Federal Court Cour fédérale

Date: 20220411

Docket: T-419-20

Citation: 2022 FC 417

Toronto, Ontario, April 11, 2022

PRESENT: The Honourable Madam Justice Furlanetto

BETWEEN:

MERCK SHARP & DOHME CORP.
AND MERCK CANADA INC.

Plaintiffs

and

PHARMASCIENCE INC.

Defendant

PUBLIC JUDGMENT AND REASONS
(Identical to the Confidential Judgment and Reasons Issued on March 28, 2022)

[1] This judgment arises from a patent infringement action brought under subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [*PMNOC Regulations*]. The patent at issue is Canadian Patent No. 2,529,400 [400 Patent]. The innovative drug relating to the action is JANUVIA®, which is used to treat type 2 diabetes.

[2] Merck Canada Inc. is the “first person” in accordance with the *PMNOC Regulations*. Merck Sharp & Dohme Corp. is the registered owner of the 400 Patent and is a party to the action pursuant to subsection 6(2) of the *PMNOC Regulations*.

[3] The Plaintiffs [collectively, Merck] claim that the making, constructing, using or selling by the Defendant Pharmascience Inc. [PMS] of its sitagliptin phosphate tablets in strengths of 25 mg, 50 mg, and 100 mg in accordance with PMS’ Abbreviated New Drug Submission will infringe at least one of claims 4-7, 19, 20, 22, 24 and 26 [Asserted Claims] of the 400 Patent. PMS asserts in defence that the 400 Patent is invalid for obviousness and/or insufficiency.

[4] The parties agreed to a stipulation that the only issue to be adjudicated at trial was the validity of the 400 Patent. The stipulation provided that should the court find any of the Asserted Claims of the 400 Patent to be valid, the Order sought by the Plaintiffs in the action should issue with the relief requested by the Plaintiffs.

[5] For the reasons that follow, I find the Asserted Claims of the 400 Patent valid and that the relief sought should be ordered accordingly.

I. Background

[6] The 400 Patent is listed on the Patent Register in association with the medicine sitagliptin phosphate monohydrate. Sitagliptin exists as a dihydrogen phosphate salt in crystalline monohydrate form in the tablets sold as JANUVIA®. Sitagliptin is the active ingredient in the drug product.

[7] In type 2 diabetes, cells develop insulin resistance such that the presence of insulin in the blood does not stimulate cells to take up glucose, or the pancreas does not produce enough insulin to overcome the resistance. Thus, glucose accumulates in the blood.

[8] Sitagliptin inhibits dipeptidyl peptidase-4 [DPP-4, DP-IV or DPP-IV], an enzyme that degrades one of the peptides (Glucagon-Like Peptide-1 [GLP-1]) that stimulates the secretion of insulin. This inhibitory effect modulates the level of insulin and glucose in the blood. Sitagliptin acts only when glucose is elevated in the bloodstream, thereby reducing the risk of hypoglycemia caused by low glucose levels.

[9] In 2006, JANUVIA® became the first DPP-4 inhibitor approved by the United States Food and Drug Administration [FDA] for the treatment of diabetes. It was approved by Health Canada in 2007.

[10] This action initially alleged infringement of three patents - the 400 Patent, as well as two other patents listed on the Patent Register in association with sitagliptin phosphate monohydrate – Canadian Patent Nos. 2,536,251 [251 Patent] and 2,450,740 [740 Patent]. However, the allegations in respect of the 251 Patent and 740 Patent were discontinued prior to trial.

[11] The 740 Patent is the corresponding Canadian national phase patent of Patent Co-operation Treaty [PCT] patent application WO 03/004498 [WO498]. WO498 discloses a genus of compounds that includes the chemical compound now known as sitagliptin. It specifically exemplifies sitagliptin, amongst other compounds, both as a free base and

hydrochloride salt and refers to other salts and crystalline forms as being within its scope. WO498 is referenced in the 400 Patent as discussed further below.

[12] The 400 Patent is directed to the dihydrogenphosphate [DHP] salt of sitagliptin and its crystalline monohydrate form, a process for making the DHP salt of sitagliptin as a crystalline monohydrate, its formulation as a pharmaceutical composition and its use to treat diseases affected by the inhibition of DPP-4, such as type 2 diabetes.

II. Witnesses

[13] Seven experts gave testimony at the trial; three experts were called by PMS and four by Merck. The parties agreed to stipulations as to the expertise of all expert witnesses.

A. *PMS Experts*

[14] **Dr. Vassil Elitzin** obtained his Ph.D. from Stanford University in 2004, specializing in the synthesis of naturally occurring chemical compounds. He is currently the Director of Chemistry, Manufacturing and Controls and Chief Chemist at LI-COR Biosciences. He was previously a principal scientist in the Chemical Development group at GlaxoSmithKline. His work focuses on the development of active pharmaceutical ingredients and dosage forms from discovery to commercialization. Dr. Elitzin was admitted as an expert in synthetic organic chemistry and compound characterization, with particular expertise in developing, making, and characterizing different salt and crystalline forms of compounds.

[15] Dr. Elitzin provided an opinion on whether the Asserted Claims of the 400 Patent would have been obvious to the person skilled in the art [PSA]. He also reviewed some of Merck's internal documents and provided an opinion on the course of conduct taken by the inventors towards obtaining the DHP salt of sitagliptin and the crystalline monohydrate.

[16] PMS highlights Dr. Elitzin's experience in industry; however, he was not active in industry at the relevant date for assessing obviousness of the 400 Patent. His observations as to what was happening at the time are limited to his understanding from the literature and from lectures attended during his Ph.D. studies. While in general I found Dr. Elitzin's testimony to be helpful to the Court, as highlighted below, he was selective in accepting statements from leading authorities as to the common general knowledge in the art, some of which came from publications he had relied on for his own report. I have therefore approached his evidence in those areas with caution and in some instances have preferred the evidence of Merck's experts over that of Dr. Elitzin in those areas.

[17] **Dr. Mark Hollingsworth** is an Emeritus Research Professor at Kansas State University. He has worked in academia since 1987, first as an Assistant Professor in the Chemistry Department at the University of Alberta, then as an Assistant Professor in the Chemistry Department at Indiana University, and later as an Associate Professor in the Chemistry Department at Kansas State University, where he worked from 1998 to August 2021 when he retired. He has taught and lectured extensively on solid state chemistry and the characterization of crystalline forms. Dr. Hollingsworth was admitted as an expert in organic chemistry, particularly solid state organic chemistry, including the characterization of the solid state of

organic compounds and their properties, with expertise in analytical techniques for characterizing organic solids and the crystallization of organic solids. He was further qualified as an expert in the fields of crystal growth and crystal engineering with expertise in analytical techniques for characterizing organic solids and the crystallization of organic and inorganic compounds, including by x-ray crystallography.

[18] Dr. Hollingsworth provided opinions on claims 4-7, 19, 20 and 24 of the 400 Patent and on the elements of the test for obviousness relating to those claims, both before and after a review of some of Merck's internal documents. He also analyzed Merck's raw data files relating to the x-ray powder diffraction [XRPD] characterization work done during Merck's polymorph screening and provided an analysis of this work, including with respect to the limitations found in claims 5-7 of the 400 Patent. I found Dr. Hollingsworth to be a knowledgeable and credible witness.

[19] **Dr. James E. Foley** is a retired clinical research director with experience in drug development relating to diabetes treatments. He has worked in the field of diabetes since the 1970s and began working on DPP-4 inhibitors in 1995. Dr. Foley was involved in the evaluation of the Novartis candidate drug DPP-728 as a DPP-4 inhibitor in patients, and in the clinical development and profiling of LAF-237 (vildagliptin) as a DPP-4 inhibitor. Dr. Foley was admitted as an expert in pharmacology and drug development, including specifically the history of development of DPP-4 inhibitors as a treatment for diabetes. He was further admitted as having expertise in drug discovery and development, and in lead compound identification.

[20] Dr. Foley provided background on the development of Novartis' DPP-728 and vildagliptin compounds as DPP-4 inhibitors. He gave opinions on claims 22 and 26 of the 400 Patent and on the elements of the test for obviousness as it related to those claims. I found Dr. Foley to be a knowledgeable and credible witness.

B. *Merck Experts*

[21] **Dr. James Wuest** is a Professor of Chemistry at the Université de Montréal where he has worked since 1981. He is also the Canada Research Chair in Molecular Materials. He was previously an Assistant Professor of Chemistry at Harvard University and a Research Fellow at Harvard Medical School. Dr. Wuest specializes in molecular design and synthesis of solid state forms, including salt forms, crystalline forms and their polymorphs. He has extensive experience synthesizing compounds and characterizing their resulting structures and properties. Dr. Wuest was admitted as an expert in molecular design and synthesis, with particular expertise in solid state organic chemistry, including the characterization of the solid state of organic compounds and their properties, with expertise in analytical techniques for characterizing organic solids and the crystallization of organic compounds.

[22] Dr. Wuest provided opinions on claims 4-7, 19, 20, 22 and 24 of the 400 Patent and whether those claims would have been obvious at the relevant date. He also responded to the opinions of Drs. Elitzin and Hollingsworth.

[23] PMS highlights that Dr. Wuest has never worked on a drug development team. I note that this criticism also applies to PMS' own expert, Dr. Hollingsworth. While Dr. Wuest's opinions,

like those of Dr. Hollingsworth, must be considered with this limitation in mind, where opinions relate to scientific principles and information that can be assessed from knowledge of the techniques used and literature available at the time, it does not diminish the weight to be attached to the opinions.

[24] PMS further highlights that Dr. Wuest has testified in a number of cases for innovators, including some for Merck, and was retained in litigation in the U.S. relating to the corresponding patent to the 400 Patent. It suggests that Dr. Wuest has ties to Merck because Dr. Wuest has met Merck's inventor Dr. Wenslow and had planned to give a lecture at Dr. Wenslow's company. I find these criticisms unpersuasive. Dr. Wuest does not receive any financial support for his research from Merck. His involvement in past litigation is not uncommon for an accomplished scientist in the field and he is not currently involved in the U.S. proceeding on the corresponding 400 Patent. As made clear during his cross-examination, Dr. Wuest has not discussed this litigation or sitagliptin with Dr. Wenslow and his lecture at Dr. Wenslow's company is unrelated to the litigation. There is no basis on the evidence before me to suggest that Dr. Wuest is not an independent, unbiased witness.

[25] In general, I found Dr. Wuest to be a knowledgeable witness who was of assistance to the Court. However, his view of certain background passages in the 400 Patent relating to inhibitory activity appeared strained and his positon as to whether he could speak to issues involving the potency of compounds and their therapeutic use unclear. I have therefore approached his evidence on those issues with caution.

[26] **Dr. Martyn C. Davies** is an Emeritus Professor and pharmaceutical consultant who recently retired from the University of Nottingham where he served in various roles, including as the Head of the Pharmaceutical Sciences and Pharmacy School. He has worked for many years as a consultant and has significant practical experience developing, formulating and characterizing pharmaceutical formulations and advanced drug delivery systems. Dr. Davies was admitted as an expert in pharmaceutical formulation and drug delivery, including with respect to pre-formulation assessment, formulation design and development, manufacture, characterization, testing and analysis, including for solid oral dosage forms.

[27] Dr. Davies provided an opinion on the issue of obviousness with respect to claims 4-7 and 22 of the 400 Patent from the perspective of the skilled formulator. He also responded to the opinion of Dr. Elitzin on those claims from this perspective.

[28] PMS highlights Dr. Davies history with pharmaceutical litigation on behalf of innovators. It also suggests that Dr. Davies attempted to bolster the evidence of other Merck witnesses during his testimony. PMS refers to two passages during Dr. Davies cross-examination where Dr. Davies refers to testimony of other Merck witnesses when addressing a question asked. In one instance, the testimony refers to Dr. Wenslow and in the other instance Dr. Wuest. While I agree with PMS' criticism of the first instance, the second instance appeared to result from Dr. Davies being asked about an area not covered by his expertise. In any event, I do not consider these two passages to pervade the remaining testimony provided by Dr. Davies. In my view, Dr. Davies was a knowledgeable witness and I consider his testimony to be of assistance to the Court.

[29] **Dr. Richard E. Lewanczuk** is an endocrinologist and the Senior Medical Director of Health System Integration for Alberta Health Services. He has held various roles in that organization since the 1990s. He is also a professor of medicine and physiology at the University of Alberta with a research background in diabetes, hypertension, chronic disease management, therapeutic natural products, and drug-disease interactions. Dr. Lewanczuk was admitted as an expert in internal medicine and endocrinology with extensive expertise in managing and treating type 2 diabetes. Dr. Lewanczuk was further qualified as an expert in the conduct of clinical trials for pharmaceutical agents for use in the treatment of type 2 diabetes.

[30] Dr. Lewanczuk provided background on type 2 diabetes and the history of different therapies used to treat type 2 diabetes, including the role and impact of JANUVIA® and other Merck drug products. Dr. Lewanczuk was also asked to respond to Dr. Foley's opinions regarding obviousness and claims 22 and 26 of the 400 Patent.

[31] PMS criticizes Dr. Lewanczuk for failing to disclose that he had received honoraria from Merck for sitting on an advisory panel and giving a lecture. This information was readily acknowledged by Dr. Lewanczuk on cross-examination, where he clarified that honoraria from pharmaceutical companies are common and thus are not included in his CV due to the abundance in which they are provided. Dr. Lewanczuk confirmed that he had never received research support from Merck. I do not consider the omission of the honoraria to affect Dr. Lewanczuk's credibility or suggest any form of bias. Overall, I viewed Dr. Lewanczuk as a forthright witness who readily acknowledged and helped to clarify these omissions.

