early to mid-

2000s, researchers explored the use of different PDE5-Is to treat diseases wherein vasoconstriction is involved; their use to treat PAH became an area of research in the early 2000s (Ghofrani et al (2004)) and by 2006, sildenafil had been approved for PAH.

g. By the mid-2000s, ERAs and prostanoids were used with PDE5-Is in combination therapies for patients with idiopathic PAH (IPAH), that is, where the underlying cause of PAH is unknown: (i) even before sildenafil was approved for PAH, sildenafil and bosentan were used in clinical practice—a case series involving 9 patients with IPAH reported that the combination of bosentan and sildenafil was well tolerated and highly efficient (Hoeper et al (2004)); (ii) in a separate study, the potential long term benefits of combination therapy with bosentan and sildenafil in 3 patients was reported in August 2006 (Minai & Arroliga (2006)); (iii) sildenafil exerted a marked synergistic effect when administered following an inhaled dose of iloprost; and (iv) sildenafil was being studied in combination with intravenous epoprostenol. (For points (iii) and (iv), Dr. Zusman relies on statements made by the authors of Minai & Arroliga (2006)).

h. Based on the redundant pathways that control vascular tone and cell proliferation, it was thought that endothelin receptor blockade would ultimately be used as part of a combined dose regimen. By 2005, if poor prognostic signs persisted after 3 months of bosentan, clinicians looked to add a prostanoid or sildenafil to the treatment regime, depending on the clinical circumstance. In doing so, physicians hoped to gain additional benefits from a class of medication that had a different mechanism of action than bosentan.

i. By 2004, data had emerged to support the particular combination approach with bosentan and sildenafil and/or prostanoid. The use of combination therapy was considered to have the potential to minimize dose-related side effects of bosentan. Further, dual ERAs were considered to share a common class effect in blocking both ET_A and ET_B receptors to prevent the pathological effects of endothelin conditions such as PH and other conditions related to pulmonary vasoconstriction.

j. Inhibition of ET_A receptors was widely considered to be a target for alleviating vasoconstriction. Some studies suggested that in the pulmonary hypertensive

state, blockade of both ET_A and ET_B is necessary to achieve maximal vasodilation and other studies suggested a protective role of ET_B in PH. In 2005, it was unclear whether dual ET_A/ET_B receptor antagonism or selective ET_A receptor antagonism would confer the most therapeutic benefit in cardiovascular disease or in PAH. As of August 2006, the general view was that dual receptor antagonism or selective ET_A receptor antagonism could produce beneficial effects because no clear clinical use for selective ET_B antagonists had yet been defined, and ET_B receptor blockade alone impaired the clearance of endothelin and reduced NO-mediated vasodilation (Lee & Channick (2005); Lee & Rubin (2005)).

k. By the mid-2000s, other ERAs were in the research pipeline, including: (i) the selective ET_A antagonist sitaxsentan, which was approved for PAH in Canada and the US in 2006 and 2007, and the subject of investigational studies with a PDE5-I for hypertension and PH; sitaxsentan was subsequently withdrawn from the market due to liver toxicity; (ii) Actelion's dual ET_A/ET_B antagonist tezosentan, which was being studied for acute and chronic heart failure; (iii) a selective ET_A antagonist darusentan, which was being studied for heart failure; (iv) additional ERAs that were being studied in laboratory models, animal studies or Phase I (healthy human volunteer) clinical trials.

(d) *CGK – Opinions of Plaintiffs' Expert Witnesses (Dr. Vachiery and Dr. Chakinala)*

[132] Drs. Vachiery and Chakinala disagree with Dr. Zusman on the CGK. While they do not materially disagree with Dr. Zusman about a number of the underlying "facts" that were reported in the scientific literature, they strongly disagree with Dr. Zusman about the conclusions that he suggests the skilled person would draw from them. Drs. Vachiery and Chakinala opine that the skilled person would recognize the hierarchies of scientific evidence, and that these hierarchies play a role in how the skilled person would have evaluated and understood the available information. PAH therapy was at an early stage in 2006. A number of the studies Dr. Zusman

relied on to support his opinion of the skilled person's CGK would not have been generally known and accepted in the way that Dr. Zusman presents.

[133] Dr. Vachiery's and Dr. Chakinala's opinions of the CGK are as follows:

a. The first pharmaceutical intervention that was approved specifically for PAH was epoprostenol. It was approved in 1995. Before then physicians were forced to treat patients with drugs that do not address PAH directly, and often the only true treatment was lung or heart and lung transplantation. Epoprostenol was (and still is) an effective drug.
b. Bosentan was the second drug approved for PAH, and the first approved oral therapy. Since epoprostenol requires continuous, intravenous infusion, bosentan represented a sea-change in PAH treatment. It was approved in 2001 and essentially remained the only approved ERA up to August 2006. Two other ERAs had just been approved or were close to approval in certain countries at that time: ambrisentan (results of Phase 3 clinical trials in 2006, approved in the US in 2007 and approved in Europe after 2008) and sitaxsentan (approved in Europe as of August 2006, and approved later in Canada, but then withdrawn from the market worldwide).
c. Approved therapies were tied to the WHO-FC classes: (i) as of 2006, and even as of 2008, there were no approved PAH-specific drugs for WHO-FC Class I patients; the primary goal of treating PAH was to slow disease progression, as opposed to what is now a more aggressive treatment goal of improving patient outcomes, and consequently, Class I patients were often monitored for clinical worsening and only started on treatment when their symptoms had progressed; (ii) as of 2008 there were relatively few treatment options for patients in Class II because the studies had focused on more seriously ill patients in Classes III/IV; patients in Class II would typically be started on sildenafil, or alternatively trepostinil, the only non-oral therapy that was approved for Class II patients; (iii) for patients in Class III, approved oral therapies included bosentan, and later sildenafil, ambrisentan, and sitaxsentan (precisely when each of these therapies

were available depended on where the patient resided); the prostanoids trepostinil, iloprost, and epoprostenol were also approved for Class III; (iv) while bosentan was approved for Classes III and IV, patients in Class IV have difficultly breathing even at rest and the primary intervention for Class IV patients was epoprostenol by infusion due to its presumed superior efficacy; Class IV patients would also be considered for transplantation or palliative care.

d. Bosentan is a dual ERA that binds to both ET_A and ET_B receptors. Generally, these two receptors have opposing functions and it was believed that increased selectivity for ET_A might provide greater efficacy and/or fewer side effects compared to dual ERAs. Interest in the field was somewhat moving away from dual ERAs, toward selective ET_A antagonists. Sitaxsentan and ambrisentan, the only other ERAs besides bosentan that were close to approval as of 2006, are both selective ET_A antagonists.

e. The skilled person would not agree that ERAs and PDE5-Is have a class effect just because they act on the same receptors. This was especially true for ERAs because it was unclear to the skilled person whether differences in ET_A and ET_B receptor activity would make a difference in treating PAH patients. And since only one dual ERA had been approved, there was also the potential for significant differences between dual ERAs.

f. ERAs were not without limitations, and they did not offer a cure for PAH (PAH remains incurable today); as of 2008, epoprostenol remained the preferred treatment for patients with severe PAH.

g. While sildenafil and other PDE5-Is were approved for erectile dysfunction, as of 2008, only sildenafil had been approved for PAH.

h. As of 2006, PAH therapies had only been studied and used for a short time. There was a considerable knowledge gap regarding the best use of PAH medications, including whether it was safe and effective to combine them. Combination treatment would not have been the standard of care, given the lack of evidence supporting this approach.

i. Even as of 2008, the standard of care for PAH treatment was monotherapy, for several reasons: (i) the clinical trials conducted to that time had compared the

treatments to placebo; (ii) the trials were relatively short (around 12 weeks) and measured outcomes such as the 6-minute walking score, which was not necessarily indicative of clinical outcome; (iii) most PAH treatments had only recently become available and they were costly, which created hurdles to prescribing more than one treatment at a time. If the disease was not being managed effectively with one therapy, that therapy would be stopped and the patient would be switched to another treatment option (sequential monotherapy).

j. The American College of Chest Physicians (ACCP) 2007 treatment guidelines for PAH stated that combination treatments for PAH were being investigated but at the time, there was no consensus evidence available on combination treatment. The ACCP guidelines do not mention combination therapy with bosentan and sildenafil, or with other ERAs and PDE5-Is. Similarly, the 2004 European Society of Cardiology (ESC) guidelines do not mention combination therapy using ERAs and PDE5-Is (sildenafil had not been approved for PAH when these guidelines were published). The ESC guidelines do mention combination therapy generally, but gave it the lowest level of evidence for efficacy (C) and the lowest grade of recommendation short of being discouraged (Class IIb).

k. As of 2006, one clinical trial, STEP-1, showed that adding inhaled iloprost to bosentan was safe and efficacious, although these results were limited by a relatively small sample size (67 patients).

l. With the exception of STEP-1, trials investigating combination treatment were either ongoing or inconclusive: (i) COMPASS-1 investigating bosentan and sildenafil, and PACES investigating sildenafil and IV epoprostenol, were ongoing and the results were not available; (ii) COMPASS-2, a large-scale, international randomized controlled trial investigating bosentan and sildenafil, was still enrolling patients as of March 2008; (iii) BREATHE-2 investigating bosentan and epoprostenol did not meet its primary endpoints and the results were inconclusive; (iv) COMBI investigating the addition of inhaled iloprost to bosentan was terminated early after a futility analysis failed to show a positive effect; (v) bosentan significantly decreased the plasma concentration of sildenafil when

administered in combination (Paul et al (2005)), this would cause the skilled person to have reservations on the potential benefits of combination treatment.

m. The papers cited by Dr. Zusman that discussed the idea of combination treatments (Channick et al (2004); Lee & Channick (2005)) acknowledged that a considerable amount of additional research was needed. The case studies he relied on, including Hoeper et al (2004) and Minai & Arroliga (2006), were small, retrospective case series/reports that did not provide sufficient evidence to conclude that the combination of bosentan and sildenafil would work in PAH patients. These case series did not reflect the standard of care and they were meant to be hypothesis-generating. The skilled person would require more information on whether bosentan could be combined with other PAH treatments, let alone whether other ERAs could be combined.

n. As of 2006, some PAH patients received an additional treatment to their pre-existing treatments; this was not common practice and the decision was based on a hypothesis and limited, anecdotal evidence—it was not "evidence-based medicine". Generally, patients who received an additional treatment would have been in circumstances where the treating physician had no other option for that patient other than transplant or palliative care (salvage therapy).

(e) *Analysis on CGK*

[134] As noted above, Sandoz takes the position that all of the prior art documents referred to in Dr. Zusman's report (including the patent references) would have formed part of the skilled person's CGK. Alternatively, Sandoz states all of the prior art documents would have formed part of the state of the art.

[135] With some exceptions (such as the ACCP and ESC treatment guidelines), the parties' experts do not provide a definitive opinion on whether a particular reference was or was not generally known and accepted, so as to become part of the CGK. Instead, the experts' opinions

of CGK focus on specific information referred to in the prior art references and how the skilled person would have understood it.

[136] However, CGK and state of the art are distinct concepts with different roles in the analyses of the issues at play. Identifying the CGK is the first step of the obviousness inquiry, whereas a comparison of the inventive concept to the state of the art is the third. The state of the art is the cumulative effect of the relevant prior art, and is understood by reading the prior art in light of the CGK of the skilled person: *Tearlab* at para 81; *Beloit* at 294; *Bourns Inc v Raychem Corp* (1997), [1998] RPC 31 at 40.

[137] In some cases, there may be little practical difference between CGK and the state of the art, but in this case, Sandoz's position is inconsistent with Dr. Zusman's evidence.

[138] Dr. Zusman's report states he was instructed about the differences between CGK and the public knowledge known as "state of the art". He notes the following instructions: public knowledge includes any public disclosure before August 29, 2006, while CGK is derived from a common sense approach to what would in fact be known to a skilled person who is good at their job; in some industries, CGK may include patent specifications that are well known amongst those versed in the art; CGK does not necessarily include scientific papers, no matter how wide the circulation—a disclosure in a paper only becomes CGK when it is generally known and accepted without question by the bulk of those engaged in the particular art.

[139] According to Dr. Zusman, only the information included in paragraphs 44-104 and 124-125 of his report formed part of the CGK. Dr. Zusman does not mention many of the prior art references in those paragraphs.

[140] Turning to the patent references in particular, Dr. Zusman only considers these references in the section of his report that describes the state of the art. He does not opine that any of the patent references formed part of the CGK. Certain patent references are said to be relevant because they would have led the skilled person to test the combination of ERAs and PDE5-Is, or they would have led the skilled person to combine macitentan with a PDE5-I. The following are patent references from Dr. Zusman's report:

a. US 2004/0063731 (US 731) published April 1, 2004, describes the use of PDE5-Is in combination with at least one ERA;
b. US 5,250,534, published October 5, 1993, describes a class of PDE5-Is, including sildenafil, for treating conditions that include angina, hypertension, and heart failure;
c. US 5,859,006, published January 12, 1999, describes a class of PDE5-Is, including tadalafil, for treating conditions that include hypertension, PH, angina, and congestive heart failure;
d. WO 99/64004 (WO 004), published December 16, 1999, describes a class of PDE5-Is said to be useful for the treatment of a wide range of "cGMP-associated" conditions including hypertension, angina, heart failure, and erectile dysfunction; the disclosure refers to classes of therapeutic agents that can be administered with the PDE5-Is including, for endothelin antagonists, "bosentan, ABT-627, and those described in U.S. Patent No. 5,612,359 and U.S. Patent Application Serial No. 601035,832";
e. WO 00/27848, published May 18, 2000, describes PDE5-Is, including udenafil, for treating erectile dysfunction;

f. WO 02/053557 (WO 557) is an Actelion patent application published July 11, 2002 and referenced at page 1 of the 770 Patent; WO 557 describes substituted pyrimidine-sulfamides useful as ERAs, including ET_A-selective and dual acting; a diagram of macitentan's chemical structure is depicted among diagrams of chemical structures said to be "another group of preferred compounds", and macitentan falls within claim 11, which lists 72 compounds by their chemical names;

g. WO 2006/026395 (WO 395) is a patent application filed by the developer of sitaxsentan (a selective ET_A antagonist) and published on March 9, 2006; WO 395 describes combination therapies comprising at least one ET_A antagonist and a PDE5 inhibitor; it states that embodiments of the invention would be useful to treat a number of vascular disorders, including erectile dysfunction, hypertension, heart failure, complications of diabetes, and PAH; it includes claims to the combination of an ET_A antagonist and a PDE5 inhibitor for the treatment of a number of conditions; although WO 395 states that non-selective ERAs would not function as effectively, the skilled person having knowledge of the efficacy of bosentan and sildenafil would not be dissuaded from studying combinations of dual ERAs with PDE5-Is. WO 395 describes testing of sildenafil and sitaxsentan in human subjects in pharmacokinetic drug interaction and efficacy studies and states minimal drug interactions and side effects were observed in treatments with the combination, while maintaining a successful therapeutic effect.

[141] I am aware that Dr. Zusman supported some statements within his CGK discussion by citing to passages from three patent references (WO 004, WO 557, and WO 395); however, it is unclear why he did so. The passages often referred to basic "textbook" information (such as the definitions for hypertension and erectile dysfunction). While patent references often include CGK as background information, Dr. Zusman does not indicate that these patent references in particular would have been generally known and accepted in the field as of 2006 or explain why

they would be. Sandoz has not established that WO 004, WO 557, WO 395, or the other patent references relied on as prior art would have formed part of the skilled person's CGK as of 2006.

[142] Sandoz argues that the reference to WO 557 in the 770 Patent constitutes an admission that macitentan was disclosed (*Shire Biochem Inc v Canada (Minister of Health)*, 2008 FC 538 at para 25); however, the plaintiffs do not dispute that macitentan was disclosed in WO 557 or that WO 557 is citable prior art. There is no admission that WO 557 was CGK, and the evidence fails to establish that WO 557 was CGK.

[143] I will address the patent references under step 3 of the obviousness framework. I will now turn to the substance of the parties' submissions about CGK.

[144] Sandoz submits that much was known and generally accepted in the field, and the skilled person would have expected that the combination of macitentan (an ERA) with a PDE5-I would be useful for treating a disease involving vasoconstriction. As discussed above, it was known that there were three classes of PAH-specific drugs, grouped according to their mechanism of action as prostanoids, ERAs, and PDE5-Is. In addition, Sandoz submits it was CGK that: (i) monotherapies were associated with short-term benefits and a proportion of patients would deteriorate after initial improvement on monotherapy; (ii) the class effects of known drugs extended beyond a shared mechanism of action, and included shared side effects, among other shared effects; (iii) combination therapies (including an ERA and a PDE5-I) were known and being used in the treatment of PAH in clinical practice, the scientific basis for combination therapy was known and understood, and patients receiving combination therapy had a safe and

effective response; and (iv) the specific combination of bosentan and sildenafil was used in clinical practice.

[145] The plaintiffs paint a different picture of the CGK. They say there were only hypotheses about class effects and about combination therapy, but the evidence supporting combination therapy was not established to an acceptable level of confidence. The plaintiffs note that PAH treatments had only recently become available and the clinical experience with them as of 2006 was limited. Only two ERAs (bosentan and sitaxsentan) and one PDE5-I (sildenafil) were approved in at least one country for PAH. The best uses of the available medicines, including whether or how to combine them, was unknown as of August 29, 2006.

[146] The plaintiffs state the standard of care for PAH in 2006 was monotherapy, due in large part to the lack of scientific evidence relating to combinations. Only one randomized, controlled clinical trial (BREATHE-2) had been published for any combination therapy, and it investigated the combination of bosentan and the prostanoid epoprostenol in 33 patients but failed to meet its clinical endpoint. The authors of BREATHE-2 cautioned against the use of its results, noting that larger trials designed to assess the long-term safety and efficacy of this combination were required. No clinical trial had been conducted or published on the combination of an ERA and PDE5-I. Treatment guidelines from professional organizations, such as the ACCP and the ESC, did not recommend any combination treatments for PAH, which reflects this lack of knowledge. Dr. Vachiery opined that the ACCP guidelines stated that combination treatment was being investigated, but there was no consensus evidence available at the time. He stated that there may have been some patients who received an added treatment to their pre-existing treatment, this

would have been a last resort by the physician (other than organ transplant or palliative care), and it was not evidence-based medicine.

[147] The plaintiffs argue that Dr. Zusman is an expert "hired for the purpose of testifying" (*Beloit* at 295; *Bayer AG v Apotex Inc*, 2007 FCA 243 at paras 24-25) who was not active in the field at the relevant time and could only conduct his obviousness review with hindsight. The Courts have repeatedly cautioned against a hindsight analysis in the obviousness inquiry: *Janssen Inc v Teva Canada Limited*, 2020 FC 593 at para 169; *Valeant Canada LP/Valeant Canada SEC v Generic Partners Canada Inc*, 2019 FC 253 at para 76; *Bridgeview Manufacturing Inc v 931409 Alberta Ltd*, 2010 FCA 188 at para 50; *Beloit* at 295. The plaintiffs say Drs. Vachiery and Chakinala, in contrast, are recognized experts who were active in the field at all relevant times, and they can situate their analyses from the point of view of the skilled person.

[148] Sandoz submits that the plaintiffs' experts were overly dismissive of the prior art and skeptical of any teachings that were not backed up by clinical trials. They adopted a pessimistic and failure-seeking interpretation of the prior art. This is antithetical to the skilled person: *Free World* at para 44; *Arctic Cat Inc v Bombardier Recreational Products Inc*, 2016 FC 1047 at para 164, aff'd 2018 FCA 125; *Shire Biochem Inc v Canada (Minister of Health)*, 2008 FC 538 at paras 64-65; *Apotex Inc v Sanofi-Syntholabo Canada Inc*, 2008 SCC 61 at para 25. According to Sandoz, the plaintiffs' experts elevated CGK to something accepted as a standard treatment (which would require evidence from clinical trials), when CGK only needs to be a good basis for further action. Dr. Zusman took a much more fair and reasonable approach, recognizing the

skilled person would and did apply their knowledge to the care of an individual patient, even knowing that some things had not yet been proven.

[149] Sandoz states Dr. Vachiery was dismissive of the case studies reported by Hoeper et al (2004) and Minai & Arroliga (2006), failing to recognize that the skilled person would have been aware of the prior art teachings and would have accepted these teachings as a good basis for further action: *Eli Lilly Canada Inc v Apotex Inc*, 2020 FC 814 at para 130. Hoeper et al (2004) reported on the long-term use of bosentan and sildenafil, stating "combining bosentan and sildenafil might be feasible in patients with IPAH. This combination was well tolerated by all patients and proved to be highly efficient." Sandoz states that Dr. Vachiery admitted on cross-examination that Hoeper et al (2004) reports on real patients and he admitted that some respected physicians treating PAH patients were using this combination of therapies. According to Sandoz, this case report provided a key teaching to the skilled person that bosentan in combination with sildenafil was safe and effective. Sandoz states a number of later publications relied on the Hoeper et al (2004) case report, including articles authored by Drs. Clozel, Chakinala, and Vachiery. Additionally, Sandoz notes that in an editorial by McLaughlin & Hoeper (2005), the authors stated, "[t]o us the question is not bosentan or sildenafil, but bosentan and sildenafil?"

[150] As noted in the section outlining the evidence, Sandoz also points to Dr. Vachiery's and Dr. Chakinala's ongoing relationships with the plaintiffs. I have been mindful of this criticism, particularly since the relationships extended to projects for macitentan in particular, and Drs. Vachiery and Chakinala did not disclose the details and extent of their involvement with the

plaintiffs in their expert reports. I was attentive to possible bias and did not perceive any. Both experts provided reasoned opinions and explained why their opinions diverged from those of Dr. Zusman. They did not take unreasonable positions under cross-examination.

[151] Drs. Vachiery and Chakinala sometimes pointed to a lack of evidence in the prior art to establish the safety and efficacy of combination treatments for PAH. This is not an irrelevant consideration—it is tied to whether the skilled person would be led in a particular direction. However, the 770 Patent does not disclose an advantage of the claimed combination in terms of its safety or efficacy and I was mindful of this point in considering the difference between the inventive concept and the state of the art, discussed under step 4.

[152] I agree with Sandoz that the plaintiffs' experts were sometimes overly critical of teachings in the prior art that were not backed up by controlled clinical trials. The plaintiffs' experts state that case series/reports such as those published by Hoeper et al (2004) and Minai & Arroliga (2006) were merely "hypothesis-generating". In my view, however, the hypotheses had already been generated and the results of retrospective case studies that reported on the co-administration of two or more PAH drugs to patients would have been noteworthy because they presented some evidence in support of this alternative therapy that was based on a combination of two drugs.

[153] However, the skilled person would evaluate and take into account the quality of the evidence. In this regard, I accept the opinions of Drs. Vachiery and Chakinala that the case reports of bosentan and sildenafil administered to patients did not demonstrate that ERAs and

PDE5-Is could be combined to treat PAH. Even for the particular combination of bosentan and sildenafil, they provided preliminary rather than definitive evidence that this combination worked for the patients who participated in the study. This was the authors' conclusion in Hoeper et al (2004): "the data presented provide preliminary evidence that the combination of bosentan and sildenafil may be safe and effective in selected patients with idiopathic PAH; theoretical reasoning favours an effect of the combination, however switching to sildenafil may have been equally effective as combining bosentan and sildenafil". The acknowledgement that the effect in these patients could have been due to sildenafil alone, rather than the combination of bosentan and sildenafil is an important one.

[154] This question had not been resolved by the time the findings in Minai & Arroliga (2006) were published, in August 2006. The authors reported observations in three patients who received the addition of sildenafil as "rescue therapy". In the first patient, sildenafil was added as rescue therapy for worsening symptoms despite bosentan therapy, and in the other two patients, sildenafil was used as rescue therapy to allow successful discontinuation of IV epoprostenol or subcutaneous treprostinil sodium. The authors noted a "paucity of objective evidence" and stated that in spite of preliminary reports, it remained unclear whether combination therapy is truly superior to monotherapy.

[155] Also, Dr. Chakinala opined that the lack of scientific evidence regarding combination therapy was reflected in the treatment guidelines. The ACCP treatment guidelines published in 2007 (based a review of the evidence up to September 1, 2006) treated combination therapy as an open question. The ACCP 2007 treatment guidelines noted that trials were underway, and

stated that until additional evidence becomes available, “add-on or combination therapy might be considered in the context of enrollment into clinical trials”. Dr. Chakinala characterized the recommendations for combination therapy in the ESC treatment guidelines as being “the lowest level of evidence for efficacy” and “the lowest grade of recommendation short of being discouraged”.

[156] Sandoz argues that Dr. Chakinala’s characterization is misleading. The ESC treatment guidelines were admitted to be part of the CGK, and combination therapy were endorsed with the same level of recommendation as anticoagulants, oxygen, calcium channel blockers and other therapies that, despite a “low” level of evidence, were all being used to treat PAH patients. Combination therapies that had not been the subject of randomized, controlled drug trials were nonetheless endorsed in the treatment guidelines, rather than discouraged (which would have been identified as a Class III recommendation).

[157] I disagree that Dr. Chakinala’s characterization is misleading. Combination therapy was not specifically discouraged but the guidelines reflect a field that had not reached a consensus about combination therapy and its role in treatment. Those in the field were watching the developments, but they acknowledged that important questions had not been answered.

[158] Sandoz also points to statements in Channick et al (2004), Lee & Channick (2005), and Lee & Rubin (2005). In Channick et al (2004), the authors stated that “bosentan may have a role as part of a combination of drugs such as a prostanoid or sildenafil.” In Lee & Rubin (2005), the authors included combination therapy in their recommended therapies for PAH and in Lee &

Channick (2005), the authors confirmed that "the combination of bosentan and sildenafil is already being used in clinical practice." Dr. Chakinala testified that Channick et al (2004) reiterated a hope in the field of using combination therapies, and admitted that the reference in Lee & Channick (2005) about adding sildenafil to existing bosentan treatment was a type of salvage treatment being used. Sandoz points out that despite claiming that nobody knows which compounds to combine or the safety of combinations, Dr. Vachiery conceded that the combination of bosentan and sildenafil had been used in clinical practice.