[32] PMS also criticized Dr. Lewanczuk for providing views on salt selection and whether sitagliptin was previously disclosed in the prior art, when this evidence was admittedly outside of his expertise. I agree that there were a few instances where Dr. Lewanczuk strayed outside his expertise, principally when seeking to respond to comments on these same issues made in Dr. Foley's report. I have not given those aspects of his opinion any weight when reaching my decision.

[33] While I consider Dr. Lewanczuk's report to have went into unnecessary detail in certain areas, his comments on claims 22 and 26 and his response to Dr. Foley's opinion on those claims were of assistance to the court.

[34] **Dr. William R. Roush** is the Executive Vice President of Chemistry of IFM Therapeutics where he is responsible for leading drug discovery medicinal chemistry research activities. He has over 40 years of experience in organic and medicinal chemistry and is an Emeritus Professor of Chemistry at the Scripps Research Institute. Between 2005-2017 he was the former Executive Director of Medicinal Chemistry in the Drug Discovery Division of Scripps' Translational Research Institute where he directed research for optimizing drug candidates for drug discovery projects internal to Scripps. Prior to 2017, he also acted as a consultant to pharmaceutical and biotechnology companies. Dr. Roush was admitted as an expert in organic and medicinal chemistry, and specifically in the areas of synthesis and characterization of organic compounds. Dr. Roush was further qualified as having expertise in drug discovery and development and in lead compound identification.

[35] Dr. Roush was asked to opine on the 400 Patent and whether the PSA would have chosen to investigate sitagliptin or any of its salts as a potential DPP-4 inhibitor for treating type 2 diabetes as of June 24, 2003, without having the benefit of the 400 Patent. He was also asked to respond to Dr. Foley. In doing so, he provides opinions on claims 4, 22 and 26 of the 400 Patent and whether claims 22 and 26 are obvious. In providing these opinions, Dr. Roush conducts a prior art search and reviews the steps a medicinal chemist would take to identify a lead candidate for drug development.

[36] PMS asserts that Dr. Roush has extensive ties to brand pharmaceutical companies. It highlights that at the relevant date Dr. Roush was in academia and not in industry. PMS criticizes Dr. Roush for asserting that he had acquired some expertise on DPP-4 inhibitors after preparing his report and for dedicating a portion of his report to the success of JANUVIA®, while admittedly having no personal knowledge of that success.

[37] I agree these are critiques that can be made of Dr. Roush's evidence. However, I do not agree that Dr. Roush presented as a biased witness or that these critiques establish that the substance of Dr. Roush's evidence is not credible. Further, I do not consider Dr. Roush's comments on the process involved in lead candidate identification to be affected by the date of his experience. The bigger problem the Court has with Dr. Roush's evidence is that aspects of it are from the perspective of the medicinal chemist who is evaluating and directing Structure Activity Relationship [SAR] studies on compounds of the prior art to advance the next stages of research. As will be discussed further below, this is not a focus of the 400 Patent. While I will need to consider whether the PSA would be motivated to move from WO498 to the inventive

concept of the 400 Patent, I do not consider a separate medicinal chemist to be a necessary member of the skilled team interpreting the 400 Patent. As such, certain aspects of Dr. Roush's evidence are not relevant to my analysis.

C. *Fact Witnesses*

[38] There were two fact witnesses introduced by the Plaintiffs. The first, Christine Vincent, is a law clerk with the solicitors for the Plaintiffs. She provided an affidavit attaching several documents obtained from Health Canada's website associated with generic submissions involving sitagliptin. The affidavit also attached pleadings from the *Merck Sharp & Dohme Corp v JAMP Pharma Corporation* T-667-20 proceeding. The significance of these pleadings to the present action was not made known to the Court through the Plaintiffs' submissions. Ms. Vincent's affidavit was accepted and it was agreed that she would not be cross-examined.

[39] The second fact witness, Dr. Robert M. Wenslow, is one of the inventors of the 400 Patent. Dr. Wenslow was the discovery representative for the Plaintiffs and, on agreement of the parties, was the only inventor examined under Rule 237(4) of the *Federal Courts Rules*, SOR/98-106 [*Federal Courts Rules*].

[40] Dr. Wenslow joined Merck in 1997 as a Senior Research Chemist in the Process Research & Development Department. At the time of sitagliptin's development, Dr. Wenslow led a team of scientists in the Physical Measurements group, which was then part of the Analytical Research department, and directly supervised the work of his co-inventors Drs. Russell Ferlita and Alex Chen, as well as Yaling Wang.

[41] The Physical Measurements Group formed part of the broader multi-disciplinary DPP-4 project team that was involved in sitagliptin's development. The primary responsibility of the Physical Measurements Group was to perform solid state characterization of candidate drug compounds, including XRPD, solid state nuclear magnetic resonance [NMR] spectroscopy, differential scanning calorimetry [DSC] and thermogravimetric analysis [TGA]. As a lead member of the group, Dr. Wenslow regularly discussed and collaborated with the broader DPP-4 project team and reviewed research reports and data generated on sitagliptin, including those of the remaining co-inventors Drs. Karl Hansen, Ivan Lee, Stephen Cypes and Vicky Vydra.

[42] As admitted by Dr. Wenslow, he was not directly assigned to the sitagliptin project until March/April 2002, around the time the phosphate salt was chosen for further development (Trial Transcript [TT], Volume [V]4, Page [P]:349 Line [L]:8-13; TT V5, P:190 L:18). As one of his primary responsibilities upon joining the group, he reviewed the development work up to that point and had discussions with other members of the DPP-4 group to familiarize himself with the work that had been completed prior to his joining the project (TT V4, P:349 L:16 – P:350 L:1).

[43] Dr. Wenslow provided an overview of the invention story, both through oral testimony and through affidavit evidence, including with reference to various documents outlining the history of the invention. PMS accepted all but one of the documents as being authentic and the vast majority for the truth of their contents by way of joint agreement of the parties.

[44] While it was not disputed that Dr. Wenslow could appear at trial and submit an affidavit introducing those documents covered by the agreement, large portions of the content of his

affidavit were hotly contested as being hearsay, improper opinion evidence, covering subject matter beyond the pleadings, and/or being contrary to rules 232 and 248 of the *Federal Courts Rules*. In light of the timing of these objections, and on the basis of their nature and number, which in many cases included parsing words and/or sentences from within paragraphs, it was determined that the Court would benefit from hearing Dr. Wenslow's full oral testimony at trial and that the admissibility of the objected to portions of his affidavit evidence would be dealt with as a preliminary matter as part of this decision. Time was reserved for argument on the motion to take place at the close of the evidence. The parties also agreed that counsel for PMS would provide an update after Dr. Wenslow testified as to whether any objections would be withdrawn. However, in the end, the motion was not narrowed. Instead, PMS sought to add additional objections arising from Dr. Wenslow's oral testimony. PMS was directed to identify the additional objections and the impugned portions of the affidavit to which they related.

[45] As determined by oral ruling during argument on the motion, after-the-fact objections to direct testimony not related to impugned portions of the affidavit were rejected as it was viewed that the failure of PMS to raise the objection during the testimony precluded Merck from properly responding to the objections at the relevant time and potentially curing any deficiency: *Teva Canada Ltd v Pfizer Canada Inc*, 2017 FC 526 (*Venlaflaxine 2*) at paras 32- 42. Answers given on cross-examination were also rejected as being improper objections as such answers were elicited by PMS directly. The remaining objections are set out in the Appendix attached to this decision. The Appendix lists the original objections to the affidavit, along with the objections to the asserted related oral testimony and provides my specific dispositions on each. Below, I provide some general comments on the four primary grounds of objection raised.

(1) Hearsay

[46] Hearsay evidence is evidence that is adduced for its truth without the contemporaneous opportunity to cross-examine the declarant: *R v Khelawon*, 2006 SCC 57 [*Khelawon*] at para 35. Hearsay evidence is presumptively inadmissible unless it falls under one of the recognized exceptions to the hearsay rule: *Khelawon* at paras 2, 34, and 42; *Pfizer Canada Inc v Teva Canada Limited*¸ 2016 FCA 161 [*Venlafaxine*] at paras 86-87.

[47] Hearsay evidence may also be admitted under the principled approach if the party adducing it can establish it is necessary and reliable: *Khelawon* at paras 42; *Coldwater First Nation v Canada (Attorney General)*, 2019 FCA 292 [*Coldwater*] at para 48. A statement is reliable if there is no real concern about whether the statement is true because of the circumstances in which it was made, or if the circumstances allow its truth and accuracy to be sufficiently tested (*Khelawon* at paras 61-63), such as if it is supported by contemporaneous documentary evidence (*Coldwater* at para 49-50). Necessity is a flexible criterion and is not to be equated with the unavailability of a witness: *Khelawon* at para 78; *Coldwater* at para 53. The nature and practical exigencies of a proceeding can impact the evaluation of necessity (*Coldwater* at paras 54-55), such as avoiding an impracticably large number of affidavits or witnesses, and the resulting promotion of speed and efficiency (*Coldwater* at para 59; *R v Baldree*, 2013 SCC 35 [*Baldree*] at para 72). One criterion may have an impact on the other (*Khelawon* at paras 46 and 77) such that if the reliability of the impugned evidence is sufficiently established, the necessity requirement can be relaxed (*Baldree* at para 72).

[48] This modern approach to hearsay recognizes that evidence may be admissible from departmental supervisors or individuals who take on an oversight role and although not performing all of the work, have enough personal knowledge to testify about the conduct, activities and events that have taken place: *Coldwater* at paras 42-46.

[49] PMS argues that much of Dr. Wenslow's evidence consists of statements made about work performed by others or their state of mind and reasoning processes. It asserts that Dr. Wenslow had a limited supervisory role that is insufficient to allow him to testify broadly about the conduct, activities, and events in Merck's sitagliptin development process. It contends that if Merck wanted this evidence admitted, it needed to call other inventors or Merck employees as witnesses.

[50] Merck argues that much of the impugned evidence is not hearsay as it arises from Dr. Wenslow's personal knowledge gained in his supervisory capacity. It asserts that the impugned evidence is admissible under the principled approach to hearsay.

[51] As set out further in the Appendix, the majority of the objections made based on hearsay cannot succeed, as they are either not hearsay and/or are admissible under the principled approach to hearsay. I find that Dr. Wenslow's role within the team was such that he functioned in a larger supervisory capacity that allows him to speak about many aspects of the team's experimental work. Moreover, as to reliability, the impugned statements generally refer to information from documents that have already been accepted by PMS as being admissible for the

truth of their contents without further proof, or which raise facts that have otherwise already been admitted into evidence.

[52] As to necessity, it is difficult to reconcile the inconsistent position taken by PMS to agree to accept Dr. Wenslow's testimony as the only testimony of the invention story for the purpose of discovery, while asserting it is now insufficient for trial. In some instances if PMS' objections were to prevail, they would result in PMS reading-in certain facts from discovery as its evidence, while requiring Merck to introduce those same facts through additional witnesses. The *PMNOC Regulations* seek to promote efficiencies and to avoid the impracticality of a large number of affidavits or witnesses where such testimony is not required. The overly technical position taken by PMS, splitting and parsing sentences, where the reliability of the impugned statements are supported by contemporaneous documents or other evidence runs contrary to the fundamental guidelines set out in section 6.09 of the *PMNOC Regulations*.

(2) Opinion Evidence

[53] The general rule is that a fact witnesses must limit their testimony to the facts of which they are aware and not to inferences or opinions drawn from those facts: *White Burgess Langille Inman v Abbott and Haliburton Co*, 2015 SCC 23 at para 14. This rule applies unless the witness is in a better position than the trier of fact to form the conclusions made, the conclusions are ones that a person of ordinary experience can make, the witness has the experiential capacity to make the conclusions, or where giving opinions is a convenient mode of stating facts too subtle or complicated to be narrated as facts: *Toronto Real Estate Board v Commissioner of Competition*,

2017 FCA 236 at para 79. The line between fact and opinion is not always clear: *Graat v The Queen*, [1982] 2 SCR 819 at 835.

[54] PMS objects to all or part of 26 paragraphs of Dr. Wenslow's affidavit and related oral testimony on the basis that he is providing impermissible opinion evidence. PMS asserts that Dr. Wenslow gives unhelpful, and potentially misleading opinion evidence that does not meet the limited and narrow exceptions for a fact witness. Merck asserts that many of the alleged objections relate to factual evidence regarding the observations and conclusions drawn by Merck employees at the time. Merck argues that if any opinion evidence is provided, it is admissible because Dr. Wenslow is well positioned to provide that evidence and has the experiential capacity to do so.

[55] The majority of the statements alleged to be opinion set out the reasoning behind the choices made by the DPP-4 development team and are admissible for this purpose. While some of the statements are technical in nature, this does not automatically negate the statements, especially where such statements reflect the understanding of the development team at the time. In some cases, Dr. Wenslow adds "gloss" to his description of events. However, in most cases such comments are not of such a character that would mislead the Court or be prejudicial to PMS and do not warrant the exclusion of the evidence. Such comments can most effectively be dealt with by considering the weight to be given to the statement. With few exceptions, the objections made in this category are dismissed.

(3) Beyond the Pleadings

[56] Relevance is a threshold requirement for the admission of evidence. Evidence is relevant if it tends to establish a fact in issue. To succeed on showing that evidence should be excluded for relevance, the moving party must show that the evidence is "obviously irrelevant": *Coldwater* at para 14. PMS has failed to do so in this case.

[57] The impugned evidence is relevant to the obvious to try analysis and the inventor's course of conduct. While all of the details of Merck's invention story were not specifically pleaded in Merck's Reply, the evidence is clearly responsive to the issues in the proceeding and to PMS' evidence. The objections in this category accordingly have been dismissed.