[159] I accept the opinions of Drs. Vachiery and Chakinala that the skilled person would not have expected the combination of any ERA with a PDE5-I to be useful for treating diseases involving vasoconstriction, including PAH. I find the skilled person would consider that there was not an acceptable level of confidence that bosentan and sildenafil were effective as a combination therapy. There was some positive and encouraging evidence in this regard; however, the data were limited. The skilled person would have considered the evidence insufficient to extrapolate the teachings about bosentan and sildenafil to a combination of any ERA and a PDE5-I, based on shared mechanisms of action.

[160] In Channick et al (2004), the authors referred to a study of combined epoprostenol and bosentan, and considered combination therapy of bosentan with other therapeutic agents as a question that "remains to be answered". Similarly, Lee & Rubin (2005) included combination therapy as a possible consideration for patients who saw no improvement or deterioration on monotherapy, but within the treatment algorithm, the authors added a question mark next to "combination therapy" and a footnote indicating that trials studying add-on combination

treatment regimens were underway. The statement in Lee & Channick (2005) about the combination of bosentan and sildenafil in clinical practice is a reference to the Hoeper et al (2004) case report, and for the reasons I noted above, this case report did not establish that bosentan and sildenafil worked as a combination therapy.

[161] Furthermore, I disagree with Sandoz that the skilled person was steered toward the combination of an ERA and PDE5-I in particular, or even steered toward combination therapy. I find that the prior art references relied on by Dr. Zusman do not support a focus in the field on therapy using an ERA and PDE5-I in combination, nor do they reflect a field that was moving in that direction. Consistent with the expert opinions of Drs. Vachiery and Chakinala, these references report on numerous, incremental advances without a discernable direction toward ERAs used in combination, or even a direction toward combination therapy generally as of 2006. I prefer the evidence of Drs. Vachiery and Chakinala as they were experts in the field at the time and as a result, in a better position to opine on how the skilled person would have viewed the body of research generally. In addition, I find that their opinions more closely reflect the meaning of the prior art passages when read in context. The references Dr. Zusman relied on did not focus on combination therapies, or on combination therapy using an ERA and PDE5-I in the way that he did. The direction that Dr. Zusman discerns from his selection of passages from the prior art references is not apparent from reading those passages in the context of the references themselves, or in the context of the prior art references when considered together.

[162] Dr. Zusman refers to three review articles published close to August 2006: Lee & Channick (2005), Lee & Rubin (2005), and McLaughlin & McGoon (September 2006). The

tenor of these articles was that multiple avenues were being explored and the reported results—both positive and negative—were of interest. Lee & Rubin (2005) notes the lack of direct, prospective comparisons between different PAH medications to guide decisions to use one treatment over another. This article also states that the expert consensus statement on primary pulmonary hypertension (now referred to as PAH) published in 1993 by the ACCP was a 14-page document, and had "evolved into a 92-page, updated evidence-based monograph", reflecting the expansion in treatment decisions. The authors did include comments on combination therapy, but in this regard, they wrote that the addition of a second PAH drug may be reasonable for patients who deteriorate or have a suboptimal response to monotherapy, and "[a] handful of case series and observational cohort studies preliminarily have shown promising results using various combinations of sequential add-on therapy". Dr. Zusman pointed to the statement that "there may be important interactions between the NO, [endothelin], and prostacyclin pathways" to support his opinion that there was a focus on targeting the interactions between the pathways. However, this statement (made in Lee & Channick (2005) and Lee & Rubin (2005)) was an acknowledgement that interactions between the pathways were not fully understood.

[163] In addition to the NO, endothelin, and prostacyclin pathways, McLaughlin & McGoon (2006) describe other mechanisms implicated in PAH. When discussing combination therapy in particular, McLaughlin & McGoon (2006) note that the evidence on combination therapy with bosentan included a study with epoprostenol that failed to demonstrate benefits, that other study results were expected imminently, and more studies were underway.

[164] I find research in the field was progressing in multiple directions, without a focus on ERAs, the endothelin pathway, combination therapy over monotherapy, or any particular combination of drugs to treat PAH. Research was not focused on combinations of ERAs and PDE5-Is.

[165] In summary, I find the CGK as of 2006 showed there were multiple areas of research being explored and no focus on combination therapy for PAH; this was one avenue being explored in addition to a number of avenues of research into new monotherapies. While the literature reporting on the co-administration of bosentan and sildenafil provided preliminary evidence that this combination was effective, questions remained on the key point of whether the results were due to the combination. Positive evidence for some combination therapies was building; however, these were early days for PAH therapies and the evidence in support of combination treatment was limited.

(4) *Step 2*: Identify the Inventive Concept

[166] The parties submit that Asserted Claims are not ambiguous, and the inventive concept of each claim is readily discernable from reading the claims without requiring recourse to the 770 Patent disclosure. While the 770 Patent disclosure states that the patentee "surprisingly found that the combination of [macitentan] with a compound having PDE5-inhibitory properties results in an unexpected synergistic effect in the treatment of diseases wherein vasoconstriction is involved", the parties and their experts agree that a synergistic effect is not part of the inventive concept. Accordingly, they submit that the inventive concept of claim 21 is the use of macitentan in combination with a PDE5-I to treat a disease wherein vasoconstriction is involved

in human patients. The inventive concept of claims 22-31 is the same, except that these claims specify PDE5-Is (claims 22-25), diseases involving vasoconstriction (claims 26-28), or both (claims 29-31).

[167] I agree with the parties on the above points. This is not a case where additional details from the patent specification as a whole permit the inventive concept of one or more claims to be "fully and fairly understood": *Allergan Inc v Sandoz Canada Inc*, 2020 FC 1189 at para 173. In any event, in my view there is no difference between the inventive concept as identified from reading the Asserted Claims alone, or with the benefit of additional information in the 770 Patent specification: *Sanofi* at para 77; *Apotex Inc v Shire LLC*, 2021 FCA 52 at paras 67-69. I agree that the skilled person would not interpret synergy to form part of the inventive concept. The skilled person would understand the statement about synergy to refer to the observed results from experiments in rat models.

[168] As discussed previously, the WO 557 patent application was filed by Actelion and claimed a group of compounds with ERA activity, one of them being macitentan. Sandoz states the 770 Patent does not include a description of the selection of macitentan and simply takes macitentan to be a compound that was previously disclosed and known. The plaintiffs cannot "import" a selection of macitentan (from among the numerous compounds disclosed in WO 557) into the inventive concept of the Asserted Claims. Furthermore, Sandoz states the plaintiffs should be held to an admission that the 770 Patent is not a selection patent, which admission was made in their pleading in another Court proceeding.

[169] Regarding the alleged admission, even if I were inclined to hold the plaintiffs to a statement they made in the context of another proceeding, the alleged admission goes no further than to assert that the 770 Patent is not a selection patent as described in *Sanofi*: that is, a second patent with claims to a subset of compounds falling within a broader class of compounds claimed in a prior patent, and selected for a special character that is peculiar to the subset. In a selection patent, the discovery that the members of the selected group possess a substantial advantage (or avoid a disadvantage) over the prior claimed class is the inventive concept that supports a new claim that is distinguishable from the prior claim only in the number of compounds that are covered. That is not the situation with the 770 Patent. The invention of the 770 Patent relates to a combination. All Asserted Claims include a limitation of "in combination" with a PDE5-I and that limitation is not claimed in WO 557.

[170] There is no dispute that macitentan is part of the inventive concept for every Asserted Claim. If macitentan was not already identified in the prior art as a compound to be combined with a PDE5-I, the skilled person would have had to take that step, unless it was not necessary to identify macitentan specifically because any ERA would be expected to work.

[171] In summary, the inventive concept of the Asserted Claims is the use of macitentan in combination with a PDE5-I to treat a disease involving vasoconstriction, or the use of macitentan in combination with specific PDE5-Is and/or with specific diseases according to the dependent claims.

(5) *Step 3*: Differences Between the State of the Art and the Inventive Concept

(a) *The Parties' Submissions*

[172] Sandoz submits that the cumulative effect of the relevant prior art—the state of the art—was that the class effects of the available therapies were known and would have led the skilled person to combine monotherapies with the expectation that the combination therapies would work based on their differing mechanisms of action. There were numerous disclosures of the combination use of an ERA with a PDE5-I to treat diseases involving vasoconstriction, including PH/PAH. Combination therapies (including an ERA with a PDE5-I) were in fact used in clinical practice to treat PAH, with a safe and effective response in patients.

[173] As a result, Sandoz submits the only difference between the state of the art and the inventive concept is limiting the ERA that would be combined with a PDE5-I, to macitentan. Sandoz states macitentan was known and was considered the "next generation" ERA, and the skilled person merely needs to take macitentan and combine it with a PDE5-I to treat diseases involving vasoconstriction, as taught by the prior art publications.

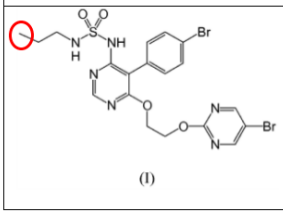
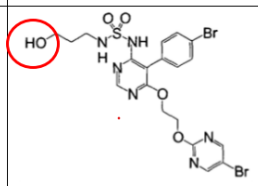
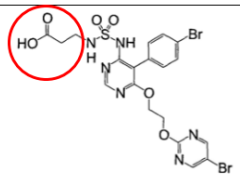
[174] As noted previously, Sandoz submits the state of the art includes all of the CGK and any prior art that is found not to be CGK. In this section I have considered the cumulative effect of the prior art references discussed under CGK above with the remaining prior art references that Sandoz asserts to form part of the state of the art.

[175] Sandoz repeats and relies on its submissions regarding the CGK, and submits the following references are of significance to exemplify the state of the art, for the reasons

summarized below. References marked with an asterisk have already been considered in the CGK section:

a) US 5,859,006 (1999) (US 006) disclosed a class of PDE5-Is, including tadalafil, for treating conditions that include hypertension, PH, angina and congestive heart failure, and that the PDE5-Is could be used in combination with other therapeutic agents.
b) WO 004 (1999) disclosed a class of PDE5-Is for the treatment of cardiovascular diseases, and that they could be used in combination with other therapeutic agents including ERAs such as bosentan.
c) US 731 (2004) extended this concept to a wide array of ERAs. It described the use of a PDE5-I in combination with at least one ERA for the treatment of diseases wherein vasoconstriction is involved. The preferred ERA was bosentan or other ERAs that were known at the time.
d) Hoeper et al (2004)* provided a key teaching to the skilled person that bosentan in combination with sildenafil was safe and effective.
e) Channick et al (2004)* suggested bosentan may have a role as part of a combination of drugs and Lee & Channick (2005)* stated bosentan and sildenafil was being used in clinical practice.
f) Lee & Rubin (2005)* stated that the addition of a second PAH drug may be reasonable for patients who deteriorate on monotherapy and that combination therapy may increase efficacy while minimizing toxicity, and included combination therapy in their recommended therapies for PAH.
g) WO 395 (March 2006): WO 395 claimed, *inter alia*, using the PDE5-I with an ERA for treatment of PH or a vascular condition. WO 395 noted over 30 dual and ET_A-selective ERAs that were being developed. Dr. Vachiery's report omitted WO 395 from his consideration of prior art. He admitted on cross-examination that Claim 6 of WO 395 encompasses dual ERAs that are not preferentially selective for ET_A or ET_B.
h) WO 2006/051502 (May 2006) (WO 502): Dr. Clozel is a named inventor of WO 502, which discloses various ERAs for treatment of, *inter alia*, hypertension, PH,

coronary diseases, portal hypertension and diabetic complications. These ERAs can be administered orally. With the exception of compounds covered and the results of testing on the compounds (e.g., activity against ET_A/ET_B receptors), the disclosure of WO 502 is the same as WO 557. WO 502 disclosed the ET_A and ET_B affinities for two example ERAs. Dr. Clozel admitted the only difference between macitentan and the WO 502 Example 1 is the hydroxyl group, and the only difference between macitentan and WO 502 Example 2 is the substitution of the methyl group for the carboxyl group:

MAC (^{Ex}P1; ^{Ex}D12)	WO502 Example 1 (^{Ex}D15)	WO502 Example 2 (^{Ex}D16)
 (I)		

i) Minai & Arroliga (August 2006)* reported results of the long-term therapy with bosentan and sildenafil in three PAH patients who showed improvement, and the combination was well tolerated.

[176] The plaintiffs submit the difference between the state of the art and the inventive concept of claim 21 are: (i) macitentan was effectively unknown to the skilled person as of 2006; only the chemical structure of macitentan was disclosed in WO 557 (it was the only reference that referred to the compound at all), and nothing was known about its specific prospects, properties, or uses; (ii) it was not known if any ERA in combination with PDE5-I would work for any disease, including PH/PAH; (iii) interactions between bosentan and sildenafil taught away from combination use; and (iv) it was not known if ERAs had a class effect such that properties of macitentan can be extrapolated from what was known about other ERAs—differences in chemical structures and selectivity for ET_A versus ET_B taught away from the expectation of class effects. In addition to this, the difference between the state of the art and the inventive concept

of claims 22-31 would be the use of the particular PDE5-Is and the specific diseases to be treated.

[177] With respect to WO 557, the plaintiffs state it only discloses macitentan as one of many compounds with ERA activity, and discloses its chemical structure. WO 557 includes tables with ERA activity data for many other compounds, but not for macitentan. Therefore, it does not teach the skilled person that macitentan should be the compound that is used in combination with a PDE5-I to treat PAH.

[178] The plaintiffs argue that the prior art taught away from combination treatment. Specifically, a pharmacokinetic study by Paul et al (2005) found that bosentan significantly decreased the plasma concentration of sildenafil. The WO 395 patent application described a study of bosentan and sildenafil that was terminated due to pharmacokinetic drug interaction problems. The prior art also taught away from the expectation of class effects among ERAs. As of 2006, the skilled person was aware of the uncertainty surrounding dual ET_A/ET_B versus selective ET_A antagonists. In addition, bosentan was the only ERA approved as of 2006 and the subsequent market withdrawal of sitaxsentan showed there were differing safety profiles of ERAs.

[179] With respect to US 006, Dr. Zusman refers to a statement in the patent that the disclosed PDE5-Is "may also be used in combination with other therapeutic agents which may be useful in the treatment of the above-mentioned disease states". According to Dr. Zusman, this statement illustrates that as early as 1999, upon the development of new PDE5-Is useful for treating

conditions wherein vasoconstriction is involved, the skilled person "had combination therapies in mind". There is no dispute that the skilled person had combination therapies in mind as of 2006. This was evident from multiple prior art references. However, this patent reference (from 1999) did not resolve the uncertainties in the field or add to the body of knowledge described in the CGK analysis. Sandoz does not point to an aspect of this patent that changes the landscape on what was known about combination therapy as of 2006.

(b) *Analysis*

[180] With respect to WO 004 and US 731, I agree with Dr. Vachiery's opinion. WO 004 mentions bosentan as one of many potential compounds that can be used in combination with the PDE5-Is that are disclosed. US 731 discusses the combination of a PDE5-I with ERAs but does not report any pre-clinical or clinical trial data in support. I would add that WO 004 also does not report any pre-clinical or clinical trial data on combination therapy, despite including a claim to the compounds when administered with another cGMP PDE inhibitor, a prostanoid, an α-adrenergic agonist, an endothelin antagonist, an angiotensin AT_1 antagonist, an angiotensin converting enzyme inhibitor, a renin inhibitor, or a serotonin 5-HT_{2c} agonist. The skilled person would not consider WO 004 and US 731 as demonstrating that any ERA would be useful in combination with a PDE5-I .

[181] WO 395 is the most relevant patent reference. It is a patent application filed by the developer of sitaxsentan (a selective ET_A antagonist) and it was published on March 9, 2006. WO 395 describes combination therapies comprising at least one ET_A antagonist and a PDE5-I.

[182] Contrary to Sandoz's suggestion that Dr. Vachiery omitted WO 395 from the prior art, Dr. Vachiery discusses WO 395 within his expert report. Drs. Vachiery and Chakinala state that WO 395 indicates to the skilled person the need for the development of an ET_A selective antagonist over dual ERAs, particularly when used in combination with a PDE5-I. Sandoz points out that Dr. Chakinala admitted on cross-examination that he had not read WO 395. While it is surprising that Dr. Chakinala gave an opinion on a document that he did not read, he explained in cross-examination that he was already familiar with the same information from other sources and knew that the information was factually correct.

[183] In my view, WO 395 added to the prior art in that it indicated positive results from the combination of sitaxsentan and sildenafil in human subjects, but without disclosing the results themselves. The only statement relating to the results of the efficacy study was, "[m]inimal drug interaction and side effects with treatment will occur in the combination [sitaxsentan] and Sildenafil of groups (iv) and (v) while maintaining successful therapeutic effect." WO 395 contributed to the body of knowledge with some information about this ERA that had been used in combination with sildenafil; however, the information does not allow the skilled person to conclude that any ERA would be expected to work when combined with sildenafil or another PDE5-I. In fact, it suggests the opposite. WO 395 points out that sitaxsentan is an ET_A selective antagonist and differs from bosentan, a dual ET_A and ET_B antagonist. It states that, "[u]se of a nonselective [endothelin] receptor interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimens and/or reduction in side effects."

[184] Turning to WO 502, Sandoz introduced this reference as an exhibit during Dr. Clozel's cross-examination. No expert opined on this reference; thus, there is no expert opinion evidence explaining what this reference teaches or how it would be understood by the skilled person. In any event, Sandoz does not explain how it contributes to the skilled person's knowledge of combination therapy for diseases involving vasoconstriction.

[185] In conclusion, while Sandoz relies on the patent references above as prior disclosures of the combination use of an ERA with a PDE5-I to treat diseases involving vasoconstriction, including PH/PAH, the key references supporting Sandoz's position that the class effects of the available therapies were known remain the same non-patent references that I have already considered in the analysis of the CGK. For the reasons explained in that section, the skilled person would not have considered that the available evidence regarding a combination of bosentan and sildenafil had been established to a sufficient level of confidence so as to provide a basis for extrapolating those results to combinations of other drugs in those classes, based on their shared mechanisms of action. None of the additional references, considered with what was discussed within the CGK section, change the landscape. The cumulative effect of the relevant prior art—the state of the art—would not have led the skilled person to combine monotherapies with the expectation that the combination therapies would work based on their differing mechanisms of action.

[186] I disagree with Sandoz that the only difference between the state of the art and the inventive concept is limiting the ERA that would be combined with a PDE5-I to macitentan. The skilled person was not focused on combination therapies with an ERA and a PDE5-I, did not

expect that any ERA could be combined with a PDE5-I for use in a disease involving vasoconstriction, and did not understand there would be a class effect for ERAs when used in combination with other drugs (including PDE5-Is), particularly in view of divergent teachings on the impact of ET_A/ET_B selectivity.

(6) *Step 4:* Was the Difference Obvious?

[187] As noted above, Sandoz submits the only difference between the state of the art and the inventive concept is limiting the ERA to macitentan, which was obvious to the skilled person. The inventor, Dr. Clozel, merely did what had already been done and what the skilled person was thinking at the time: administer two drugs with two different mechanisms of action in combination. Sandoz argues claim 21 is obvious because all the skilled person had to do is take macitentan, a next generation ERA, and combine it with a PDE5-I to treat a disease wherein vasoconstriction is involved, just as taught by the prior art. With respect to narrowing the PDE5-I to sildenafil, vardenafil, tadalafil, and udenafil, these were known PDE5-Is, and therefore, claims 22-31 would also have been obvious to the skilled person.

[188] As I previously explained in the introduction to the obviousness analysis, as one aspect of my analysis I have considered whether the skilled person would expect any combination of an ERA and PDE5-I to be useful for treating a disease involving vasoconstriction, based on known class effects. This would obviate the need for identifying macitentan. For the reasons I have given, I find that the skilled person would not expect that any ERA would be useful in combination with a PDE5-I. The invention was not obvious due to the fact that macitentan is an ERA and any ERA would be expected to work in combination with a PDE5-I.

[189] The next aspect of Sandoz's argument necessarily assumes that macitentan is identified from among the numerous ERAs that had been disclosed in the prior art references as of 2006. However, Sandoz's arguments in this regard are somewhat confusing. One argument suggests that the skilled person would have immediately identified macitentan in particular, while the other suggests that macitentan would have fallen within a limited group of ERAs that the skilled person would have considered as being obvious to try.

[190] Turning to the first argument, Sandoz starts with the point that macitentan was not a new compound. Sandoz states that macitentan was "known and disclosed" because the 770 Patent expressly admits that WO 557 disclosed macitentan as well as its use in the treatment of diseases involving vasoconstriction. In addition, Dr. Chakinala admitted that as of 2006, the skilled person would be aware of macitentan and would know that it is a nonselective ERA, and Dr. Vachiery admitted that the skilled person "would have heard about macitentan".

[191] I do not accept this argument. There was no direct path to macitentan specifically. Macitentan had not been specifically identified as a candidate compound in the prior art. It was one of the compounds with ERA activity disclosed in WO 577, along with many other compounds with ERA activity. Sandoz provides no reason why the skilled person would focus on WO 557 as a starting point, let alone identify macitentan as the candidate compound from WO 557. Sandoz does not accurately characterize what Drs. Vachiery and Chakinala said was known about macitentan as of 2006, and takes their testimony out of context. When Dr. Vachiery was asked what was known about macitentan at the relevant time, he answered:

> I would say that the [skilled person] would probably not know that macitentan was existing and when -- if you may wish to look at the

> Exhibit Q, which is an article that I authored, we -- where my co-author and myself list the compounds that were currently under investigation. Macitentan, as of 2009, was not even there as a potential treatment for PH, so at best [the skilled person] would have heard about macitentan but would not know the specific aspects or the role or the effects of macitentan on the pulmonary vascular bed or any disease where vasoconstriction is concerned. So it was not in any of the documents that we reviewed as authors in terms of guidelines or perspective.

[192] The same is true of Dr. Chakinala:

> Q. Lastly on this particular topic, what, if anything, was known about macitentan as of August 29, 2006, what would the [skilled person] have understood. And you start that discussion at paragraph 199 of your report.
>
> A. I think as of August 2006 the [skilled person] would really only be aware of macitentan if reviewing patent documents that discuss many different ERA compounds that were out there, and if they had access to that kind of documentation they would understand that macitentan was a nonselective ERA and I think the patent was the WO 557 patent. But beyond that they would have very little additional experience or knowledge about it until patent 770 was reviewed.

[193] I agree with the plaintiffs that macitentan was effectively unknown to the skilled person as of August 2006. The only prior art that refers to it is WO 557 and, as I have said above, Sandoz has not established that the skilled person would focus on this patent application to select an ERA for combination with a PDE5-I. I disagree with Sandoz that all the skilled person would need to do is "take macitentan and combine it with a PDE5-I to treat a disease involving vasoconstriction".

[194] Sandoz also argues that it would have been obvious to try macitentan in combination with a PDE5-I because the skilled person would have identified it within a limited group of candidate compounds that would then be tested, and would have expected that combination to be useful.

Sandoz states there was a motivation to find effective treatments for PAH, and testing candidate compounds would not have required significant effort. Sandoz argues that if a particular route is an obvious one to take or try, it is not rendered less obvious merely because there are a number, even a large number, of other obvious routes: *Janssen Inc v Teva Canada Limited*, 2015 FC 184 at para 113. The fact that there may have been other ERA compounds disclosed in WO 557 or in the prior art does not render the combination in the Asserted Claims non-obvious.

[195] Sandoz states there was a particular motivation to use combinations of therapeutic agents with different mechanisms of action, because of the significant chance that a PAH patient could deteriorate on monotherapy. Sandoz states the skilled person would be steered toward combining an ERA with a PDE5-I, and these drug classes would be attractive given their ease of administration as oral agents. Sandoz argues that the possible combinations of these therapies were "incredibly limited"—there were a finite number of identified, predictable solutions because there were a very limited number of PDE5-Is and a very limited number of ERAs. The skilled person would be steered toward macitentan as the particular ERA to combine with a PDE5-I.

[196] The plaintiffs argue that Sandoz's approach would mean that an interest in pursuing a research idea would render it obvious and unpatentable, which is contrary to the teaching of *Sanofi* at paragraph 65. The degree of motivation cannot transform a possible solution into an obvious one: *Apotex Inc v Pfizer Canada Inc*, 2009 FCA 8 at para 44. Even if there was general motivation to improve PAH treatments, there was no specific motivation to combine macitentan and a PDE5-I.

[197] I find there were not, as Sandoz argues, limited numbers of possible combinations of drug therapies. The patent references in evidence disclose large numbers of ERAs. In my view, even accepting that the skilled person would be steered toward combining an ERA with a PDE5-I, a fundamental gap in Sandoz's obviousness argument is that there is no basis, apart from hindsight, that would lead the skilled person to identify a group of candidate ERA compounds that would include macitentan for testing.