(4) Rule 232 and 248 Objections

[58] Rules 232 and 248 aim to avoid a party being prejudiced by the late disclosure of documents and to prohibit "trial by ambush": *Airbus Helicopters, S.A.S. v Bell Helicopter Textron Canada Limitée*, 2017 FC 170 at para 81; *Apotex Inc v Sanofi Aventis*, 2010 FC 481 at para 6. Rule 248 only applies where a party fails to produce documents, or refuses to answer a proper question and later seeks to introduce such evidence at trial: *Human Care Canada Inc v Evolution Technologies Inc*, 2018 FC 1302 [*Human Care*] at paras 60-61; *Pollard Banknote Limited v BABN Technologies Corp*, 2016 FC 883 at para 215. The Court retains the discretion to admit evidence that is given in violation of rule 248.

[59] In general, where a party seeks to introduce evidence that is perceived as being inconsistent with testimony given on discovery, the correct approach is to present the

inconsistency to the witness through cross-examination: §16.178, Sidney N Lederman, Alan W Bryant and Michelle K Fuerst, ed, *Sopinka, Lederman and Bryant: The Law of Evidence in Canada*, 5th ed (Toronto, LexisNexis Canada, 2018); *JD Irving Limited v Siemens Canada Limited*, 2016 FC 69 at para 43.

[60] PMS raises 14 objections under rules 232 and 248. One of these objections is to an email that was not disclosed prior to Dr. Wenslow's discovery or in response to undertakings. The email chain confirms the date certain experiments were conducted. This information is not controversial in light of the admission into evidence of other details relating to those experiments in documents that have been accepted as being admissible for the truth of their contents. As a result, I see no prejudice to admitting the document.

[61] The remainder of the rule 248 objections fall into three groups. The first group relate to subject matter that was not refused during discovery, but rather relate to statements that PMS perceives as being inconsistent. These are not appropriate for a rule 248 objection. The second group are based on refusals to very specific points that have only a tenuous connection to the evidence being objected to. The third group relate to objections that lack foundation or were not sufficiently particularized in PMS' submissions.

[62] In addition to the formal objections raised to Dr. Wenslow's evidence, PMS also seeks an adverse credibility finding against Dr. Wenslow. It asserts that this finding is separate and distinct from the issue of admissibility, yet sits "hand in glove" with these admissibility objections. It argues that Dr. Wenslow has not acknowledged that his evidence is grounded in

hearsay and that his affidavit is based on information and belief. Pursuant to Rule 81(2) of the *Federal Courts Rules,* PMS asserts that an adverse inference must be drawn as Merck has not provided evidence from persons having personal knowledge of material facts.

[63] While evidence was not provided by those who conducted the experiments, as set out earlier in my decision, in most instances I consider Dr. Wenslow to have sufficient knowledge through his interaction within the DPP-IV development team to be able to provide the evidence given. Such evidence outlines the invention story supported by the contemporaneous documents, accepted as being admissible for the truth of their contents. I find such evidence to be credible and any elaborations given shall be addressed through weight.

III. Issues

[64] The following issues were identified in the parties' Joint Statement of Issues as being those in dispute for this action:

A. **Obviousness:** As of the claim date (June 24, 2003), would the subject matter defined by the Asserted Claims have been obvious and/or obvious to try to a PSA?

B. **Insufficiency:** Does the 400 Patent satisfy the requirements of subsections 27(3)(a) and (b) of the *Patent Act*, R.S.C., 1985, c. P-4 (the *Patent Act)*?

[65] In addition to these issues raised by the parties, and before determining the validity of the 400 Patent, the Court must construe the Asserted Claims of the 400 Patent. In order to do so, the Court must put the 400 Patent in context by determining whether it is a selection patent and by defining the PSA of the 400 Patent.

IV. The 400 Patent

[66] The 400 Patent is entitled “Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor”. It is the national phase entry of a PCT application filed on June 18, 2004 based on a US priority patent application, filed June 24, 2003. The 400 Patent will expire on June 18, 2024.

[67] The Field of the Invention, at page 1 of the 400 Patent, states that the invention of the 400 Patent relates to the DHP salt of the compound 4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, now known as sitagliptin, which is a potent inhibitor of DPP-4. It explains that the DHP salt and its crystalline hydrates are useful for the treatment and prevention of diseases and conditions for which an inhibitor of DPP-4 is indicated, in particular type 2 diabetes, obesity and high blood pressure. It also states that the invention further concerns pharmaceutical compositions comprising the salt and crystalline hydrates and processes for preparing them.

[68] The Background to the 400 Patent refers to several articles relating to DPP-4 inhibition for the treatment of type 2 diabetes. It also refers to Merck & Co’s prior patent application WO498 as disclosing a class of compounds that are potent inhibitors of DPP-4 and to the disclosure of 4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine within this class.

[69] The summary of the invention characterizes the invention as the DHP salt of 4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine and its crystalline hydrates; in particular, the crystalline

monohydrate. It explains that the DHP salt and crystalline hydrates have advantages in the preparation of pharmaceutical compositions, such as “ease of processing handling, and dosing”. They also exhibit “improved physical and chemical stability, such as stability to stress, high temperatures and humidity, as well as improved physicochemical properties, such as solubility and rate of solution”, which make them particularly suitable for pharmaceutical dosage forms. The section states that the invention further concerns “pharmaceutical compositions containing the novel salt and hydrates as well as methods for using them as DP-IV inhibitors, in particular for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.”

[70] The Detailed Description includes as structural formulas (I), (II) and (III) respectively, depictions of the monobasic DHP salt of 4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine in its racemic, *R*-enantiomer and *S*-enantiomer forms.

[71] The 400 Patent teaches that the monobasic DHP salt of 4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine is a 1:1 salt with one molar equivalent of mono-protonated compound to one molar equivalent of DHP anion. It also teaches that the salts of the compounds of each of formulas (I), (II) and (III) can be crystalline monohydrates. The crystalline monohydrate of the *R*-enantiomeric form (structural formula (II)) of sitagliptin DHP salt is the form of the medicine used in JANUVIA®.

[72] The 400 Patent teaches that the DHP salt of structural formulas (I) – (III) in its crystalline monohydrate form can act as an active pharmaceutical ingredient and exhibits pharmaceutic

advantages and enhanced chemical and physical stability over the free base and hydrochloride salt previously disclosed in WO498, in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient.

[73] Page 6 of the 400 Patent teaches how pharmaceutical compositions of the invention may be administered to patients. The 400 Patent notes that the dosage regimen is to be selected considering the "type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; and the renal and hepatic function of the patient" (page 6, lines 3-5). It notes that the "skilled physician, veterinarian, or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition" (page 6, lines 5-7). The 400 Patent goes on to provide general guidance as to the various dosage ranges for tablet and intravenous [IV] administration, noting that intranasal and transdermal administration is also possible (page 6, lines 8-22).

[74] It describes dosage forms of the compositions and provides examples, at pages 18 and 19, of the DHP salt of sitagliptin monohydrate formulated as a tablet by direct compression and roller compaction and as an IV formulation. The 400 Patent notes that the DHP salt of sitagliptin monohydrate of structural formula (I) has high solubility in water (72 mg/mL) making it especially amendable to the preparation of formulations.

[75] The 400 Patent teaches that the DHP salt exhibits potent DPP-4 inhibitory properties, useful for the prevention and treatment of type 2 diabetes, obesity and high blood pressure.

[76] The 400 Patent outlines general methods for crystallizing the monohydrate of the DHP salt of structural formula (I) and provides more detailed instructions for preparing the crystalline monohydrate of structural formula (II). It also includes structural characterization spectra (XRPD, NMR, TGA and DSC) for the crystalline monohydrate of structural formula (II).

A. *Is the 400 Patent a Selection Patent?*

[77] A selection patent is a patent devoted to the selection of a particular compound, or compounds, from a larger grouping of compounds previously disclosed in general terms and claimed in a pre-existing genus patent: *Apotex Inc v Shire LLC*, 2021 FCA 52 [*Shire*] at para 31.

[78] As set out in *Apotex v Sanofi*, 2008 SCC 61 [*Sanofi*] at paragraph 10, three conditions must be satisfied for there to be a selection patent:

> 1. There must be a substantial advantage to be secured or disadvantage to be avoided by the use of the selected members.
>
> 2. The whole of the selected members (subject to "a few exceptions here and there") possess the advantage in question.
>
> 3. The selection must be in respect of a quality of a special character peculiar to the selected group. If further research revealed a small number of unselected compounds possessing the same advantage, that would not invalidate the selection patent. However, if research showed that a larger number of unselected compounds possessed the same advantage, the quality of the compound claimed in the selection patent would not be of a special character.

[79] Where the patent is a selection patent, the asserted advantage or nature of the characteristic possessed by the selected group must be stated in the specification in clear terms: *Eli Lilly Canada Inc v Novopharm Limited*, 2010 FCA 197 [*Eli Lilly*] at para 78; *Sanofi* at

para 114. Such disclosure serves to define the characteristic features of the inventive compounds that purport to distinguish them over other compounds in the genus.

[80] The classification of a patent as a selection patent serves to assist the Court in understanding "the nature of the beast" it is dealing with (*Shire* at para 33; *Eli Lilly* at para 28) for the purpose of the Court's analysis of validity. The classification contextualizes the patent and makes it easier to compare the facts of the particular case before the court with other previous fact scenarios: *Shire* at para 33; *Eli Lilly* at paras 27-28. However, the validity analysis and the requirements for a valid patent stay the same, whether the patent is a selection patent or not: *Shire* at para 34; *Eli Lilly* at paras 33-34. The finding that the characteristics of a selection patent have or have not been met does not constitute an independent basis upon which to attack the validity of the patent: *Shire* at para 32; *Eli Lilly* at paras 27-28, 33, 48.

[81] PMS raises a preliminary objection to the characterization of the 400 Patent as a selection patent. It asserts that Merck is prohibited from raising this characterization because it was not expressly in Merck's pleadings. I do not find this argument persuasive.

[82] PMS raised the issue of selection patents in its Statement of Defence, where it pleaded that if the Plaintiffs assert that the 400 Patent is a selection patent, such framework does not "save the 400 Patent." Merck traversed this allegation in its Reply. It is clear that PMS has not been "caught by surprise" by any assertion that the 400 Patent is a selection patent. In any event, there has been no claim that the 400 Patent is "saved" by recourse to the law of selection patents. As acknowledged by Merck, the same rules of validity still apply. Both parties assert that the

obviousness analysis does not turn on whether the 400 Patent is characterized as a selection patent. Nonetheless, the Court must determine the "nature of the beast" in order to provide context for its validity analysis.

[83] In this case, the 400 Patent refers to the compound 4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, now know as sitagliptin, as being disclosed within the genus of compounds in WO498, and as to its pharmaceutically acceptable salts being generically encompassed within the scope of WO498, without specific disclosure of the DHP salt of sitagliptin (structural formula I). As stated in the Background to the Invention, at page 1:

> WO 03/004498 (published 16 January 2003), assigned to Merck & Co, describes a class of beta-amino tetrahydrotriazolo[4,3-*a*]pyrazines, which are potent inhibitors of DP-IV and therefore useful for the treatment of Type 2 diabetes. Specifically disclosed in WO 03/004498 is 4-oxo-4-[3-(trifuoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine. Pharmaceutically acceptable salts of this compound are generically encompassed within the scope of WO 03/004498.
>
> However, there is no specific disclosure in the above reference of the newly discovered monobasic dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula I below.

[84] WO498 exemplifies the compound now known as sitagliptin as one of 33 examples specifically disclosed within the application. It discloses a process for making sitagliptin and its hydrochloride salt and claims the compound, together with the 33 compounds exemplified and their pharmaceutically acceptable salts, in a separate claim of the application.

[85] WO498 refers to phosphoric acid as being one of the eight particularly preferred pharmaceutically acceptable non-toxic acids that may be used to prepare a salt with the basic compounds of WO498, which would include sitagliptin (page 10, lines 14-25).

[86] Similarly, WO498 refers to the salts prepared from the genus of compounds as being in the solid form and states that they "may exist in more than one crystal structure" and "may be in the form of hydrates" (page 9, lines 32-34).

[87] It is clear that the DHP salt of sitagliptin and the monohydrate are generically encompassed within WO498, but not specifically exemplified or claimed. Indeed, the 400 Patent refers to the DHP salt and crystalline monohydrate as being "newly discovered" and novel.

[88] The 400 Patent asserts that the crystalline DHP salt of sitagliptin has pharmaceutical advantages over the sitagliptin free base and hydrochloride salt in WO498; in particular, enhanced chemical and physical stability, which provide advantageous properties in preparing solid pharmaceutical dosage forms. At stated at page 4, lines 26-34 of the 400 Patent:

> The crystalline dihydrogenphosphate salt of the present invention exhibits pharmaceutic advantages over the free base and the previously disclosed hydrochloride salt (WO 03/004498) in the preparation of a pharmaceutical drug product containing the pharmacologically active ingredient. In particular, the enhanced chemical and physical stability of the crystalline dihydrogenphosphate salt monohydrate constitute advantageous properties in the preparation of solid pharmaceutical dosage forms containing the pharmacologically active ingredient.
>
> The dihydrogenphosphate salt of the present invention, which exhibits potent DP-IV inhibitory properties, is particularly useful for the prevention or treatment of Type 2 diabetes, obesity, and high blood pressure.

[89] As explained by Dr. Wuest, enhanced chemical stability would be understood by the PSA to mean that there is reduced chemical degradation/decomposition when sitagliptin is prepared and formulated into a medicine using the crystalline monohydrate DHP salt; thus, ensuring that its therapeutic effect is beneficially maintained. Enhanced physical stability means that the crystalline monohydrate DHP salt does not readily convert to other physical forms that might have unknown or undesirable properties. The physical stability is also shown in the TGA and DSC analyses at Figures 4 and 5, which demonstrate the high thermal stability of the crystalline monohydrate (Wuest Report, Ex 29, paras 22, 51-53).

[90] The 400 Patent, at page 7, lines 10-11, also states that the crystalline monohydrate has "high solubility in water", with a solubility of about 72 mg/mL. I accept Dr. Davies' explanation that this reference refers to the solubility classification under the Biopharmaceutics Classification System [BCS] and would be understood to be indicating the solubility in light of intended dose. Under the BCS, a "highly soluble" drug is one where the highest dose is soluble in 250 mL of dissolution medium. The high solubility of the monohydrate indicates that the monohydrate is especially suitable for formulation without the need for dissolution enhancing techniques (Davies Report, Ex 42, paras 44-46, 48).

[91] The only comparison made in the 400 Patent is between the DHP salt of sitagliptin crystalline monohydrate and the sitagliptin free base and hydrochloride salt.

[92] The 400 Patent is not devoted, as described in *Shire*, to the selection of sitagliptin over the other compounds of WO498. Nonetheless, the PSA would understand that a selection of

sitagliptin has taken place. Dr. Wuest explained this further on cross-examination as follows (TT V6, P:497 L:12-P:498 L:21):

> Q. Okay. Let's go to the section of the patent that's entitled "Summary of the Invention," which is on the next page.
>
> Under the heading "The Summary of the Invention", it states:
>
> > "The present invention is concerned with a novel dihydrogen phosphate salt of the DP-IV inhibitor sitagliptin and crystal hydrates thereof, in particular a crystalline monohydrate."
>
> You'll agree with me, Dr. Wuest, there's nothing here telling the reader that the invention is about discovering sitagliptin or sitagliptin's ability to inhibit DP-IV.
>
> A. It would be clear from reading this particular section by someone of with [*sic*] skill in this art that this particular compound and its salts and the crystalline forms thereof have been selected through a process. So there is a step that's been taken from the prior art to the new art in the 400 patent; namely, that there is now been placed a focus on sitagliptin and its salts.
>
> Q. It doesn't say that, though, does it? Does it say anything here about selecting sitagliptin from the prior art? It doesn't say that here. It talks about a novel salt form and a novel hydrate form.
>
> A. I'm not sure I understand how you can maintain that. I'm looking at this from the perspective of the skilled person who has the 400 patent in front of them and knowledge of the prior art. That knowledge would include the knowledge that sitagliptin and its hydrochloride salt [are] in the 498 application.
>
> And so the issue that -- is how you would get from that to where of this summary -- this situation that is described in this summary. So there's clearly a selection of that particular compound because this describes a new salt of that particular compound.
>
> Q. When you say "of that particular compound," you meant sitagliptin?
>
> A. That's right.

[93] The 400 Patent gives no reason for honing in on sitagliptin over the other compounds disclosed within WO498. However, it relies on this choice for the further development work disclosed in the patent. As acknowledged by Dr. Hollingsworth, the PSA knew from the 400 Patent that Merck had selected sitagliptin as its lead compound for further development, and had successfully made the DHP salt and identified the crystalline monohydrate as being amenable to sitagliptin formulations (TT V3, P:281 L:4-28). The PSA knew that the solubility, and relative stability of the DHP salt of sitagliptin crystalline monohydrate had been determined and had been selected over sitagliptin free base and the hydrochloride salt (TT V3, P:281 L:10-15; P:282 L:3-8).

[94] This is no different than *Sanofi* where the genus patent exemplified the racemate of the compound, but did not specifically disclose the dextro-rotatory isomer of the racemate, or the advantages of using the bisulfate salt in combination with the dextro-rotatory isomer, which were the subject matter of the later selection patent.

[95] There is no explanation as to why sitagliptin was chosen for further development. However, the fact that there has been a selection of a particular salt and crystalline form of a particular compound from the genus of compounds, salts and crystalline forms encompassed within WO498, and that the particular salt and crystalline form are said to have advantages over sitagliptin free base and its hydrochloride salt, which are disclosed in WO498, in my view favours the 400 Patent being considered a selection patent. Whether the proposed invention of the 400 Patent is inventive over WO498 and whether the disclosure of the 400 Patent is sufficient is a matter to be dealt with separately below.

B. *Claims Construction*

[96] The principles of claim construction were summarized by the Federal Court of Appeal [FCA] in *Tearlab Corporation v I-Med Pharma Inc.*, 2019 FCA 179 at paragraphs 30 to 34:

> [30] The general principles of claim construction are now well established and were set out by the Supreme Court in three cases (*Whirlpool* at paras. 49-55; *Free World Trust v. Électro Santé Inc.*, 2000 SCC 66, [2000] 2 S.C.R. 1024 at paras. 31-67 [*Free World Trust*]; *Consolboard Inc. v. MacMillan Bloedel (Sask.) Ltd.*, 1981 CanLII 15 (SCC), [1981] 1 S.C.R. 504 at p. 520 [*Consolboard*]). These principles can be summarized as follows.
>
> [31] The *Patent Act* promotes adherence to the language of the claims, which in turn promotes fairness and predictability (*Free World Trust* at paras. 31(a), (b) and 41). The words of the claims must, however, be read in an informed and purposive way (at para. 31(c)), with a mind willing to understand (at para. 44). On a purposive construction, it will be apparent that some elements of the claimed invention are essential while others are non-essential (at para. 31(e)). The interpretative task of the court, in claim construction, is to separate and distinguish between the essential and the non-essential elements, and to give the legal protection to which the holder of a valid patent is entitled only to the essential elements (at para. 15).
>
> [32] To identify these elements, the claim language must be read through the eyes of a POSITA, in light of the latter's common general knowledge (*Free World Trust* at paras. 44-45; see also *Frac Shack* at para. 60; *Whirlpool* at para. 53). As noted in *Free World Trust*:
>
> > [51] …The words chosen by the inventor will be read in the sense the inventor is presumed to have intended, and in a way that is sympathetic to accomplishment of the inventor's purpose expressed or implicit in the text of the claims. However, if the inventor has misspoken or otherwise created an unnecessary or troublesome limitation in the claims, it is a self-inflicted wound. The public is entitled to rely on the words used *provided* the words used are interpreted fairly and knowledgeably. [Emphasis in the original.]

> [33] Claim construction requires that the disclosure and the claims be looked at as a whole "to ascertain the nature of the invention and methods of its performance, … being neither benevolent nor harsh, but rather seeking a construction which is reasonable and fair to both patentee and public" (*Consolboard* at p. 520; see also *Teva Canada Ltd. v. Pfizer Canada Inc*., 2012 SCC 60, [2012] 3 S.C.R. 625 at para. 50). Consideration can thus be given to the patent specifications to understand what was meant by the words in the claims. One must be wary, however, not to use these so as "to enlarge or contract the scope of the claim as written and … understood" (*Whirlpool* at para. 52; see also *Free World Trust* at para. 32). The Supreme Court recently emphasized that the focus of the validity analysis will be on the claims; specifications will be relevant where there is ambiguity in the claims (*AstraZeneca Canada Inc. v. Apotex Inc*., 2017 SCC 36, [2017] 1 S.C.R. 943 at para. 31; see also *Ciba* at paras. 74-75).
>
> [34] Finally, it is important to stress that claim construction must be the same for the purpose of validity and for the purpose of infringement (*Whirlpool* at para. 49(b)).

[97] The 400 Patent is to be construed from the viewpoint of the PSA to which it pertains as of its publication date, January 13, 2005.

(1) PSA of the 400 Patent

[98] The PSA is the hypothetical person to whom the patent is addressed. This may be a single individual or a team of individuals representing different disciplines, depending on the nature of the invention. The PSA is deemed to be unimaginative and uninventive, but at the same time is understood to have an ordinary level of competence and knowledge incidental to the field to which the patent relates and to be reasonably diligent in keeping up with advances: *Merck & Co v Pharmascience Inc*, 2010 FC 510 [*Merck*] at para 35-36, 39; *Teva Canada Limited v Janssen Inc*, 2018 FC 754, at paras 65-66, aff'd 2019 FCA 273.

[99] While the experts agreed that the PSA is a team of individuals, PMS' experts assert that the team is limited to those that would be involved in the steps of pharmaceutical development that bridge the gap between the active pharmaceutical ingredient [API] and finished dosage form; that is, an analytical chemist, process chemist and formulator. Merck's experts do not disagree that the team comprising the PSA would include a chemist, or chemists, with knowledge of analytical techniques and processing, but also assert that the PSA would include a medicinal chemist and a medical doctor as the invention involves the selection of sitagliptin and its use as a DPP-4 inhibitor.

[100] As set out above, I agree that the 400 Patent requires that a selection of sitagliptin has taken place. However, that does not mean that it must follow that the patent is directed to a medicinal chemist. The determination of the PSA involves consideration as to who would have an interest in the teachings of the patent.

[101] The 400 Patent does not disclose the type of studies or data that would be characteristically of interest to the medicinal chemist, such as SAR studies or IC_{50} values. The 400 Patent does not describe *the process* involved in selecting sitagliptin over the other compounds of WO498, including over the free base and hydrochloride salt exemplified within WO498. Rather, it is directed to the identification of the DHP salt of sitagliptin and its crystalline monohydrate with its purported advantageous properties. While I would agree that someone on the skilled team would need to have a general understanding as to how to get from WO498 to the teachings of the 400 Patent, in my view this does not require that the team of individuals that comprise the PSA include a separate medicinal chemist. Rather, it would be sufficient for one of

the members of the team to have some general background knowledge of medicinal chemistry and/or lead compound identification. Indeed, I note that even PMS considered it important to have an expert who could speak to lead compound identification as part of its case – i.e., Dr. Foley.

[102] In my view, the team of individuals that comprises the PSA would also include a clinician or someone with knowledge of the treatment of type 2 diabetes. Both the Field of the Invention and the Summary of the Invention refer to the use of the DHP salt of sitagliptin crystalline monohydrate for the treatment and prevention of type 2 diabetes and other diseases and conditions for which an inhibitor of DPP-4 is indicated. It also refers to the use of the DHP salt of sitagliptin crystalline monohydrate in pharmaceutical compositions to treat patients with these conditions as being part of the invention. Indeed, Claims 22 and 26 are directed to such uses.

[103] Page 6, lines 5-7 of the 400 Patent states that an "ordinarily skilled physician, veterinarian, or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition". Drs. Elitzin and Foley state that this passage makes clear that a different skilled person was intended to deal with the dosing regimen for the drug than the skilled person to whom the patent is directed. However, I prefer the evidence of Merck's experts on this passage.

[104] As set out in *Merck*, a patent may be directed to different persons, each having a different interest (*Merck* at para 39).

[105] I accept the evidence of Dr. Lewanczuk that page 6 is indicating that this part of the patent's teachings - i.e., dosing regimen and therapeutic use - is directed to the skilled clinician as opposed to other members of the team that comprise the PSA (Lewanczuk Report, Ex 55, paras 104-109).

[106] Notably, despite his arguments that a skilled clinician would not be included as a member of the PSA, Dr. Foley testified to the importance of the clinician in evaluating aspects of the patent. As acknowledged by Dr. Foley, it is the clinician who would be keeping up with the literature and patent filings pertaining to DPP-4 inhibitors, and it is the clinician who would have appreciated whether there was any therapeutic advantage being described in the 400 Patent relating to the monohydrate or DHP salt of sitagliptin over what had been described in WO498 (TT V1, P:53 L:20-P:54 L:8).

[107] Indeed, each of Drs. Foley and Lewanczuk provided useful insight as to the skilled clinician's understanding of those portions of the 400 Patent dealing with the use of the monohydrate. Dr. Foley was asked to speak to claims 22 and 26 of the 400 Patent and to the prior art landscape involving clinical studies using DPP-4 inhibitors. PMS relies heavily on Dr. Foley's testimony relating to his understanding and interpretation of these claims.

[108] When asked about this in oral argument, PMS asserted that Dr. Foley's evidence was only intended to provide background on the invention story. However, this response runs contrary to the mandate set out in the Foley Report and to his opinions, which speak directly to the obviousness analysis.

[109] In my view, the PSA would include someone with clinical knowledge of the treatment of patients with type 2 diabetes, who could be a medical doctor and/or someone who has acquired this knowledge through experience on a clinical team.

[110] Accordingly, I find that the PSA would include a chemist with experience in compound characterization and processing, and some general background knowledge of medicinal chemistry and/or lead compound identification. This could be one individual with this skill-set or separate analytical and process chemists. The team would also include a formulator, and a clinician or individual with clinical knowledge of the treatment of patients with type 2 diabetes.

[111] While the experts were not entirely at *idem* as to the experience of the members of the team comprising the PSA, they appeared to consistently agree that the members of the team could have a Bachelor's, Master's or Ph.D., depending on the years of supplemental experience. The number of years needed would be greater for someone with a Master's degree and greater still for someone with a Bachelor's degree. All experts agreed that at least one year of experience would be required for a member of the team, even if holding a Ph.D.

(2) Construction of the Asserted Claims of the 400 Patent

[112] The 400 Patent includes 27 claims, nine of which are in issue for this action: claims 4-7, 19, 20, 22, 24 and 26. The parties are in general agreement as to the construction to be given to these claims.