[198] As a first step, Sandoz has not established that the skilled person would be directed to WO 557. Sandoz suggests that the skilled person would identify candidates that were approved or in development, or they would be looking for a "better bosentan" or "next generation" ERAs. There is no rational basis for this approach. Sandoz does not explain, and the state of the art does not define, the characteristics or attributes that could be used to narrow the field of potential ERA candidates. Macitentan was not a candidate that had been approved, and there is no prior art reference that identifies it as a candidate that was in development. Apart from hindsight, Sandoz provides no rationale as to why the skilled person would focus on WO 557 to find a "better bosentan" or a "next generation" ERA. WO 395 was published in March 2006, nearly four years after WO 557 was published. WO 395 provides the rationale for the path those researchers pursued—they believed selective ET_A inhibitors were, in effect, the better bosentan or next generation ERA, specifically stating that for the purposes of the invention, "bosentan or any other non-specific endothelin receptor antagonist would not represent an ET_A-specific antagonist". WO 395 states:

> Combination Therapies
>
> [067] The principle drawback for using sildenafil in treating PAH is that it requires a high dose three times a day (much higher than the dose for erectile dysfunction, which is 15 mg to 75 mg

> periodically). Currently, the only endothelin receptor antagonist which has been approved for use in PAH is bosentan, which is a nonselective compound that blocks both the A and the B receptors. Use of a nonselective ET receptor interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects.
>
> [068] For instance, ET_A causes vasoconstriction, while ET_B causes vasodilatation. Bosentan works by blocking both ET_A and ET_B receptors. Sitaxsentan works by only blocking the ET_A and leaving the ET_B unimpaired. The mechanism by which ET_B causes vasodilatation is through stimulating the production of nitrous oxide and prostacylin. Nitrous oxide (NO) in turn activates the guanyl cyclase which increases the level of cGMP. The cGMP is responsible for relaxing the blood vessel. PDE5 acts to break down cGMP, so a PDE5 inhibitor also raises the level of cGMP, causing vasodilatation. Thus, when used together, increasing cGMP through the ET_B receptor and preventing its breakdown leads to increased vasodilatation and better efficacy of both drugs. Nonselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production. Additionally in a recent study, Bosentan, a non-selective antagonist, was tested with sildenafil, but the study was terminated due to pharmacokinetic drug interaction problems.

[199] Even assuming that the skilled person would begin with WO 557, I find the evidence does not establish how the skilled person would select a group of compounds from the large group of compounds disclosed in that patent application, for the reasons below.

[200] Sandoz argues that WO 557 disclosed: (i) the chemical structure of macitentan; (ii) that the ERA compounds therein could be used in combination with vasodilators or other therapeutics that treat high blood pressure or cardiac disorders, including PH (and Dr. Chakinala admitted that PDE5-Is are vasodilators); (iii) a testing protocol to evaluate the potency of the compounds (this means that although the IC_{50} value of macitentan is not disclosed, a routine test is sufficient to

test the potency of the compounds); (iv) the route of administration for the ERA compounds, which goes to safety; and (v) how the compounds can be used, which goes to efficacy.

[201] To identify macitentan as a candidate from WO 557, Sandoz argues the skilled person would first look to the potency (binding affinity to ET_A and ET_B receptors) of the compounds. Dr. Zusman opined that some of the most potent ET_A receptor blocking antagonists in WO 557 were 9 compounds listed as example numbers 100 to 108. According to Sandoz, these 9 compounds share the same core structure as macitentan, and a chemist would know how to substitute functional groups to arrive at macitentan. Sandoz states the skilled person would also look to WO 502. Sandoz argues that the disclosure of WO 502 is the same as WO 557, except that WO 502 discloses different chemical compounds and different test results. WO 502 disclosed ET_A and ET_B affinities for two example ERAs. Sandoz relies on Dr. Clozel's testimony (who I note was called as a fact witness and not qualified as an expert witness; she also stated that she is not a chemist) that example 1 of WO 502 differs from macitentan in the addition of a hydroxyl group and example 2 differs from macitentan in the substitution of a methyl group for a carboxyl group.

[202] Dr. Zusman stated that there were a number of factors that the skilled person could use to choose a candidate compound, among these being the potency, which in this case would be the binding activity for ET_A and ET_B receptors. While WO 557 does not disclose the potency of macitentan, Sandoz argues that the skilled person would test macitentan for its inhibitory properties, and the methods for testing endothelin receptor binding affinity were disclosed in WO 557.

[203] Dr. Zusman stated that other considerations for selecting candidate compounds would be bioavailability, rate of metabolism, route of metabolism, inherent half-life of the compound, the interaction of the compound with other drugs that might be commonly administered to the same patient population, the availability of precursor compounds necessary for the synthesis of the candidate molecule, the cost of producing the molecule, the difficulty or ease of formulating the compound into a form that could be administered to human subjects. He stated that to acquire that information, a medicinal chemist could infer some information from the chemical structure, and other information would be acquired by testing. The chemical structure of macitentan was disclosed in WO 557, and the skilled person could look at tables of data in WO 557 disclosing characteristics of other compounds, and focus on macitentan and possibly other compounds as candidates for drug development.

[204] Apart from a bare assertion that the skilled person would take these factors into consideration and do these tests on an unspecified number of compounds, Sandoz has not led evidence from a medicinal chemist or other evidence to establish how this process would lead the skilled person to focus on macitentan or a group of compounds that includes macitentan as candidate compounds. Sandoz has not established that this path would lead the skilled person to define a group of compounds that includes macitentan, from among the compounds disclosed in WO 557, in order to test them in combination with a PDE5-I.

[205] I find that, even if the skilled person were focused on WO 557, it disclosed a large number of compounds with ERA activity. Without hindsight, there is no justification for the skilled person to take the steps that Sandoz alleges would have led the skilled person to identify

macitentan among a group of compounds selected for testing from WO 557. The steps would only be taken with a view to the invention.

[206] In conclusion, Sandoz has not established that the difference between the state of the art and the inventive concept was obvious.

B. *Utility*

[207] The utility of a claimed invention must either be demonstrated or soundly predicted based on the information and expertise available at the material date, which is no later than the filing date: *Patent Act*; s 2; *Apotex Inc v Wellcome Foundation Limited*, 2002 SCC 77 at para 56 [*Wellcome*]; *Apotex Inc v Janssen Inc*, 2021 FCA 45 at para 37 [*Abiraterone*].

[208] The doctrine of sound prediction presupposes that further work needs to be done; it balances the public interest in early disclosure of new and useful inventions, even before their utility has be verified by tests (which can take years in the case of pharmaceutical products), and the public interest in avoiding cluttering the public domain with useless patents, and granting monopoly rights in exchange for misinformation: *Wellcome* at paras 66, 77. Sound prediction cannot mean a certainty since it does not exclude all risk that some of the area covered may prove devoid of utility: *Wellcome* at para 62, citing *Monsanto Co v Commissioner of Patents*, [1979] 2 SCR 1108 at 1117.

[209] The three requirements for a sound prediction of utility are set out in *Wellcome* at paragraph 70. There must be: (i) a factual basis for the prediction, (ii) an articulable and sound

line of reasoning from which the desired result can be inferred from the factual basis, and (iii) proper disclosure.

[210] The *Patent Act* does not prescribe the degree or quantum of usefulness required, or that every potential use be realized—a scintilla of utility that is related to the nature of the subject matter is sufficient: *AstraZeneca Canada Inc v Apotex Inc*, 2017 SCC 36 at paras 53-55 [*AstraZeneca*]; *Abiraterone* at para 37.

[211] The factual basis may be established by supplying the test data: *Pfizer Canada Inc v Canada (Minister of Health)*, 2007 FCA 209 at para 153. The factual basis can also rely on scientifically accepted principles or information that would form part of the CGK of the skilled person: *Eurocopter* at paras 152-155.

[212] The 770 Patent discloses data that were not part of the CGK or the prior art. The parties disagree on whether the data are sufficient to support a soundly predicted utility. My analysis below concludes that sufficient information was disclosed in the 770 Patent to allow the skilled person to soundly predict that the claimed invention would be useful for the particular utility claimed: *Teva Canada Limited v Novartis AG*, 2013 FC 141 at para 323 [*Novartis AG*].

[213] The 770 Patent disclosed that macitentan is an ERA, and it disclosed certain results from experiments that compared the blood pressure lowering effects of macitentan alone, a PDE5-I alone, and macitentan in combination with the PDE5-I, in two *in vivo* rat models for hypertension. The data for the reduction in blood pressure were reported as an “area between the

curves" (ABC), which is a quantification of the difference between two curves that, in this case, plotted blood pressure measurements that were calculated for the rats. The first curve plotted the measurements for the control period (no drug administered) and the second curve plotted the measurements for the treatment period (rats were administered macitentan alone, the PDE5-I alone, or the combination). Example 1 reported the decrease in blood pressure in Dahl salt-sensitive (Dahl-S) rats after administering macitentan alone (ABC of 236), tadalafil alone (ABC of 310), and the two in combination (ABC of 923). Example 2 reported the decrease in blood pressure in spontaneous hypertensive rats (SHR) after administering macitentan alone (ABC of 44), tadalafil alone (ABC of 286), and the two in combination (ABC of 444). Example 3 reported the decrease in blood pressure in SHR after administering macitentan alone (ABC of 38), sildenafil alone (ABC of 229), and the two together (ABC of 317).

(1) The Experts' Opinions

[214] Dr. Zusman reviewed Actelion's internal documents for the experimental work corresponding to results reported as Examples 1-3 in the 770 Patent. He opined that the rat experiments did not demonstrate that the claimed combination of macitentan and a PDE5-I would be useful in humans for treating diseases wherein vasoconstriction is involved for the following reasons: (i) animal studies are not predictive of the same positive results in humans and the dosages administered were much higher than what would be used in humans; (ii) Dahl-S and SHR are rat models of systemic hypertension—they do not demonstrate utility for treating any other disease wherein vasoconstriction is involved; (iii) the SHR model was not useful for testing ERAs; furthermore, based on the graphs, macitentan had little to no effect on mean arterial pressure in the SHR model and the magnitude and duration of effects from combining

macitentan with tadalafil or sildenafil are consistent with the effects achieved from administering tadalafil or sildenafil alone; (iv) the rat studies had small sample sizes, a large standard error of the means (SEM, a measure that is used to estimate the variability in the calculation of the mean), and did not report p-values (which is a statistical measure of the probability that an observed difference was due to chance).

[215] For similar reasons, Dr. Zusman opines that the rat studies did not provide a basis for soundly predicting that the claimed combination of macitentan and a PDE5-I would be useful in humans for treating diseases wherein vasoconstriction is involved. There was no articulable or sound line of reasoning that would link the results from the rat models for systemic hypertension to other diseases in humans, particularly disease conditions that involve the pulmonary vasculature, since systemic hypertension relates to the systemic vasculature. Furthermore, there was no sound line of reasoning to draw any conclusions regarding the efficacy of macitentan, alone or in combination therapy, from an SHR model that was inappropriate to test an ERA. There is no sound rationale that would link the factual basis, derived from the rat studies, to a prediction that the Asserted Claims would be useful.

[216] On the point of proper disclosure, Dr. Zusman opined that the factual basis for the prediction was not part of the CGK, because the skilled person understood that positive results in animal studies required confirmatory testing in humans. Furthermore, Dr. Zusman stated that only some of the experimental results were disclosed in the 770 Patent. The full set of data from Actelion's internal documents included [redacted]. Based on the data that were disclosed in the 770 Patent, the skilled person is unable

to determine whether the ABC values, which were reported as definitive values without any indication of statistical significance or variability, accurately reflected the extent and duration of any benefit from the combined effect. Furthermore, if the 770 Patent had disclosed the graphs that were used to calculate the ABC values, the skilled person would notice that macitentan had little to no effect on mean arterial pressure in the SHR model. Therefore, the factual basis and sound line of reasoning, if any, were not properly disclosed in the 770 Patent.

[217] Drs. Vachiery and Chakinala disagree with Dr. Zusman on each of the above points. They say the 770 Patent disclosed the substance of the results from Actelion's work, and these results provide the factual basis for demonstrating and soundly predicting the utility required to support the claimed invention. Experimental results using the two rat models provide predictive signals that extend to any disease of vasoconstriction, because the blood pressure lowering effect was the key observation, regardless of whether it was occurring in the systemic or pulmonary vasculature. While a disclosure of the additive blood pressure reduction results would have been of value, the skilled person would have appreciated that the ABC numbers showed the overall effect of the administration of the intervention. The results disclosed in the 770 Patent are consistent with the conclusions that were drawn by the researchers who conducted these studies at Actelion, namely, that the combination of macitentan and sildenafil or tadalafil lowered blood pressure more than the additive effect of each drug as a monotherapy. This was sufficient to demonstrate that the Asserted Claims had utility.

[218] Similarly, with regard to sound prediction, Drs. Vachiery and Chakinala opined that the results from the rat studies as disclosed in the 770 Patent, along with the CGK about the role of

the endothelin and NO pathways in diseases involving vasoconstriction, provided the factual basis and sound line of reasoning that the claimed invention has utility and is capable of a practical purpose. While the results from these animal experiments are not wholly predictive of what would occur in humans, they provide the necessary positive signal to warrant further investigation.

(2) Analysis

[219] Sandoz contends that the inventors did not demonstrate utility in humans by the filing date and Dr. Zusman's opinion in this regard was unrefuted. According to Sandoz, Drs. Chakinala and Vachiery admitted that animal models have limited probative value to patients and results from rat studies would not necessarily translate to benefits in humans—rat studies were only a signal to do more testing.

[220] With respect to sound prediction, Sandoz states that a challenge based on soundly predicted utility will succeed if: (i) the prediction was not sound, or (ii) irrespective of the soundness of the prediction, there is evidence of lack of utility in respect of some of the area covered: *Wellcome* at para 56.