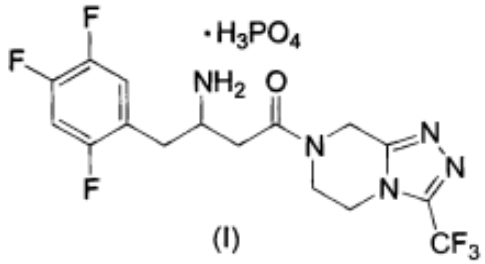
[113] Claims 4-7, 19, 20, 22, 24 and 26 of the 400 Patent read as follows:

> 4. The salt of Claim 2 characterized in being a crystalline monohydrate.
>
> 5. The salt of Claim 4 characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 7.42, 5.48, 3.96 angstroms.
>
> 6. The salt of Claim 5 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 6.30, 4.75, and 4.48 angstroms.
>
> 7. The salt of Claim 6 further characterized by characteristic absorption bands obtained from the X-ray powder diffraction pattern at spectral d-spacings of 5.85, 5.21 and 3.52 angstroms.
>
> 19. A process for preparing the salt of Claim 1 comprising the step of contacting one equivalent of 4-oxo-4-[3-(trifluoromethyl)-5,6-didydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine in an organic solvent or aqueous organic solvent with about a one equivalent of phosphoric acid at a temperature in the range of about 25-100^{o}C.
>
> 20. The process of Claim 19 wherein said organic solvent is a C_1-C_5 linear or branched alkanol.
>
> 22. Use of the salt of Claim 4 as active ingredient in the manufacture of a medicament for use in the treatment of type 2 diabetes.
>
> 24. The process for preparing the crystalline monohydrate of Claim 4 comprising the steps of:
>
> (a) crystallizing said dihydrogenphosphate salt of Claim 1 at 25^{o}C from a mixture of isopropanol and water, such that the water concentration is above 6.8 weight percent;
>
> (b) recovering the resultant solid phase; and
>
> (c) removing the solvent therefrom.
>
> 26. A use of a therapeutically effective amount of the salt according to Claim 4 for the treatment of type 2 diabetes in a patient in need of such treatment.

[114] Claim 4 is a dependent claim, which stems from Claim 2 of the 400 Patent, which itself depends from Claim 1.

[115] Claim 1 is directed to the DHP salt of sitagliptin and its hydrate, without any specific stereochemistry:

> 1. A dihydrogenphosphate salt of 4-oxo-4-[3-(trifluoromethyl)-5,6-didydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine of structural formula 1:

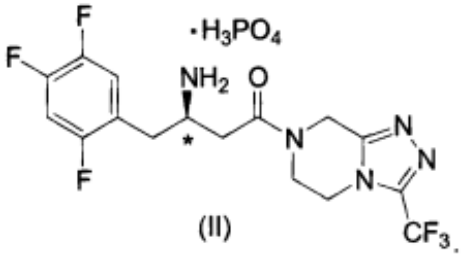


(I)

> or a pharmaceutically acceptable hydrate thereof.

[116] Claim 2 is directed to the *R*-enantiomer of the DHP salt of sitagliptin and its hydrate:

> 2. The salt of Claim 1 of structural formula II having the (*R*)-configuration at the chiral center marked with an *



(II)

[117] It is understood from these dependencies that Claim 4 (and all claims that depend from claim 4) claim the *R*-enantiomer of the DHP salt of sitagliptin in its crystalline monohydrate form.

[118] Claims 5-7 include characterization data arising from the XRPD spectra for the crystalline monohydrate form. The PSA would know that the *d*-spacings arise from the formulaic conversion of the 2θ values of the crystalline form as obtained through calculation using Bragg's law: $n\lambda=2d\sin\theta$ (Hollingsworth Report, Ex 68, para 143).

[119] Claims 19 and 20 set out general methods for preparing the non-stereospecific DHP salt of sitagliptin monohydrate. Through the process description, it is understood that about one molar equivalent of phosphoric acid should be reacted with about one molar equivalent of free base. Claim 20 specifies that the organic solvent is a C_1-C_5 linear or branched alkanol.

[120] Claim 24 provides a process for making the *R*-enantiomer of the DHP salt of sitagliptin in its crystalline monohydrate form. The PSA would understand that this process does not specify its starting materials (TT V3, Conf, P:58 L:15-P:59: L:6), but only requires that crystallization occur from the DHP salt at a temperature of 25ºC using a mixture of isopropanol and water, such that the water concentration is above 6.8 weight percent. The process also requires that the crystals be recovered and the solvent removed. The process does not specify the process for solvent removal (TT V3, P:309 L:8-17).

[121] The PSA would understand from the teachings of the 400 Patent that the crystalline monohydrate is vulnerable to conversion to its dehydrated (anhydrous) form if heated to above 40ºC under very dry nitrogen flow and that it will convert back from the anhydrous form to the monohydrate under ambient conditions (page 18, lines 5-8 of the 400 Patent) (TT V2, P:223

L:17-21; TT V2, Conf, P:41 L:2-7; TT V3, P:311 L:16-24; TT V6, P:523 L:4-13). The skilled person would understand that ambient conditions would be room temperature.

[122] Claims 22 and 26 are directed to the therapeutic use of the DHP salt of sitagliptin crystalline monohydrate. Claim 22 claims the use of the DHP salt of sitagliptin crystalline monohydrate as the active ingredient in the manufacture of a medicament to treat type 2 diabetes. Claim 26 claims the use of a therapeutically effective amount of the DHP salt of sitagliptin crystalline monohydrate for treating a patient with type 2 diabetes. No specific dose is claimed. As explained by Dr. Lewanczuk, the PSA would understand a "therapeutically effective amount" to mean an amount of the claimed compound that effectively contributes to improving the patient's glycemic control by lowering blood glucose levels (Lewanczuk, Ex 55, para 111).

V. Obviousness

A. *Legal Principles*

[123] Section 28.3 of the *Patent Act* provides that the subject matter of a claim in an application for a patent in Canada must be subject matter that would not have been obvious on the claim date (here, June 24, 2003) to the PSA, having regard to information that was made available to the public: (a) more than one year before the filing day by the applicant, or by a person who obtained knowledge directly or indirectly from the applicant; and, (b) before the claim date, by a person not mentioned in (a).

[124] Obviousness is a difficult test to satisfy because it necessitates showing that the PSA would have come directly and without difficulty to the invention, without the benefit of

hindsight: *Bridgeview Manufacturing Inc v 931409 Alberta Ltd (cob Central Alberta Hay Centre)*, 2010 FCA 188 at para 50.

[125] The Supreme Court of Canada in *Sanofi* set out a four-step approach to the obviousness analysis at paragraph 67 of its decision, as follows:

> (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 of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

[126] In areas of endeavour where advances are often won by experimentation, an "obvious to try" analysis may be appropriate to take into consideration at the fourth step of the obviousness inquiry. The critical question is whether it "was more or less self-evident to try to obtain the invention" having regard to the following factors, while noting that "[m]ere possibility that something might turn up is not enough" (*Sanofi* at paras 66, 68-69):

> 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?

[127] The Court must be cautious, however, when approaching the obvious to try analysis as it remains as only one factor amongst many that may assist in the obviousness inquiry: *Bristol Myers Squibb Canada Co v Teva Canada Limited*, 2017 FCA 76 [*Atazanavir*] at para 38; *Sanofi* at para 64. It is not intended to displace other tests. As the Supreme Court in *Sanofi* made clear, the Court favours "an expansive and flexible approach that would include 'any secondary considerations that [will] prove instructive'": *Sanofi* at para 63; *Atazanavir* at para 61.

B. *Common General Knowledge [CGK] and Prior Art*

[128] The reference for the test for obviousness is the PSA. After identifying the credentials and characteristics of the PSA (as done earlier in these reasons), the next step is to identify the CGK of the PSA. CGK means knowledge generally known by the PSA at the relevant time (*Sanofi* at para 37), in this case June 24, 2003.

[129] CGK is to be distinguished from the prior art, which is a broad category encompassing all previously disclosed information in the field. CGK includes knowledge of patents, but does not include knowledge of all patents; nor does it include knowledge of all journal articles or other technical information. It is the subset of patents, journal articles and technical information of which the PSA has become generally aware and which has been accepted: *Eurocopter v Bell Helicopter Textron Canada Ltée*, 2013 FCA 219 [*Eurocopter*] at paras 64-65; *Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc.*, 2016 FCA 119 at para 24.

[130] The parties differ on their positions as to what constitutes the CGK of the PSA and whether this would include general information pertaining to DPP-4 inhibitors and the treatment of type 2 diabetes in addition to CGK relating to salt formation and crystal form identification. As I have already determined that the PSA would include someone with clinical knowledge, it is my view that CGK relating to DPP-4 inhibition and treatment of type 2 diabetes would be known to this PSA (TT V1, P:55 L:11-27). Indeed, the 400 Patent references this information as part of the relevant background to the invention.

(1) DPP-4 Inhibition and Treatment of Type 2 Diabetes

[131] By 1997, type 2 diabetes was recognized as a serious disease condition that required medical attention to avoid long-term health risks. GLP-1 and its role in stimulating secretion of insulin had been identified. It was known that DPP-4 acted to degrade GLP-1 and that inhibiting DPP-4 could have effects on modulating insulin and glucose levels in the blood.

[132] The 400 Patent acknowledges certain information known to the PSA as of June 24, 2003 regarding the inhibition of DPP-4 as an approach to treat type 2 diabetes. As stated at page 1 of the 400 Patent:

> Inhibition of dipeptidyl peptidase-IV (DP-IV), an enzyme that inactivates both glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), represents a novel approach to the treatment and prevention of Type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM). The therapeutic potential of DP-IV inhibitors for the treatment of Type 2 diabetes has been reviewed: C.F. Deacon and J.J. Holst, "Didpeptidyl peptidase IV inhibition as an approach to the treatment and prevention of Type 2 diabetes: a historical perspective," Biochem, Biophys. Res. Commun., 294: 1-4 (2000); K. Augustyns, et al., "Didpeptidyl peptidase IV inhibitors as new therapeutic agents for the treatment of Type 2 diabetes," Expert, Opin. Ther. Patents, 13:

> 499-510 (2003); and D.J. Drucker, "Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of Type 2 diabetes," Expert Opin. Investig. Drugs, 12: 87-100 (2003).

[133] By admission of the patentee, through inclusion of these references in the background to the 400 Patent, the Deacon, Augustyns and Drucker papers form part of the relevant prior art: *Shire Biochem Inc v Canada (Minister of Health)* 2008 FC 538 at para 25; *Eli Lilly Canada Inc v Novopharm Ltd*, 2007 FC 596 at para 142; *Pfizer Canada Inc v Novopharm Ltd*, 2005 FC 1299 at para 78. These papers summarize the developments known in the field regarding compounds that had already shown DPP-4 inhibitory activity, including Probiodrug's compound P32/98 and the Novartis compounds, DPP-728 and LAF-237.

[134] As noted by Drs. Foley and Lewanczuk, P32/98 (depicted at paragraph 206 below) had already been tested for potency in animal studies (Foley Report, Ex 1, Schedule E19) and was reported to enhance the insulin response and improve glucose tolerance in diabetic humans administered with a 60 mg single dose (Lewanczuk, Ex 55, para 102 and Appendix K).

[135] It was also known that DPP-728 (depicted at paragraph 206 below) had shown activity in animal studies and some clinical efficacy in a 4-week Phase II study in humans (Foley Report, Ex 1, paras 30 and 54 and Schedule E19; TT V1, P:55 L:11-27). The results of a study reported by Ahrén in 2002, showed the safety and tolerability of DPP-728, with only minimal adverse events. The study reported lower glucose levels in human patients without hypoglycemia when administered in 100 mg and 150 mg doses and identified inhibition by DPP-728 as a feasible treatment for type 2 diabetes (Foley Report, Ex 1, para 54(f) and Schedule E11; Lewanczuk, Ex 55, para 102).

[136] Kinetic studies showed that DPP-728 did not function as a simple competitive inhibitor, but as a substrate for the DPP-4 catalytic site. A derivative of DPP-728 (LAF-237, depicted at paragraph 206 below), eventually known as vildagliptin, was developed by Novartis to improve on the compound's kinetics and dissociation rate (Foley Report, Ex 1, Schedule E19).

[137] In 2003, Villhauer reported on the *in vivo* efficacy of vildagliptin in rat models (Foley Report, Ex 1, Schedule E17). Other *in vivo* work in monkeys also indicated that vildagliptin had a longer half-life in inhibiting DPP-4 than DPP-728, and might be suitable for a once-a-day treatment (Foley Report, Ex 1, para 54(g)).

[138] As acknowledged by the 400 Patent, the PSA also would have known about WO498 and about the class of compounds disclosed in WO498 as being putative inhibitors of DPP-4, with the potential to be used in the treatment or prevention of diseases where DPP-4 is involved, such as type 2 diabetes (Lewanczuk, Ex 55, at paras 115, 117, 121, 122). Dr. Foley testified that this was the only document published by June 24, 2003 that included the compound now known as sitagliptin (TT V1, P:61 L:17-23). It did not include any specific activity or efficacy data for any of its compounds. As of June 2003 no results of any clinical evaluation from Merck had been published on any of the compounds from WO498 (TT V1, P:56 L:17-27).

(2) Salt Formation and Selection

[139] The PSA of the 400 Patent would also possess certain CGK relating to salt formation and selection.

[140] It was undisputed by the experts that by June 24, 2003 standard high throughput techniques for salt screening were known and used in the industry and allowed for numerous salt forms to be screened at one time. The experts agreed that salt formation was expected to improve the possibility of forming stable crystalline solids. However, they did not agree as to how salt screening would be approached.

[141] Dr. Wuest's view was that salt screening was an essential but iterative process. Citing Gould and Stahl 2002 (which were also attached to Dr. Elitzin's report) and the 1996 chapter on "Salt Forms of Drugs and Absorption" in the *Encyclopedia of Pharmaceutical Technology*, authored by Bighley, Berke and Monkhouse, Dr. Wuest stated that the first course of action for drug development was to consider the free acid or free base form of the active compound. Only if the free acid or free base was unacceptable for development would salt formation be necessary. The first salt to be considered for a basic compound would typically be the hydrochloride salt and only if that salt proved unacceptable would other mineral salts, such as phosphate, be considered. Stahl highlighted that phosphate salts had a tendency to form hydrates, which generally had lower solubility and slower dissolution rates than their corresponding anhydrous forms.

[142] According to Dr. Elitzin, salt screening was a matter of routine by 2003 and took place at the outset of every drug development program. He did not agree that consideration of the free base would influence whether a salt screen was conducted, but referred in his report to initial physicochemical characterization of the free acid or base API that would be used for comparison purposes. His view was that hydrochloride salts would not necessarily be the first choice as it

was known that the solubility of hydrochloride salts could be impacted by the common ion effect in gastric acid medium.