[221] Sandoz argues that the work at Actelion or the rat study results that were disclosed in the 770 Patent did not support a sound prediction of utility, as the results contained flaws that would prevent the skilled person from concluding that they were scientifically valid. Specifically, Sandoz states: (i) the rat models, Dahl-S and SHR, were systemic hypertension models, and the studies measured systemic blood pressure only; Dr. Chakinala admitted that systemic blood

pressure cannot be used to calculate pulmonary blood pressure and they are not predictive of each other; (ii) Dr. Zusman provided uncontroverted evidence that macitentan showed no effects on systemic mean arterial pressure in the SHR model; (iii) the skilled person would not be able to draw conclusions regarding the significance of the reported results; the SEMs of the study results were wide (± [redacted] to [redacted]% of the stated mean arterial pressure values) and highly variable; when the "error bars" representing the SEMs are included on the curves for mean arterial pressure values, the skilled person would see a potential for overlap, and overlapping error bars mean that the difference between the control and treatment curves are not statistically significant; (iv) the rat studies do not provide information on potential drug-drug interactions in humans; (v) the dosage used in the studies was so high as to raise the possibility that the observed effects were off-target effects.

[222] Sandoz contends that there is no sound line of reasoning linking the rat studies to diseases involving vasoconstriction other than systemic hypertension, and Dr. Zusman's opinion in this regard was not challenged. There was no sound line of reasoning to infer efficacy of the combination to treat PH or PAH in humans, as well as erectile dysfunction, angina pectoris, diabetic arteriopathy, and heart failure. Sandoz submits that the 770 Patent fails to disclose the line of reasoning that would explain how a result that was due to effects on the endothelin and NO pathways could predict the utility of macitentan for treating diseases that cannot be treated using an ERA. Dr. Zusman opined that diabetic arteriopathy and angina pectoris are conditions of vascular obstruction, not vasoconstriction, and animal models may not be predictive of clinical outcomes for heart failure and erectile dysfunction. According to Sandoz, Drs. Vachiery and Chakinala conceded in cross-examination that ERAs were proven not useful for diabetic

arteriopathy, angina pectoris, heart failure, and erectile dysfunction as of 2007 or 2008, and Dr. Chakinala conceded that numerous subtypes of PH and PAH could not be treated with ERAs as of 2007. Sandoz relies on *Pfizer Canada Inc v Ratiopharm Inc*, 2010 FC 612 [*Ratiopharm*], where the Court concluded that there was no basis to soundly predict that sildenafil would be useful to treat certain subtypes of PH, based on the results of clinical studies that had been disclosed in the patent.

[223] With regard to proper disclosure, Sandoz submits it was not CGK that test results from these rat models would provide predictive evidence for the utility of the combination in diseases of vasoconstriction, and the patent disclosure does not explain the line of reasoning. Sandoz also submits the test results disclosed in the 770 Patent were incomplete and exaggerated to support a synergistic effect. Specifically, the graphs showing the curves used to calculate the ABC values were not disclosed. Without this information, the skilled person would not understand whether the reduction in blood pressure was transient or sustained over time. By failing to disclose the graphs, Actelion obfuscated macitentan's lack of effect in the SHR model and the wide SEM values for the mean arterial pressure measurements that were used to calculate ABC values. The lack of statistical information means the skilled person could not determine the variability in the data and meaningfulness of the results. The skilled person could not validate any claim of superiority, synergism, or efficacy of the combinations. Sandoz also submits that the failure to disclose other results, including the additive effect on blood pressure reduction or the lack of effect on heart rate, rendered the disclosure incomplete to support a purported invention. This indicates the patentee intended to hide information that did not support the invention.

[224] The plaintiffs argue that Dr. Zusman's criticisms of the rat studies fail to consider the purpose of these experiments and the standard for assessing utility. Specifically, the importance of the experiments was the demonstration that a decrease in blood pressure was indeed happening, not where it was occurring. Statistics are irrelevant because the experiments in their totality showed that the combination of macitentan and a PDE5-I caused a reduction in blood pressure, and Sandoz's criticisms are contrary to the principle that testing should be considered cumulatively when assessing demonstrated utility: *Abiraterone* at para 41. On cross-examination, Dr. Zusman acknowledged that the SHR model was not useless for evaluating ERAs.

[225] The plaintiffs state it is not necessary that tests conclusively prove the requisite utility; it is sufficient that test results are strongly suggestive of utility, and that there is no other logical explanation for the test results: *Abiraterone* at para 49. The utility requirement is to be interpreted in line with its purpose—to prevent the patenting of fanciful, speculative or inoperable inventions: *AstraZeneca* at para 57. The invention of the 770 Patent is not fanciful, speculative, or inoperative, and the utility requirement is met. Furthermore, not every potential use needs to be realized: *AstraZeneca* at para 55.

[226] The plaintiffs argue that *Ratiopharm* is a "promise doctrine" case that would be decided differently in view of the Supreme Court of Canada's decision in *AstraZeneca*. They point out that recently, sound prediction of utility was satisfied by the patent disclosure describing a clinical trial without including the results—the logic of the study along with the CGK supported the reasoning: *Pharmascience Inc v Teva Canada Innovation*, 2022 FCA 2 at paras 12-14. In a

more similar case (although under the old promise doctrine) where the claims were directed to the use of compounds in treating human cancers, the Court found a sound prediction where these compounds reduced tumour size in mice: *Novartis AG* at para 290. In *Wellcome*, the sound line of reasoning was based on *in vitro* testing in cell lines, which showed a chain termination effect of the virus.

[227] The plaintiffs argue that, in the event utility was not demonstrated as of August 29, 2007, sound prediction was established. The skilled person knew ERAs and PDE5-Is were useful to treat diseases involving vasoconstriction. The 770 Patent disclosure indicated macitentan was an ERA and showed reduction in blood pressure in two rat models when used in combination with PDE5-Is. Together with the CGK, the 770 Patent provided the skilled person with a factual basis to support a sound line of reasoning that macitentan in combination with PDE5-I was useful for treating diseases involving vasoconstriction.

[228] My analysis begins with Sandoz's criticisms of the data that support the utility of the claims.

[229] With respect to the experimental results, I disagree with Sandoz that the results contained flaws that would prevent the skilled person from concluding that they were scientifically valid.

[230] Turning first to the Dahl-S and SHR models, I accept the evidence of Drs. Vachiery and Chakinala that these models were useful for measuring a reduction in blood pressure. All of the

experts agreed that the endothelin and NO pathways are pathways that operate in the vasculature throughout the body, to effect vasoconstriction or vasodilation.

[231] Second, I do not accept Sandoz's assertion that the drug dosages administered to the rats were so high as to "raise the possibility that the observed effects were off-target effects". Drs. Vachiery and Chakinala stated that drugs are often tested at high doses in animal experiments to obtain the strongest response, and animals have different rates of metabolism. Dr. Zusman only stated that PDE5-I doses were high compared to the approved doses of PDE5-Is for administration to humans. Dr. Zusman did not opine that the doses used in Actelion's experiments were outside of the range that would be used for an *in vivo* animal experiment. Even accepting that the doses were "high" for this purpose, Sandoz did not lead evidence to explain what the off-target effects would be, or how administering PDE5-I compounds to the rats at these doses would spoil the experimental results.

[232] Third, I turn to the alleged flaws in the data and results themselves. Contrary to Sandoz's argument, Dr. Zusman did not provide uncontroverted evidence that macitentan showed no effects on systemic mean arterial pressure in the SHR model. Dr. Zusman stated that macitentan showed little to no effects, without quantifying the effects. He did not state that the ABC values showing an effect were calculated incorrectly. Furthermore, Dr. Zusman's evidence was not uncontroverted. Drs. Vachiery and Chakinala opined that the results reported in the Actelion research documents and in Examples 2-3 of the 770 Patent showed that macitentan did have an effect on decreasing blood pressure in the SHR model, and that when combined with sildenafil or

tadalafil, the effect was amplified. I accept their evidence. Based on the ABC values, macitentan had an effect in both rat models.

[233] Sandoz further states that Actelion failed to provide statistical analyses and without them, the skilled person would not be able to draw conclusions about the significance of the results. Sandoz raises possible issues with the reliability of the data based on statistical measures (i.e., the SEMs were wide and variable). Dr. Zusman does not conduct a statistical analysis and Sandoz has not established that the data are, in fact, unreliable, based on a statistical analysis of the SEMs or otherwise.

[234] Furthermore, I am not satisfied that the skilled person would require a statistical assessment of the observed results or would need to know the statistical significance of the results in order to consider them to be a reliable factual basis to support the utility of the claimed invention. In my view, the skilled person would note that multiple experiments were conducted, in two rat models and using two PDE5-Is, and the observed trends were consistent. It is not necessary that tests conclusively prove the requisite utility: *Abiraterone* at para 41.

[235] Finally, Sandoz asserts that the rat studies do not provide information on potential drug-drug interactions in humans. They point to Dr. Vachiery's testimony in cross-examination to support their position. However, Dr. Vachiery disagreed:

> Q. Then you would agree with me that testing in rat studies does not demonstrate any information on the potential for drug-drug interactions for humans, correct?
>
> A. Well, I'm not sure I would agree with that because, again, the metabolism might be different in an animal model, and surely in an animal than in human. But still it gives you an idea that a

> combination of drugs, two drug given together, may interact in a positive or a negative way in an animal. So that would probably and surely raise a red flag for investigators to further pursue clinical development.
>
> Q. You said the word “may”, so that's a mere possibility; is that correct?
>
> A. Animal models are animal models. They inform you. Again, the same is true for the efficacy. In most instances we would like to have some signal, as I said yesterday, signal for efficacy and signal for safety. If you have the signal then you can trust and move on that the intervention, in this case a combination of drug, might be applicable to humans. One important thing is that because we do not have perfect models to test hypothesis in -- I mean, let me rephrase that. There are very few animal models of human diseases but still you need to pass that bar to ensure that you have those signals, positive signal for safety and positive signal for efficacy, otherwise there’ll be no drug development unfortunately.

[236] I find there was a factual basis for predicting the utility of the subject matter of the Asserted Claims based on: (i) the experimental test results showing that macitentan, an ERA, lowered blood pressure when administered in combination with sildenafil or tadalafil, two PDE5-Is, in two different rat models for hypertension; (ii) these blood pressure lowering effects were greater than the effect of each drug as a monotherapy; and (iii) the CGK provided the context and logical explanation for these observed effects (particularly the knowledge of NO and endothelin pathways that are involved in vasoconstriction and the knowledge of the way that an ERA or PDE5-I would affect steps in these pathways to modulate a vasodilatory effect). Points (i) and (ii) were not part of the CGK, but they were disclosed in the 770 Patent. The requirement for proper disclosure was satisfied.

[237] There was a sound line of reasoning to predict that the observed effects from the experiments would extend to any disease wherein vasoconstriction is involved because the

observed effects were vasodilatory effects. There could be utility in a vasodilating effect, even when abnormal vasoconstriction is not an underlying cause of a disease. Similarly, there was a sound line of reasoning to predict that the observed effects would extend to any PDE5-I because macitentan in combination with two PDE5-Is produced consistent blood pressure reduction effects, and the logical explanation was based on the known mechanism of action for PDE5-Is.

[238] Sandoz also states that, irrespective of the soundness of the prediction, there is evidence of lack of utility in respect of some of the area covered.

[239] In this regard, I find Sandoz's reliance on *Ratiopharm* is misplaced. Whether utility was soundly predicted is a fact-driven exercise, based on the evidence. In *Ratiopharm*, the Court concluded that there was a consensus amongst all of the experts. All of the expert witnesses testified that the results disclosed in the patent at issue in *Ratiopharm* would not enable the skilled person to soundly predict that sildenafil would effectively treat pulmonary hypertension. Furthermore, those opinions would have been based on evidence of the skilled person's knowledge as of the filing date for that patent.

[240] In this case, none of the experts opined that some subtypes of PH or PAH could not be treated with ERAs as of 2007. This was not part of Dr. Zusman's opinion on utility, and Sandoz relies on the alleged concession by Dr. Chakinala in cross-examination. I disagree with Sandoz that Dr. Chakinala conceded that numerous subtypes of PH and PAH could not be treated with ERAs as of 2007. Dr. Chakinala was asked a different question—whether it was known that ERAs could treat a number of subtypes of PH and PAH as of 2007. He responded yes for many

subtypes, and for other subtypes his answer was not an unqualified "no". Rather, he stated that there was not widespread evidence or a clear cut answer that ERAs could treat these subtypes, and "clinicians like myself in select cases where the patients behaved more like they were in group 1, we could have tried on an off label basis an ERA, but there certainly was no indication or rigorous clinical trials or widely accepted recommendations."

[241] Sandoz also relies on alleged concessions made by Drs. Vachiery and Chakinala in cross-examination, that ERAs were not useful for diabetic arteriopathy, angina pectoris, heart failure, and erectile dysfunction as of 2007 or 2008.

[242] Sandoz does not accurately characterize the plaintiffs' experts' testimony. Sandoz relies on the following exchange with Dr. Vachiery:

> Q. So going back to my original question, in 2008 the person skilled in the art would not have known -- would have known that ERAs are not useful to treat angina pectoris, correct?
>
> A. That's correct.
>
> Q. And the person skilled in the art in August 2008 would also know that ERAs are not useful to treat heart failure; is that correct?
>
> A. This is correct, although the POSITA would also understand that there were studies underway and already completed looking at the effect of an endothelin receptor antagonist in the context of heart failure.

[243] Dr. Vachiery went on to explain that studies were underway to investigate the effect of ERAs in heart failure, and the interest in using ERAs for heart failure continued over the years. Dr. Vachiery continued:

> […] So the story has not been closed and hasn't ended as of 2008, but at that time there were only small studies or reports that were

> suggesting that it could be, in effect, in the treatment of diseases that are not necessarily pulmonary arterial hypertension.
>
> Q. Right. And so the skilled person would pay attention to those studies and inform themselves on potential uses as you say, correct?
>
> A. They would. They would not use these drugs to treat patients but they would inform themselves on the results of those trials and make them understand that it could be one of the treatment options for patients.

[244] Similarly, Dr. Chakinala stated he was not aware that ERAs were used to treat erectile dysfunction, angina pectoris, diabetic arteriopathy, or heart failure in 2007:

> Q. I see. And in 2007 were ERAs known to be used for the treatment of erectile dysfunction?
>
> A. Not that I'm aware of.
>
> Q. How about angina pectoris?
>
> A. No.
>
> Q. Diabetic arteriopathy?
>
> A. No.
>
> Q. And heart failure?
>
> A. ERAs were studied in heart failure significantly but were not used to treat heart failure.

[245] Considered in context, these statements do not establish that ERAs were proven not useful for diabetic arteriopathy, angina pectoris, heart failure, and erectile dysfunction as of 2007 or 2008. Importantly, the invention is macitentan in combination with a PDE5-I, not macitentan alone. There must be "a lack of utility of some of the area covered" by the combination of macitentan with a PDE5-I, and Sandoz has not established that is the case.

[246] With respect to demonstrated utility, the skilled person would not consider that the utility of the Asserted Claims had been demonstrated as of the filing date. The Asserted Claims relate to use of the combination for the treatment of diseases in humans. While the results of the rat studies are meaningful results that demonstrated an effect on blood pressure, if the results would not necessarily translate to the same effect in humans (and this was the evidence), then the results did not demonstrate utility. Further work needs to be done, which is the doctrine of sound prediction. I appreciate that the line between sound prediction and demonstrated utility is vague, and some commentators have expressed the view that there is a point where the cumulative weight of evidence supporting a sound prediction can reach a sufficient level to establish demonstrated utility: *Abiraterone* at para 50. I do not intend to suggest that there is a bright line that requires, in every case, testing in human patients in order to support demonstrated utility for a drug intended to treat a disease in humans. However, based on the evidence in this case, the skilled person would not find that the cumulative weight of Actelion's test results, considered in light of the CGK, had reached the level of demonstrated utility.

[247] In summary, Sandoz has not established that the Asserted Claims are invalid based on a lack of utility. The requirements for a sound prediction of utility were met. While there was insufficient information in the prior art to lead the skilled person directly and without difficulty to the solution taught in the 770 Patent, the skilled person, considering the CGK together with the test results disclosed in the 770 Patent, had the factual basis and sound line of reasoning to predict that macitentan in combination with a PDE5-I would be useful to treat diseases involving vasoconstriction.

C. *Overbreadth*

[248] The subject matter of a claim will be overbroad if it exceeds the invention that was made or if it exceeds the invention disclosed in the specification: *Pfizer Canada Inc v Canada (Minister of Health)*, 2008 FC 11 at paras 45-46; *Eli Lilly Canada Inc v Apotex Inc*, 2018 FC 736 at para 131. Overbreadth arises from subsections 27(3) and 27(4) of the *Patent Act* and can be considered an extension of the bargain theory in patent law, ensuring an inventor does not claim more than what they invented in good faith and disclosed: *Seedlings Life Science Ventures, LLC v Pfizer Canada ULC*, 2021 FCA 154 at paras 50-51 and 60, citing *Western Oilfield Equipment Rentals Ltd v M-I LLC*, 2021 FCA 24 at paras 128-130.

[249] Sandoz states that to overclaim is to lose everything. Sandoz submits that every Asserted Claim is overbroad, as follows:

a) Claims 21 to 25 are overbroad because they claim the use of the combination for treating a disease wherein vasoconstriction is involved, and this includes diabetic arteriopathy, angina pectoris, and heart failure among other things. The inventor did not make such an invention, and Dr. Vachiery admitted that by 2008, it was known that ERAs are not useful for treating diabetic arteriopathy, angina pectoris, heart failure, and erectile dysfunction.
b) Claims 26 to 31 are overbroad for claiming a monopoly over all subtypes of PH and PAH. Dr. Chakinala conceded it was known as of 2007 that some subtypes of PH and PAH could not be treated using ERAs, and there is nothing in the 770 Patent describing how to treat any of these conditions using the claimed combinations.
c) Claims 21, 26, 27, and 28 are overbroad for claiming a combination of macitentan with any compound having PDE5 inhibitory properties. Dr. Vachiery asserted that one cannot know that all PDE5-Is together with ERAs will work the same way, and if he is correct, there could not have been a basis for claims 21, 26, 27, and 28.

[250] The first aspect of Sandoz's argument on overbreadth relates to sound prediction. I agree with Drs. Chakinala and Vachiery that Dr. Zusman's opinion on overbreadth is essentially a

restatement of his opinion on utility, namely that the prediction the inventor made was not sound. For the reasons I have explained in the utility analysis above, the inventor had the factual basis and sound line of reasoning to predict that macitentan in combination with a PDE5-I would be useful to treat diseases involving vasoconstriction, and this was disclosed.

[251] Sandoz also argues that the Asserted Claims are overbroad because, irrespective of the soundness of the prediction, there is evidence of lack of utility of some of the area covered by the claims: *Wellcome* at para 56. Specifically, not all subtypes of PH or PAH can be treated with ERAs, and ERAs were not used to treat diabetic arteriopathy, angina pectoris, heart failure, and erectile dysfunction by 2007.

[252] The plaintiffs raised an objection to Sandoz's argument that the claims are overbroad because not all subtypes of PH or PAH can be treated with ERAs. They point out that this argument was not pleaded in Sandoz's statement of defence, or raised in Dr. Zusman's expert report. I agree. Sandoz did not plead that claims 26-31 are overbroad for covering subtypes of PH or PAH. This challenge was raised for the first time in closing arguments and I will not consider this allegation of overbreadth.

[253] For diabetic arteriopathy, angina pectoris, heart failure, and erectile dysfunction, similar arguments were made in the context of utility. For the reasons explained in the utility analysis above, Sandoz has not established that any Asserted Claim is overbroad by reason of a lack of utility of some of the area covered by the claim.

D. *Sufficiency of Disclosure*

[254] A patent specification must provide enough information to enable the skilled person to practice the invention: subsection 27(3) of the *Patent Act*; *Teva Canada Limited v Pfizer Canada Inc*, 2012 SCC 60 at para 51, citing *Pioneer Hi-Bred Ltd v Canada (Commissioner of Patents)*, [1989] 1 SCR 1623 at 1637-38.

[255] Sandoz argues that the specification does not enable the skilled person to practice the subject matter of the claims 21-25 in order to treat angina pectoris and diabetic arteriopathy. Dr. Zusman opined that the underlying pathophysiology of angina pectoris and diabetic arteriopathy relate to structural obstruction to blood flow, and are not due to vasoconstriction. These conditions are distinct in the clinical sense from diseases involving vasoconstriction, such as hypertension, PH, or PAH, and do not have a pathophysiology predominantly tied to the NO or endothelin pathways. Thus, it is not clear from the 770 Patent how these conditions can be treated using the claimed combination of macitentan and PDE5-I.

[256] Sandoz also argues that Dr. Vachiery admitted that by 2008, it was known that ERAs are not useful for treating erectile dysfunction, angina pectoris, diabetic arteriopathy, and heart failure, and Dr. Chakinala admitted that it was known as of 2007 that some subtypes of PH and PAH could not be treated using ERAs. Although Dr. Zusman did not opine that the specification is insufficient in respect of conditions other than angina pectoris and diabetic arteriopathy, based on the alleged admissions of Drs. Vachiery and Chakinala, Sandoz states the skilled person is "left to guess" how the combination of macitentan and a PDE5-I would treat diabetic

arteriopathy, angina pectoris, erectile dysfunction, heart failure, and some subtypes of PH and PAH.

[257] The plaintiffs argue that the skilled person can readily grasp the nature of the invention and be able to put it into practice. The 770 Patent teaches the administration of the compounds and their applicable uses. Drs. Chakinala and Vachiery opined that the skilled person would understand how macitentan and a PDE5-I work to treat diseases wherein vasoconstriction is involved, and how the invention can be used (i.e. put into practice) for the treatment of such diseases.

[258] It is difficult to reconcile Sandoz's positions on obviousness and sufficiency. With respect to obviousness, Sandoz argued that all the skilled person had to do is take macitentan and combine it with a PDE5-I to treat a disease wherein vasoconstriction is involved, just as taught by the prior art. With respect to sufficiency, Sandoz states that there is nothing disclosed in the 770 Patent describing how to treat erectile dysfunction, angina pectoris, diabetic arteriopathy, heart failure, and some subtypes of PH and PAH, and the skilled person is "left to guess" how the combination of macitentan and a PDE5-I could be used to treat these conditions.

[259] Sandoz has not explained, from the skilled person's perspective, what information is missing from the 770 Patent that is required in order to practice the invention. All of the experts agreed that the endothelin and NO pathways were pathways that operated in the vasculature throughout the body, to effect vasoconstriction or vasodilation. As I have found above, there was a sound line of reasoning to predict that the observed effects from the experiments would

extend to any disease wherein vasoconstriction is involved because the observed effects were vasodilatory effects. Even where the pathophysiology of a disease is not predominantly tied to the NO or endothelin pathways, the skilled person would understand that the combination can be useful to treat these diseases by effecting vasodilation.

[260] In summary, Sandoz has not established that the Asserted Claims are invalid for insufficiency of disclosure.

VIII. **Conclusion**

[261] Sandoz has not established that any of the Asserted Claims is invalid. Accordingly, in view of Sandoz's concession on infringement, the plaintiffs are entitled to a declaration that Sandoz would infringe the Asserted Claims by making, constructing, using, or selling its macitentan tablets in Canada.

[262] The parties reached an agreement on costs of this action. Accordingly, the Court is not required to make a ruling on costs.

JUDGMENT in T-549-20

THIS COURT'S JUDGMENT is that:

1. Sandoz has not established its allegations that claims 21-31 (Asserted Claims) of Canadian Patent No. 2,659,770 (770 Patent) are invalid for obviousness, lack of utility, overbreadth, or insufficiency.

2. In view of this Court's ruling in paragraph 1, Sandoz's concession in this proceeding that it would infringe the Asserted Claims if it is authorized to market its macitentan tablets in Canada, and the parties' agreement that the plaintiffs are not required to establish infringement of the essential elements of any Asserted Claims:

    a. the Court declares that the making, constructing, using or selling of Sandoz macitentan 10 mg film-coated tablets (Sandoz Product), by Sandoz in accordance with its Abbreviated New Drug Submission No. 234136 would infringe the Asserted Claims of the 770 Patent, directly or indirectly;

    b. Sandoz and its subsidiary, parent, related and affiliated companies, officers, directors, employees, agents, licensees, successors, assigns and any others over whom Sandoz exercises lawful authority, direction or control, whether directly or indirectly, are enjoined from:

        i. making, constructing, using or selling the Sandoz Product in Canada;

ii. offering for sale, marketing or having the Sandoz Product marketed in Canada;

iii. importing, exporting, distributing or having the Sandoz Product distributed in Canada; and

iv. otherwise infringing or inducing infringement of the 770 Patent.

c. Sandoz shall deliver up to the plaintiffs or destroy under oath, at the plaintiffs' election, all things in Sandoz's power, possession or control, whether physical or electronic in nature, that would offend the injunction in subparagraph b above including, without limitation, any product packaging, product labels, product monographs, or other educational or promotional materials referring or relating to the Sandoz Product, except to the extent that Sandoz is required by law to retain copies of such things.

3. In view of the parties' agreement, there is no ruling on costs.

"Christine M. Pallotta"
Judge

SCHEDULE A

Court File No. T-549-20

FEDERAL COURT

B E T W E E N:

JANSSEN INC. and ACTELION PHARMACEUTICALS LTD

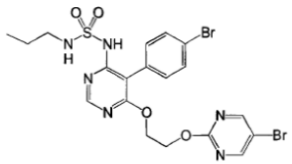
Plaintiffs

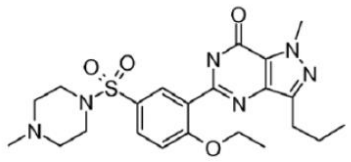
- and -

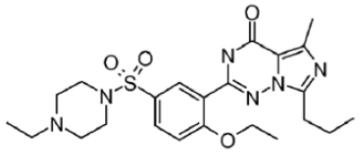
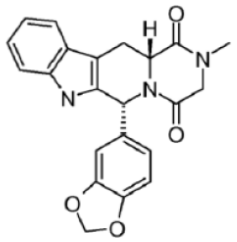
SANDOZ INC.