[143] Overall, I favour Dr. Wuest's comments as they are supported by publications (and authors) that Dr. Elitzin himself recognized as being authoritative and are also reflective of the approach taken at Merck. The statistics referenced in Stahl 2002 indicated that by June 2003, 50% of all drugs on the market were in salt form, while the other 50% remained as the free base/free acid. Of those basic drugs that were salts, more than half were hydrochloride salts. Phosphate salts were pharmaceutically acceptable inorganic salts that ranked in the top five preferred salts for basic drugs, although the number commercially made and sold by 2003 were significantly less than hydrochloride salts.

[144] Both Dr. Wuest and Dr. Elitzin agreed with the statement made in Stahl 2002 (Hollingsworth Report, Ex 68, Schedule 26) that the selection of a salt form that exhibits the desired pharmacological, toxicological and therapeutic properties was a multidisciplinary task of varying complexity.

[145] Various analytical techniques were available for salt selection and involved characterization of structural, physicochemical, and physical properties, as well as analysis of impurities and stability studies.

(3) Crystal Form Identification

[146] The parties' experts generally agreed about the CGK regarding crystal form identification, which can be summarized in the following paragraphs.

[147] By 2003, it was well-known that most pharmaceutical compounds demonstrated polymorphism. Crystals incorporating water (i.e. hydrates) were common and it was known that phosphate salts had a propensity to form hydrates.

[148] As summarized in the paper Byrn 1994 (Hollingsworth Report, Ex 68, Schedule E21 at 1148), which was accepted as being reflective of the CGK:

> The mission of those working in the field of solid-state pharmaceutical chemistry is to provide each drug in a solid form that has optimum performance in a given application. Pursuit of this mission requires recognition of several general, interrelated points: (1) Drugs can exist in a number of solid forms, each having different properties of pharmaceutical importance, including stability and bioavailability; the number and properties of these forms are largely unpredictable and vary considerably from case to case. (2) The forms of a drug may interconvert under various conditions. (3) Once a solid form is chosen for a product, methods for analysis and control of the form must be devised.

[149] It was understood that the most thermodynamically stable form of a drug substance was typically preferred for pharmaceutical development and it was a routine part of the pre-formulation process to try to identify the most stable polymorphic form. By 1990, regulatory guidelines existed for ensuring that companies filing regulatory submissions had investigated polymorphism and identified what they considered to be the most stable crystalline form of their API.

[150] By 2003, a variety of routine methods were available and known to the PSA to conduct polymorph screening and to characterize the crystal forms obtained – i.e., XRPD, NMR, TGA, DSC. A common strategy for screening included crystallization using a variety of solvents and solvent mixtures. As stated in Bernstein 2002 (Hollingsworth Report, Ex 68, Schedule E7 at page 252), another reference accepted as being reflective of the CGK:

> Our understanding of the role and choice of solvent has improved considerably and this information, combined with a knowledge of zones of stability can aid in determining crystallization conditions for obtaining metastable forms. In addition, there has also been considerable progress in understanding and utilizing the interaction of solvent with the growing crystal. Combining the detailed structural information available from the single crystal structure determinations of polymorphs with crystal morphological data (i.e. crystal habit, and the orientation of molecules projecting from the particular faces exposed) and with known intermolecular interactions between solute molecules and solvent functional groups allows the rational choice of solvent to select a particular polymorphic form. [citations omitted]

[151] In addition to solvent choice, other factors identified in Byrn 1994 (Hollingsworth Report, Ex 68, Schedule E21 at 1150), were known to influence crystallization, including concentration or degree of supersaturation; temperature, including cooling rate and the cooling profile; additives; seeds; pH; and agitation.

[152] Modelling programs existed for identifying plausible crystals forms; however, there was no ability to predict which forms could be isolated. As explained in Bernstein 2002 (Hollingsworth Report, Ex 68, Schedule E7 at page 9):

> The *possibility* of polymorphism may exist for any particular compound, but the conditions required to prepare as yet unknown polymorphs are by no means obvious....we are almost totally ignorant about the properties to be expected from any new polymorphs that might be obtained.

[153] Similarly, Byrn 1994 (Hollingsworth Report, Ex 68, Schedule E21 at page 1148) stated the challenge faced by those in the field as follows:

> ... the chief challenge in managing the phenomenon of multiple solid forms of drugs is our inability to predict how many forms can be expected in a given case: too often costly delays are encountered when a less soluble solid form suddenly appears late in a development program.

[154] Further, it was known that different polymorphs could have markedly different formulation properties, including rate of dissolution. The skilled formulator on the PSA team was aware that a number of factors can influence the amount and rate at which a medicinal ingredient gets absorbed into the body, including the inherent properties of the medicinal ingredient, such as its solubility (Davies Report, Ex 42, para 29). The solubility of a drug increases with temperature and can vary with pH. Most available drugs are poorly soluble, which can translate to low bioavailability (the amount of drug absorbed into the bloodstream) (Davies Report, Ex 42, para 38-39 and Schedule 1).

[155] The PSA knew from accepted references like Aulton 2002 and Stahl 2002 that hydrates are typically (but not always) less soluble than anhydrous forms and have slower dissolution rates (Davies Report, Ex 42, Schedule 1; Elitzin Report, Ex 66, Schedule E1). However, it was not possible to predict the properties of any polymorph, or which would have the most favourable properties for pharmaceutical development, in advance of discovering, making and testing it in appropriate assays (Davies, Ex 42, para 56-57).

C. *What is the Starting Point of the Obviousness Analysis – "State of the Art"*

[156] The obviousness analysis asks whether the distance between two points in the development of the art can be bridged by the PSA using only their CGK: *Atazanavir* at para 65. The first of the two points is the "state of the prior art" at the relevant date: *Atazanavir* at para 65; *Sanofi* at para 67.

[157] PMS asserts that the state of the prior art is defined by the 400 Patent and should be limited to the disclosure of sitagliptin and the hydrochloride salt of sitagliptin as a potent inhibitor of DPP-4 and to its usefulness to treat type 2 diabetes. It relies on *Ciba Specialty Chemicals v SNF*, 2017 FCA 225 [*Ciba*] at paragraph 60 as support for its assertion:

> To conclude, a word about "the matter cited as forming part of the prior art", the phrase used in Pozzoli and Plavix. The matter cited as forming part of the prior art is simply the prior art relied upon by the person alleging obviousness. Obviousness is not determined by reference to the prior art at large. The person alleging obviousness must point to one or more elements of prior art which make the impugned invention obvious. The choice of those elements of prior art is entirely in the hands of the party alleging obviousness, limited only by section 28.3 of the Act which sets out the cut-off date for opposable prior art. In fact, the challenger may rely on a combination of pieces of prior art under the "mosaic" theory of obviousness: *Wenzel Downhole Tools Ltd. v. National-Oilwell Canada Ltd.*, 2012 FCA 333 at paragraph 87, [2014] 2 F.C.R. 459.

[158] Merck asserts that the "state of the art" is the prior art at large, not just a single reference in isolation. It asserts that this includes all of the prior art cited by Dr. Foley relating to P32/98, DPP-728 and LAF-237 and by Dr. Roush from his prior art and literature search attached to his report. Even if a medicinal chemist is not accepted as the PSA and Dr. Roush's report is given less weight, Merck asserts that the prior art would include at least WO498 in its entirety and the

Deacon, Augustyns and Drucker papers referenced in the 400 Patent, which summarized the developments relating to P32/98, DPP-728 and LAF-237 and what was known about their DPP-4 inhibitory activity.

[159] Merck refers to *Apotex Inc v Janssen Inc*, 2021 FCA 45, which states at paragraph 25:

> Apotex makes several arguments concerning legal principles applicable to obviousness analysis. First, Apotex argues that obviousness is to be assessed by asking whether the distance between two points (the state of the art and the subject matter of the claim in question) can be bridged by the POS. Apotex argues that the second point (the subject matter of the claim) is to be determined by reference to the language of the claim. This is consistent with section 28.3 of the Patent Act and with the jurisprudence. Apotex also argues that the first point (the state of the art) is to be determined by reference not to the prior art at large, but rather to the prior art chosen by the party alleging obviousness. However, I do not understand the authorities cited by Apotex in support of this argument to limit the scope of prior art that can be considered for obviousness.

[160] In many cases, the closest prior art is identified by the challenger and frames the analysis. In other words, if the claims of the patent are not obvious in view of the prior art that is closest to the claims, they would not be obvious by considering broader prior art, which is less relevant to the purported invention. However, that does not mean that the broader prior art is not relevant to other factors, such as motivation, as discussed further below.

[161] In this case, the 400 Patent guides the analysis by identifying WO498 and the Deacon, Augustyns and Drucker references as being prior art that is relevant. While sitagliptin and the hydrochloride salt of sitagliptin are disclosed within WO498, the disclosure of these compounds

must be read and understood in context – that is, within WO498 – as this is how they would be known to the PSA (as noted by the 400 Patent).

[162] Indeed, even Dr. Hollingsworth points to WO498 as being the starting point for the analysis in his report, where he states:

> 190. In my view, the difference between the state of the art and Claim 4 (and its dependent claims) is the choice of the monohydrate crystal form of sitagliptin phosphate from the crystalline forms (including hydrates) that the PSA would have understood to be part of the WO 498 and would have presumed arose from a standard polymorph screen.
>
> ...
>
> 192. The 400 Patent identifies the WO 498 as the starting point. It acknowledges that sitagliptin and sitagliptin hydrochloride were known and disclosed (which they plainly were).

[163] Applying this to the obviousness analysis, the question to be answered is whether bridging the gap between WO498 (which discloses sitagliptin and its hydrochloride salt, amongst other compounds) and the inventive concept of the claims of the 400 Patent would have been obvious to the PSA having regarding to the CGK and prior art. This includes consideration of the Deacon, Augustyns and Drucker references and the prior art relating to DPP-4 inhibitors as discussed under the motivation section below.

D. *Inventive Concept of the Claims in Question*

[164] There is some debate in the jurisprudence as to whether the obviousness analysis requires identification of an inventive concept or whether the essential elements as construed by the claims is the more appropriate end-point: *Atazanavir* at paras 65-70, 74-78; *Ciba* at paras 64-68, 72-77.

[165] As noted in *Atazanavir*, the intention of the obviousness test set out in *Sanofi* was not to change the law of obviousness; the term "inventive concept" is not materially different from the previously used term "solution taught by the patent": *Atazanavir* at paras 65-68, 75.

[166] PMS argues that recourse should not be made to the inventive concept. Rather, the second point in the obviousness analysis should be the essential elements of the claims. It argues that the focus of the obviousness analysis should be on claim 4 and the claimed DHP salt of sitagliptin crystalline monohydrate, as the other claims do not add any features that can be inventive. It similarly asserts that if the inventive concept is to be considered, it would be focussed on the identification of sitagliptin as a phosphate salt that is in crystalline monohydrate form.

[167] Merck argues that the inventive concept must be determined as it is a mandatory part of the *Sanofi* test. It contends that PMS' argument ignores the latest word on the inventive concept from the FCA in *Shire*. Its experts assert that the inventive concept of claim 4 is the identification of sitagliptin phosphate monohydrate as a compound with: potent DPP-4 inhibitory properties; pharmaceutic advantages over sitagliptin free base and the hydrochloride salt; and particular advantages for preparing medicines of the pharmacologically active ingredient because of its enhanced chemical and physical stability (as compared to sitagliptin free base and the hydrochloride salt), and its high solubility. It asserts that claims 5-7 have the same inventive concept, but that the inventive concept of claims 19, 20 and 24 would be the process claimed to prepare the monohydrate. Similarly, it asserts that the inventive concept of claim 22 is that the monohydrate is useful to prepare medicaments to treat type 2 diabetes on account of its disclosed

properties, and that the inventive concept of claim 26 is the use of the monohydrate for treating type 2 diabetes with a therapeutically effective amount.

[168] As noted in *Shire* at paragraphs 75 and 76, while identification of the inventive concept follows from, and is informed by, claims construction, claims construction and determination of the inventive concept serve two different purposes. Claims construction occurs before any assessment of the validity of the claims; its purpose being to interpret and determine the scope of the claim by looking at its subject matter. Identification of the inventive concept occurs within the assessment of the validity of the claims. Its purpose is to determine the proposed inventive aspect of the claim, to facilitate the obviousness analysis.

[169] This is particularly important if recourse to the specification is required, such as in the case where a bare chemical formula is claimed or in the case of a selection patent: *Sanofi* at 77-78; *Shire* at para 76. In such case, not all the chemical's properties will inform its inventive concept, rather only those that provide the solution taught by the patent: *Shire* at para 76; *Atazanavir* at paras 74-75.

[170] As was acknowledged by PMS in oral argument, if the patent is a selection patent, the Court may have regard to the inventive concept and may look to the disclosure to nourish what it is about the species that is claimed that is selective over the genus. However, PMS asserts that the 400 Patent is not a selection patent and there is no advantage explicitly disclosed with respect to the crystalline monohydrate claimed in the 400 Patent.

[171] It argues in such a case where the inventive concept cannot be easily grasped, the comments of the FCA in *Ciba* at paragraphs 74-77 should apply and the inventive concept should be avoided:

> [74] The reminder in *Unilever* that it is inventive concept of the claim which is in issue, "not some generalised concept to be derived from the specification as a whole," is very apt: *Unilever* at page 569. Part of the difficulty in the search for the inventive concept is the use made, or to be made of the disclosure portion of the specification of the patent. In *Connor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] R.P.C. 28 (*Connor*), Lord Hoffman wrote at paragraph 19 that "[t]he patentee is entitled to have the question of obviousness determined by reference to his claim and to some vague paraphrase based upon the extent of his disclosure in the description."
>
> [75] This emphasis on the claims is consistent with section 28.3 of the Act which stipulates that it is "the subject-matter defined by a claim" which must not be obvious.
>
> [76] Lord Jacob was alive to the possibility that difficulties in the identification of the inventive concept could lead to "unnecessary satellite debate". His counsel was that "if a disagreement about the inventive concept of a claim starts getting too involved, the sensible way to proceed is to forget it and simply to work on the features of the claim": *Pozzoli* at paragraph 19. Lord Hoffman wrote, once again in *Connor* at paragraph 20, that the inventive concept "is a distraction almost as soon as there is an argument as to what it is."
>
> [77] There may be cases in which the inventive concept can be grasped without difficulty but it appears to me that because "inventive concept" remains undefined, the search for it has brought considerable confusion into the law of obviousness. That uncertainty can be reduced by simply avoiding the inventive concept altogether and pursuing the alternate course of construing the claim. Until such time as the Supreme Court is able to develop a workable definition of the inventive concept, that appears to me to be a more useful use of the parties' and the Federal Court's time than arguing about a distraction or engaging in an unnecessary satellite debate.

[172] The primary differences between the experts' views on the inventive concept is whether it should include the purported advantages of the DHP salt of sitagliptin crystalline monohydrate and whether the inventive concept should be considered on a claim-by-claim basis. As set out above, in my view, the 400 Patent can be viewed as a selection patent. All experts, including PMS' experts, recognized that the DHP salt of sitagliptin crystalline monohydrate purports to have enhanced chemical and physical properties.

[173] As stated by Dr. Elitzin (Elitzin Report, Ex 66, paras 67-68):

> ...the problem of the 400 Patent may be stated as a search for enhanced chemical and physical stability over the earlier sitagliptin disclosures in WO 03/004498 (free base and hydrochloride salt).
>
> ... The summary of the invention section states plainly what the authors of the patent believe the solution to these problems is, namely sitagliptin phosphate monohydrate.

[174] In my view, the inventive concept of claim 4 is the identification of the compound sitagliptin dihydrogenphosphate monohydrate with its enhanced chemical and physical properties over sitagliptin free base and the hydrochloride salt.

[175] This overall inventive concept of the 400 Patent underlies the inventive concept of the remaining dependent claims, where claim 24 is directed to a process for reliably making the compound of claim 4 and claims 19 and 20 claim processes that can make the non-stereospecific compound. Claim 22 is directed to the enhanced ability to formulate the crystalline monohydrate into a medicament, and claim 26 recognizes the therapeutic efficacy of the crystalline monohydrate to treat type 2 diabetes.

[176] I do not agree with PMS that it can be concluded upfront that the Court does not need to take a claim specific approach in its analysis. The approach will depend on the Court's findings with respect to claim 4. If I find that the compound of claim 4 is not obvious, then I agree that a process for making that compound and the use of the compound in a medicament or as a treatment would not be obvious. However, this same logic does not necessarily apply if I find that the compound is obvious. In that circumstance, the additional elements of claims 5-7, 19, 20, 22, 24 and 26 would need to be considered to determine if they impart their own inventiveness: Section 58, *Patent Act*, *Shire* at para 27.

E. *Differences between the State of the Art and the Inventive Concept of the Claims*

[177] Following from the analysis above, the differences between the state of the art and the inventive concept can be summarized as:

For Claim 4:

- identifying sitagliptin from amongst the other compounds disclosed within WO498 and the landscape of promising DPP-4 inhibitors, as a lead compound for further development;

- the choice to proceed with further salt screening and with polymorph screening;

- the formation and selection of the DHP salt of sitagliptin;

- the isolation of the crystalline monohydrate form of the DHP salt and the recognition of its enhanced chemical and physical properties for formulation over sitagliptin free base and the hydrochloride salt.

For Claims 5-7:

- the x-ray crystallographic characterization of the DHP salt of sitagliptin crystalline monohydrate

For Claim 19, 20 and 24:

- the identification of a reliable process for making the DHP salt of the crystalline monohydrate

For Claims 22 and 26:

- the recognition of the ability to use the DHP salt of the crystalline monohydrate in a pharmaceutical composition (claim 22) and in a therapeutically effective amount to treat type 2 diabetes (claim 26)

F. *Do the Differences Constitute Obvious Steps / Was it Obvious to Try*

[178] For an invention to be "obvious to try", the evidence must show, on a balance of probabilities, that it was more or less self-evident for the skilled person to try to obtain the invention. Mere possibility that something might turn up is not enough: *Sanofi* at para 66.

[179] The parties drew the Court's attention to three cases, which they asserted were factually relevant to the obvious to try analysis: *Pfizer Limited v Ratiopharm Inc*, 2010 FCA 204 [*Amlodipine*]; *Atazanavir*; and *Teva Canada Limited v Pfizer Canada Inc*, 2019 FCA 15 [*ODV*]. In two of the cases, *Amlodipine* and *Atazanavir*, the claims at issue dealt with a new salt and did not include claims to a crystalline form. Each of these cases turned on the issue of motivation, with the claims held obvious and the inventive concepts obvious to try.

[180] In *Amlodipine*, the patent at issue was a selection patent that claimed the besylate salt of amlodipine. The inventors started with the specific task of looking at amlodipine maleate to see if it could be made into a final formulation for regulatory approval. The evidence established that it was (and would be) quickly determined that there were problems with stability and stickiness and that routine salt testing would then be used. The Court agreed with the trial judge's factual finding that the skilled person "would be motivated to test sulphonic acid salts in general and would have every reason to test the besylate salt as this had already been shown to offer advantages over other salts in terms of stability" (at para 28).

[181] In *Atazanavir*, the claims of the second of two patents were to the bisulfate salt of atazanavir, and to a pharmaceutical dosage form comprising the bisulfate salt. In that case, the FCA identified the inventive concept of the second patent as "atazanavir bisulfate, a salt of atazanavir which is pharmaceutically acceptable because it has equal or better bioavailability than the atazanavir free base." It found there was no difference between the earlier patent, which claimed atazanavir and its pharmaceutically acceptable salts and atazanavir bisulfate, a salt that was pharmaceutically acceptable because of its bioavailability. The Court found that the skilled

person would have expected that a salt screen would likely identify at least one salt with improved pharmaceutical properties, specifically bioavailability, compared to the free base, with only routine work to characterize the salt's properties.

[182] In the third case, *ODV*, claims to a particular crystalline form of a particular salt of ODV (succinate salt) were held to be unobvious. In that case, the CGK included ODV as the active metabolite of venlafaxine, and ODV as a free base and fumarate salt. The prior art also disclosed ODV succinate as a potential salt, although there was some reason to believe that it might not work. The Court concluded that none of the prior case law, including *Amlodipine* and *Atazanavir*, supported a view that all salt screens and all polymorph screens were obvious to try or routine. Rather, each case had to turn on its own facts. On the evidence it found that the amount of experimentation required and the unpredictability of the outcome was high and rendered the solution taught not obvious to try. There was no finite number of predictable outcomes or number of potential experiments. The facts did not support a view that the PSA could predict that Form I ODV succinate existed, what properties it would have, or how it could be prepared, if at all.

[183] While these cases serve as useful illustrations of the application of the obvious to try analysis to cases involving new salt and polymorphic forms, I adopt the same approach as the Court in *ODV* that each proceeding must turn on its own facts, evidence and arguments. There is no overriding principle that all salt screens are obvious to try and matters of routine, or that polymorph identification will always be unobvious. None of these cases can be used to force a conclusion that is not supported by the facts and evidence, an analysis of which is set out below.

(1) Was it More or Less Self-evident that What was Being Tried Ought to Work

[184] There is no requirement to show that it is more or less self-evident that what is being tried ought to work; however, this factor remains as one of the factors to be considered in the obvious to try analysis: *Hospira Healthcare Corporation v The Kennedy Trust for Rheumatology Research,* 2020 FCA 30 [*Infliximab*] at para 90.

[185] As set out above, the PSA, as part of their CGK, would have been aware of accepted, automated methods for salt and polymorph screening that were expected to yield results. They would have known that salt form determines the physicochemical properties of the product, including its stability, solubility and dissolution rate, and would influence how the drug is absorbed, distributed, eliminated and excreted by the body (TT V1, P:74, L:10-22). While it would have been expected that salt forms could improve chemical and/or physical properties and the overall therapeutic and pharmaceutical effects of an API, it was also understood that the wrong salt form might affect the compound negatively (TT V2, P:124 L:18-P:125 L:22; TT V3, P:280 L:6-17). Each salt imparts unique properties to the parent compound (TT V2, P:167 L:21-27).

[186] It is undisputed that phosphoric acid is one of the preferred acids referenced in WO498 for possible salt formation with the basic compounds of the application. As agreed by the experts, phosphoric acid would have been one of the preferred acids that a PSA would include in a salt screening experiment with sitagliptin free base because of their differences in pK_a (i.e. the level of acidity of the acid).

[187] However, the experts disagreed as to whether it was possible to predict that the DHP salt would form. Dr. Elitzin stated that a PSA could predict with a high level of certainty whether a salt would form between an acid and a basic compound by looking at the pK_a. Dr. Wuest agreed that the PSA might expect a phosphate salt of sitagliptin to form, but stated that the possibility of isolating the salt as a solid, or a crystalline solid of particular stoichiometry, remained unpredictable. All experts agreed that it would not have been possible to predict whether a given salt would possess advantageous properties for formulation into a dosage form.

[188] There are, and were by 2003, very few phosphate salts marketed as commercial products. Between 1997 and 2001 only 1.7% of anions used in APIs of salts formed of basic entities were phosphate as compared to 46.6% for chloride (Elitzin Report, Ex 66, Schedule E-10, pages 6666-6667; Wuest Report, Ex 29, p. 36).

[189] From the CGK as stated in Stahl 2002, the PSA would be aware that phosphate salts had a high propensity to form hydrates. However, hydrates were also known to have low solubility, which was undesirable for formulation (TT V6, P:486 L:4-10). As explained by Dr. Davies this made the “high solubility” of the DHP salt of sitagliptin crystalline monohydrate so surprising and unpredictable.

[190] Whether a crystalline monohydrate could be isolated and reliably made, and found to provide advantageous chemical and physical properties, added unpredictability that was not disputed by any of the experts. As acknowledged by Dr. Elitzin, when running polymorphic screening experiments, there were a number of factors that could influence whether a crystalline

salt was found. Reading WO498, the PSA would have no way of knowing whether any of the compounds would form a hydrate. As of June 2003, WO498 proposed only a possibility that the DHP salt and crystalline monohydrate would form (TT V2, P:201 L:4-P:202 L:26). As accepted by Dr. Foley, it would not have been self-evident from WO498 that the crystalline monohydrate could be used as an active pharmaceutical ingredient (TT V1, P:77 L:11-23).

[191] PMS argues that there is no blanket proposition that in every case where a skilled person cannot predict the properties of a compound in advance of making it that this means that it will not be obvious to try to obtain the compound: *Atazanavir* at paras 19-20. I agree, each case will turn on its own facts.

[192] However, in this case, where a specific problem was not identified in WO498 or in the prior art, it is difficult to see how a course of action would have been obvious to try without there being known and expected advantages from taking further steps. Just because there were known methods does not mean that a person would necessarily apply them unless they were more or less self-evident to try: *Sanofi* at para 85; *Allergan Inc v Sandoz Canada Inc*, 2020 FC 1189 at para 193.

[193] As set out further below, it is my view that there was no motivation arising from WO498 or the prior art to take further steps with sitagliptin specifically, including by conducting a salt and polymorph screen. The PSA would not have been looking for or expecting the advantages obtained.

(2) Motivation

[194] Motivation examines whether the PSA had good reason to pursue the solution taught by the proposed invention: *AstraZeneca Canada Inc v Teva Canada Limited*, 2013 FC 246 at para 49. Merck argues that there was no motivation from WO498 and from the broader prior art to select sitagliptin as a lead compound and even if chosen, there was no motivation for the PSA to conduct a salt screen or to obtain the monohydrate. I address each of these assertions below.

(a) *Would WO498 motivate the PSA to proceed forward with sitagliptin*

[195] As set out above, the 400 Patent is a selection patent whose prior genus application (WO498) discloses a large class of compounds with some recognized utility, in this case, for treating type 2 diabetes. WO498 identifies 33 specific compounds in its examples that come within its scope, one of which is the compound now known as sitagliptin (example 7). As acknowledged by all of the experts, WO498 does not point directly or indirectly to sitagliptin as being a preferred compound of the compounds disclosed. Nor does it provide any data or scientific justification for selecting any of the compounds it discloses over any of the others as a lead compound.

[196] PMS highlights that only seven detailed examples exist within WO498 and of those seven examples only two (examples 6 and 7) resulted in the formation of a solid compound (the others are described as being either foamy solids or an oil). PMS argues that this would narrow the compounds of interest for the PSA to those of examples 6 and 7. However, there is no evidence to support this argument.

[197] Neither Dr. Elitzin nor Dr. Hollingsworth highlighted this language in examples 6 and 7. Instead Dr. Elitzin stated that there was no reason given in WO498 for exploring sitagliptin over any of the other compounds of WO498 (TT V2, P:115 L:6-9). Similarly, Dr. Hollingsworth agreed that none of the seven examples were singled out over any of the others (TT V3, P:275 L:17-P:276 L:9).

[198] When taken to the specific language of the examples, Dr. Wuest indicated that the PSA would not draw any meaningful distinction between the seven detailed examples and the rest of the examples given in WO498, and would not place any emphasis on the descriptor of the solid used within the examples. As stated by Dr. Wuest: “There are different ways of qualifying the word “solid” that a skilled person would recognize as being used in experimental procedures. ... The only thing that’s clear is that in this 498 application the material is described as a solid and the qualifier doesn’t necessarily add any significant information” (TT V6, P:476 L:22-P:478 L:20).