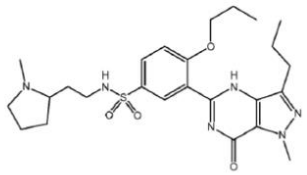
Defendant

Parties' Joint Construction Chart for Claims 21-31 of Canadian Patent No. 2,659,770

Claim	Essential Elements	Construction of Claim Terms
21. A use of the compound of formula (1) as defined in claim 1, or a pharmaceutically acceptable salt of said compound of formula (1), in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for treating a disease wherein vasoconstriction is involved.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with at least one PDE-5 inhibitor (or its pharmaceutically acceptable salt); (iii) for treating a disease where vasoconstriction is involved.	"**Use**" means the administration of the at least two specified compounds together for the specified treatment without limitation as to the timing or route of administration. The "**compound of formula (I) as defined in Claim 1**" is macitentan, having the following structure:  I ('770 Patent, Claim 1, p. 11) The term "**pharmaceutically acceptable salts**" refers to non-toxic, inorganic or organic acid and/or base addition salts ('770 Patent, p.4, ll. 1-3). "**At least one**" means that one or more of the specified compounds may be used. A "**compound having PDE5-inhibitory properties**" means a compound that, when submitted to the "Test for the determination of PDE5 IC50" described in the '770 Patent, has an IC50 equal or lower than 1 μM ('770 Patent, p. 3, lines 4-6; p. 8, line 16, to p. 9, line 15). In this

Claim	Essential Elements	Construction of Claim Terms
		context, the IC50 is the concentration of the PDE5 inhibitor required for 50% inhibition of the PDE5 enzyme. "**Treating**" means to manage and care for a patient suffering a disease wherein vasoconstriction is involved to cure or mitigate this disease. "**A disease wherein vasoconstriction is involved**" is a disorder of blood flow in the body where resistance to blood flow is increased in either the systemic or pulmonary circulations. According to the '770 Patent, this phrase means in particular, hypertension, pulmonary hypertension ("PH") (including pulmonary arterial hypertension ("PAH")), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris ('770 Patent, p. 3, lines 1-3). "A disease wherein vasoconstriction is involved" includes but is not limited to these examples.
22. The use according to claim 21, wherein the compound having PDE5-inhibitory properties is sildenafil, vardenafil, tadalafil or udenafil.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with sildenafil, vardenafil, tadalafil or udenafil (or their pharmaceutically acceptable salt); (iii) for treating a disease where vasoconstriction is involved.	All previously discussed terms have the same construction set out above. "**Sildenafil**" is the compound having the following structure:  (sildenafil) ('770 Patent, p.3)

Claim	Essential Elements	Construction of Claim Terms
		"**Vardenafil**" is the compound having the following structure:  (vardenafil) ('770 Patent, p.3). "**Tadalafil**" is the compound having the following structure:  (tadalafil) ('770 Patent, p.3)

Claim	Essential Elements	Construction of Claim Terms
		"**Udenafil**" is the compound having the following structure:  (udenafil) ('770 Patent, p.4)
23. The use according to claim 22, wherein the compound having PDE5-inhibitory properties is sildenafil or tadalafil.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with sildenafil or tadalafil (or their pharmaceutically acceptable salt); (iii) for treating a disease where vasoconstriction is involved.	All previously discussed terms have the same construction set out above.
24. The use according to claim 23, wherein the compound having PDE5-inhibitory properties is sildenafil.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with sildenafil (or its pharmaceutically acceptable salt); (iii) for treating a disease where vasoconstriction is involved.	All previously discussed terms have the same construction set out above.
25. The use according to claim 23, wherein the compound having	(i) the use of macitentan (or its pharmaceutically acceptable salt);	All previously discussed terms have the same construction set out above.

Claim	Essential Elements	Construction of Claim Terms
PDE5-inhibitory properties is tadalafil.	(ii) in combination with tadalafil (or its pharmaceutically acceptable salt); (iii) for treating a disease where vasoconstriction is involved.	
26. The use according to claim 21, wherein the disease is selected from hypertension and pulmonary hypertension.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with at least one PDE-5 inhibitor (or its pharmaceutically acceptable salt); (iii) for treating hypertension or pulmonary hypertension.	All previously discussed terms have the same construction set out above. "**Hypertension**" is a condition in which the blood vessels in the body have persistently raised blood pressure. Hypertension is also known as systemic hypertension or, colloquially, high blood pressure. "**Pulmonary hypertension**" is a condition of high blood pressure in the lungs.
27. The use according to claim 26, wherein the disease is pulmonary hypertension.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with at least one PDE-5 inhibitor (or its pharmaceutically acceptable salt); (iii) for treating pulmonary hypertension.	All previously discussed terms have the same construction as set out above.
28. The use according to claim 27, wherein the disease is pulmonary arterial hypertension.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with at least one PDE-5 inhibitor (or its pharmaceutically acceptable salt);	All previously discussed terms have the same construction as set out above. "**Pulmonary arterial hypertension**" ("PAH") is a form of pulmonary hypertension where the walls of the arteries of the lungs constrict and stiffen, resulting in, *inter alia,* the

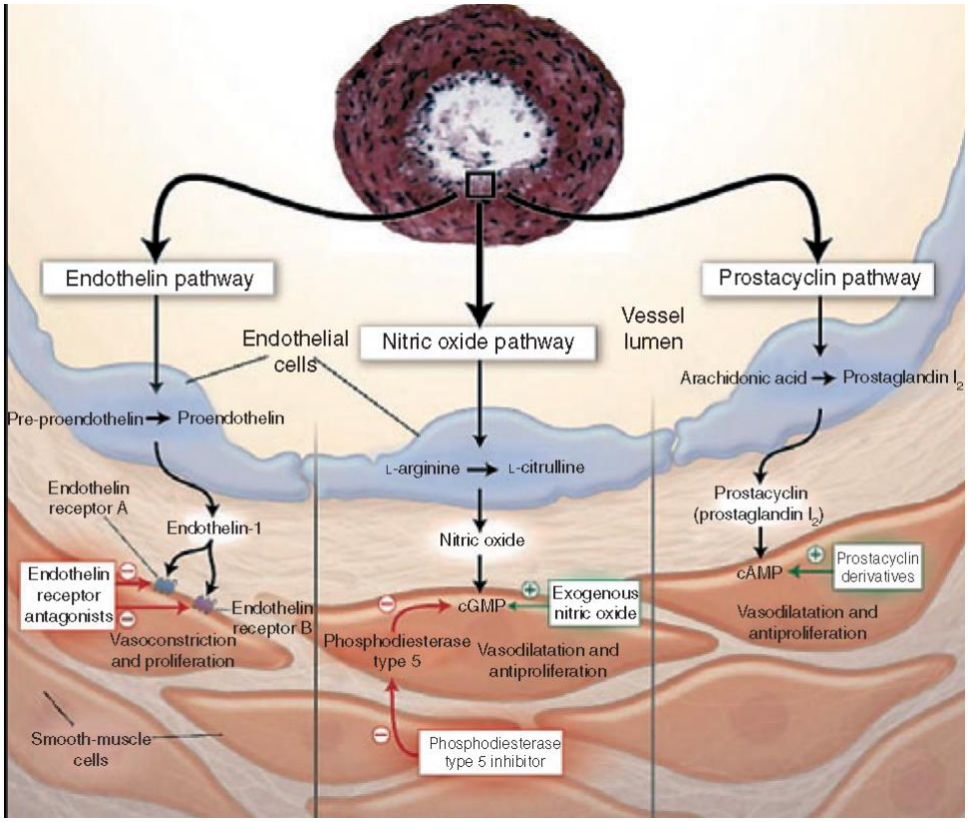
Claim	Essential Elements	Construction of Claim Terms
	(iii) for treating pulmonary arterial hypertension.	right side of the heart working harder to push blood through narrowed arteries in the lungs.
29. The use according to claim 28, wherein the compound having PDE5-inhibitory properties is sildenafil or tadalafil.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with sildenafil or tadalafil (or their pharmaceutically acceptable salt); (iii) for treating pulmonary arterial hypertension.	All previously discussed terms have the same construction as set out above.
30. The use according to claim 28, wherein the compound having PDE5-inhibitory properties is sildenafil.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with sildenafil (or its pharmaceutically acceptable salt); (iii) for treating pulmonary arterial hypertension.	All previously discussed terms have the same construction as set out above.
31. The use according to claim 28, wherein the compound having PDE5-inhibitory properties is tadalafil.	(i) the use of macitentan (or its pharmaceutically acceptable salt); (ii) in combination with tadalafil (or its pharmaceutically acceptable salt); (iii) for treating pulmonary arterial hypertension.	All previously discussed terms have the same construction as set out above.

SCHEDULE B

Short form reference used in Reasons	Full Title	Source (as presented in trial)
Channick (2004)	Channick, "Endothelin receptor antagonists in pulmonary arterial hypertension" *JACC* 43:12 Suppl. June 2004.	Exhibit D-3 of Dr. Zusman's expert report
Ghofrani et al (2006)	Ghofrani et al, "Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study." *J Am Coll Cardiol.* 2004 Oct 6;44(7):1488-96.	Exhibit D-16 of Dr. Zusman's expert report
Hoeper et al (2004)	Hoeper et al. "Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension." *Eur Respir J.* 2004;24 1007-1010.	Exhibit D-16 of Dr. Zusman's expert report
Lee & Channick (2005)	Lee SH and Channick RN, "Endothelin Antagonism in Pulmonary Arterial Hypertension" *Semin Respir Crit Care Med.* 2005 Aug;26(4):402-8.	Exhibit D-16 of Dr. Zusman's expert report
Minai & Arroliga (2006)	Minai O.A. and Arroliga A.C. "Long-term results after addition of sildenafil in idiopathic PAH patients on bosentan" *South Med J.* 2006 Aug;99(8):880-3.	Exhibit D-16 of Dr. Zusman's expert report
Lee & Rubin (2005)	Lee & Rubin, "Current treatment strategies for pulmonary arterial hypertension" *J Int Med* 2005 Sep 258:199-215	Exhibit E of Dr. Zusman's expert report
McLaughlin & McGoon (2006)	McLaughlin & McGoon, "Pulmonary arterial hypertension" *Circulation* 2006 Sep 114(13): 1417-1431.	Exhibit F of Dr. Zusman's expert report
US 731	U.S. Patent Application No. 2004/0063731, "Pharmaceutical Formulation Comprising Pyrazolo [4,3-D] Pyrimidines and Endothelin Receptor Antagonists or Thienopyrimidines and Endothelin Receptor Antagonist"	Exhibit D-31 of Dr. Zusman's expert report
N/A	U.S. Patent 5,250,534, "Pyrazolopyrimidinone Antianginal Agents"	Exhibit D-32 of Dr. Zusman's expert report
US 006	U.S. Patent 5,859,006, "Tetracyclic Derivatives; Process of Preparation and Use"	Exhibit D-33 of Dr. Zusman's expert report
WO 004	WO 99/064004, "Quinazolinone Inhibitors of cGMP Phosphodiesterase"	Exhibit D-36 of Dr. Zusman's expert report
N/A	WO 00/027848, "Pyrazolopyrimidinone Derivatives for the Treatment of Impotence"	Exhibit D-37 of Dr. Zusman's expert report

WO 557	WO 02/053557, "Novel Sulfamides and Their Use as Endothelin Receptor Antagonists"	Exhibit D-38 of Dr. Zusman's expert report
WO 395	WO 2006/026395, "Endothelin A Receptor (ET_A) Antagonists in Combination with Phosphodiesterase 5 Inhibitors (PDE5) and Uses Thereof"	Exhibit D-39 of Dr. Zusman's expert report
WO 502	WO 2006/051502, "Novel Sulfamides"	Trial exhibit D14, presented to Dr. Clozel during cross-examination
ESC Guidelines	Guidelines on diagnosis and treatment of pulmonary arterial hypertension, The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology, *Eur Heart J*, 2004 Dec 25: 2243-2278.	Exhibit C of Dr. Vachiery's expert report
ACCP Guidelines	Medical Therapy for Pulmonary Arterial Hypertension, Updated ACCP Evidence-Based Clinical Practice Guidelines, *Chest*, 2007 Jun 131(6): 1917-1928.	Exhibit D of Dr. Vachiery's Report
Paul et al (2005)	Paul et al, "Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension" *Br J Clin Pharmacol* 2005 Jul 60(1): 107-112.	Exhibit K of Dr. Vachiery's expert report

SCHEDULE C



Cite: Barst RJ. Pulmonary hypertension: Past, present and future. *Annals of Thoracic Medicine*. 2008;3(1):1 at page 1

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-549-20
STYLE OF CAUSE:	JANSSEN INC AND ACTELION PHARMACEUTICALS LTD v SANDOZ CANADA INC
PLACE OF HEARING:	HELD BY WAY OF VIDEOCONFERENCE
DATE OF HEARING:	JANUARY 24, 25, 26, 27, 28, 30, FEBRUARY 1, 3, 17 AND 18, 2022
JUDGMENT AND REASONS:	PALLOTTA J.
CONFIDENTIAL JUDGMENT AND REASONS ISSUED:	MAY 12, 2022
PUBLIC JUDGMENT AND REASONS ISSUED:	MAY 31, 2022

APPEARANCES:

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Nicholas Wong Junyi Chen	FOR THE DEFENDANT
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