[199] Dr. Wuest’s evidence was that there was no information in WO498 that would lead the PSA to select sitagliptin or sitagliptin hydrochloride as the starting point to develop a DPP-4 inhibitor over the other exemplified compounds in WO498 (TT V6, P:472 L:14-20).

[200] Similarly, Dr. Davies’ evidence was that WO498 does not provide any data or other information in the examples to distinguish any compound as a stand-out from a formulation perspective (Davies Report, Ex 42, para 76).

[201] It was suggested by Dr. Roush that the skilled team would need to make all 33 example compounds in order to properly determine if any of the compounds were appropriate to be a lead compound for further development (Roush Report, Ex 50, para 95). Dr. Foley similarly acknowledged that the PSA would not know which, if any, of the compounds WO498 addresses could be selected as a lead compound from reading WO498 (TT V1, P:67 L:1-6).

[202] There is also no differentiation between the activity of any of the compounds of WO498. Rather, WO498 only includes the general statement that the compounds of the examples of WO498, of which sitagliptin is one, has activity in inhibiting DPP-4 "generally with an IC50 of less than about 1 μM." All experts agreed that the PSA would not know the activity of sitagliptin, or of any other specific compound disclosed within WO498, from this statement and would not know which compounds were more active than others (TT V1, P:63 L:15-22; Lewanczuk, Ex 55, at paras 131, 141; Roush Report, Ex 50, para 94). There were no reported *in vivo* studies involving the compounds of WO498 and no specific IC_{50} data on sitagliptin or on any other compounds disclosed in the application (TT V1, P:62 L:1-4).

[203] The evidence indicates that the PSA would not have any specific motivation arising from WO498 to focus on the particular crystalline form of a salt of sitagliptin over the other compounds disclosed within WO498.

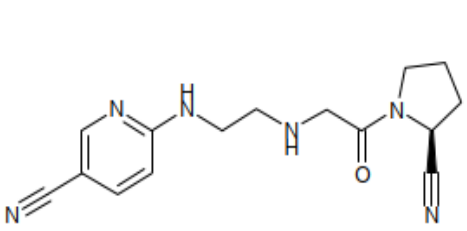
(b) *Did the prior art teach away from proceeding with sitagliptin*

[204] Merck further argues that the PSA would not have motivation from the broader prior art to focus on sitagliptin. To the contrary, it asserts that the prior art on P32/98, DPP-728 and

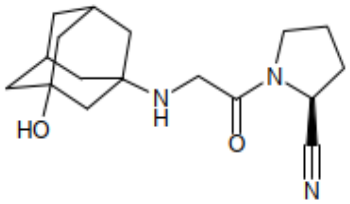
LAF237 “taught away” from using sitagliptin as a lead compound for further development. The evidence in support of this contention is set out in the expert report of Dr. Roush who conducted a literature search on what would have been known about DPP-4 inhibitors and sitagliptin as of June 2003.

[205] Dr. Roush’s evidence was that, to the extent not already known, the PSA would have quickly come across publications reporting on P32/98 and DPP-728, including that these compounds had already undergone testing in human trials, with promising results (Roush Report, Ex 50, para 36). He asserted that these compounds would have likely formed the starting point for the PSA’s work.

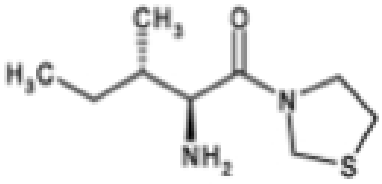
[206] As explained by Dr. Roush, P32/98, DPP-728 and LAF237 (depicted below with sitagliptin) had distinct chemical structures from sitagliptin that would have been strongly favoured. In particular, DPP-728 and LAF237 included a cyanopyrrolidine functional group (5-membered ring with a nitrogen bound to the carbon chain) and P32/98 a thiazolidine group (5-membered ring with one sulfur and one nitrogen atom) that were known to bind well to DPP-4, while maintaining the overall stability of the compound. Both of these functional groups were believed to contribute to the inhibitory activity of the compound (Roush Report, Ex 50, para 114-127).



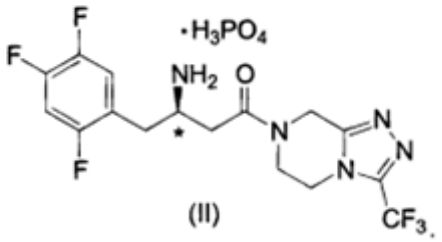
12 NVP-DPP728



13 NVP-LAF237



P32/98



Sitagliptin

[207] This evidence from Dr. Roush is not challenged by PMS. Rather, PMS argues that it is not relevant to the analysis on obviousness. PMS asserts that the choice of sitagliptin as the starting point does not form part of the inventive concept. It contends that the inventive concept is narrower, focussing only on the phosphate salt of sitagliptin in crystalline monohydrate form.

[208] As set out above, the 400 Patent teaches that prior art relating to P32/98, DPP-728 and LAF-237 is relevant background to the 400 Patent. It also teaches that the disclosure of sitagliptin and its hydrochloride salt arises from the prior genus application WO498, which includes other compounds.

[209] Prior art that teaches away from a purported invention is a relevant consideration for obviousness: *Bayer AG v Apotex Inc*, 2003 FC 1199 at paras 78-79. The question is whether the conventional wisdom in the industry at the relevant time or the prior art discouraged the PSA from exploring a particular solution: *Bauer Hockey Ltd v Sport Maska Inc (CCM Hockey)*, 2020 FC 624 at para 149.

[210] In June 2003, the only publication on sitagliptin was WO498. There was no indication as to its activity, efficacy, toxicity or tolerability. Further, the general level of potency reported in

WO498 indicated a level of potency that was 45 to 167 times less than the IC_{50} values of 0.022 µM, 0.007 µM and 0.006 µM published for DPP-728 (Roush Report, Ex 50, para 94).

[211] As acknowledged by Dr. Foley, a PSA considering a potential DPP-4 inhibitor compound would want to see what happened in animal models (TT V1, P:59 L:12-24). At June 2003, the PSA didn't know whether sitagliptin would actually work to treat type 2 diabetes in patients as there was no data to allow for that determination (TT V1, P:56 L:17-27; P:67 L:18-P:68 L:1; P:69 L:3-8).

[212] There is no evidence that the PSA would be drawn to sitagliptin as a starting point for further development. On the basis of the prior art, it cannot be concluded that there was motivation for anyone other than Merck to move forward with sitagliptin as a lead compound.

(c) *Was there motivation to try to make the phosphate salt and isolate the monohydrate*

[213] As stated above, I accept as CGK that if the PSA were looking to develop a compound they would first look to the compound in free base form.

[214] WO498 does not identify any problem with sitagliptin as a free base or hydrochloride salt. While the PSA would know that the general activity level cited in the 400 Patent – i.e., an IC_{50} of less than 1 µM – is not an activity level of high potency, all experts agreed that this general statement does not reflect the potency of any particular compound of the patent. Rather, it suggests that some compounds may be more active than others. WO498 provides no express

statement that improved activity should be targeted by further salt screening, nor does it suggest that any chemical or physical properties could be improved with another salt form.

[215] PMS argues that the PSA would know from the chemical structure of the free base that it is susceptible to degradation and that salt formation would improve its formulation properties. It relies on the following passage from Dr. Wuest's cross-examination (TT V6, P:521 L:1-16) as well as on Merck's internal findings:

> A. I think that the skilled person reading the 400 patent would be capable because of training in organic chemistry to look at the sitagliptin structure and recognize that that particular molecule has chemical vulnerability. It contains parts that are susceptible to different types of chemistry reactions. We've talked about acid-base reactions, but there are other reactions that are possible; one being hydrolysis of the amide link, another would be deamination, another would be of sensitivity to the fluorinated aromatic ring to different types of substitutions and so on and so forth. So the potential for degradation would be something that a skilled person would recognize.
>
> Q. And I take it you would have the same opinion in respect of sitagliptin hydrochloride?
>
> A. Yes, that's a possibility too.

[216] However, the comments of Dr. Wuest do not apply restrictively to the free base form. Rather, they apply to both the free base and to the hydrochloride salt. Dr. Wuest was not questioned on whether any susceptibility to degradation would be different with another salt and if so, why. There is no basis from this testimony to conclude that the PSA would be led to the conclusion PMS proposes.

[217] The evidence filed through the Vincent Affidavit was that as of 2021 at least one other generic had developed a hydrochloride salt of sitagliptin for commercial purposes (Vincent Affidavit, Ex 7).

[218] PMS's further reliance on Merck's internal findings does not assist as it imparts a level of hindsight. While it is true that the inventors understood from their own analyses and work on the compound L-221869 that degradation of the free base and hydrochloride salt was an issue, there is no basis to suggest on the information that was available to the PSA that the PSA would be able to arrive at this same conclusion without conducting some analytical work as Merck had to do. Without the information that was privy to Merck, the PSA would not be motivated to conduct a broader salt screen at the outset. The PSA might eventually get to the same point as Merck did in their analyses; however, there is insufficient evidence to suggest how readily this would happen or if it would happen at all.

[219] I agree with PMS that if there was motivation to pursue sitagliptin and to pursue a further salt form such as the phosphate salt, there would similarly be motivation to isolate the most stable polymorphic form as required by regulatory guidelines. However, the PSA would need to be motivated to take all of those other steps before it would engage in this exercise. In my view, the PSA would not be motivated to get there from WO498, the CGK and the prior art.

(3) Extent Nature and Amount of Effort Required to Achieve the Purported Invention

[220] The PSA need not be able to conduct the same experiments that the inventors did to reach the claimed invention (*Infliximab* at para 94), nonetheless the actual course of conduct of the

inventors sheds light on the amount of effort that is required to reach the claimed invention and whether it was obvious to try: *Janssen v Teva Canada Ltd*, 2020 FC 593 at para 205. This is particularly so where the knowledge of such inventors is no lower than what would be expected of the skilled person: *Sanofi* at para 70. As stated at paragraph 71 of *Sanofi*:

> ...if the inventor and his or her team reached the invention quickly, easily, directly and relatively inexpensively, in light of the prior art and common general knowledge, that may be evidence supporting a finding of obviousness, unless the level at which they worked and their knowledge base was above what should be attributed to the skilled person. Their course of conduct would suggest that a skilled person, using his/her common general knowledge and the prior art, would have acted similarly and come up with the same result. On the other hand, if time, money and effort was expended in research looking for the result of the invention ultimately provided before the inventor turned or was instructed to turn to search for the invention, including what turned out to be fruitless "wild goose chases", that evidence may support a finding of non-obviousness. It would suggest that the skilled person, using his/her common general knowledge and the prior art, would have done no better. Indeed, where those involved including the inventor and his or her team were highly skilled in the particular technology involved, the evidence may suggest that the skilled person would have done a lot worse and would not likely have managed to find the invention. It would not have been obvious to him/her to try the course that led to the invention.

[221] In this case, the inventors' course of conduct was introduced through Merck's documents and Dr. Wenslow's testimony. As set out above, portions of Dr. Wenslow's affidavit and oral testimony were objected to by PMS for admissibility. My disposition on those objections is set out in the attached Appendix. The summary that follows overviews the invention story as derived predominantly from the documents that have been admitted for the truth of their contents, as supplemented by the admissible aspects of Dr. Wenslow's testimony, and from the discovery read-ins.

(a) *The Inventors' Course of Conduct*

[222] Merck began its work on DPP-4 inhibitors in the middle of 1999. At that time, Novartis already had a compound in clinical development and Merck decided to "jump start" their program by in-licensing the Probiodrug compound P32/98 (PMS Read-ins, Ex 65, A9). Merck also synthesized LAF-237 and measured its DPP-4 activity to determine its enzyme selectivity (PMS Read-ins, Ex 65, B4).

[223] Merck first made sitagliptin free base on June 20, 2001. The priority application for WO498 was filed two weeks later, on July 6, 2001. It is unclear how many compounds from WO498 Merck studied and tested before deciding to proceed forward with sitagliptin. Studies on at least one of the compounds L-221869 (example 6 of WO498) preceded sitagliptin and was reported in the documents filed by Merck. An internal memorandum dated April 9, 2002 indicated that sitagliptin had "an improved in vitro profile over the Probiodrug compound P32/98 (L-000826), previously in development, and its backup, L-221869" (Wenslow Affidavit, Ex 17, Exhibit J, section 2).

[224] In December 2001, Merck scientist Leigh Shultz reported that the crystalline free base L-221869 showed significant degradation in bulk as compared to the amorphous fumarate salt. As such, the free base was eliminated as a development candidate in favor of a crystalline salt form. The hydrochloride salt of L-221869 was also eliminated due to its hygroscopicity, and its propensity to hydrate reversibly. Early stability data on tartrate and besylate salt forms appeared promising.

[225] In and around the same time, in December 2001, Leigh Shultz, separately concluded that the free base form of sitagliptin was not suitable for development due to degradation in bulk after conducting physical and chemical stability studies, including on hygroscopicity. Based on the solubility data for the structurally similar compound L-221869, crystalline salts of sitagliptin were expected to have improved solubility over the free base, without affecting bioavailability. It was recommended that identifying an acceptable crystalline salt form be made a priority.

[226] On December 12, 2001, Merck conducted an acid salt screen on the sitagliptin free base using a 96-well plate assay incorporating 11 standard acid stock solutions. The assay was conducted by a junior scientist Vicky Vydra that had joined Merck only months before. I agree with PMS that the experiment conducted was a "rote task" using a standard procedure that could be applied readily.

[227] Four potential crystalline salts were detected from the experiment, following XRPD analysis: phosphate, sulfate, tartrate, and besylate. In January 2002, an internal memorandum reported that the besylate and tartrate salts would likely be pursued first, while noting that the tartrate salt was also being developed in the ongoing work on L-221869. Crystalline sitagliptin hydrochloride salt was also separately made, but was given less priority based on the experience with L-221869.

[228] By March 2002, three potential salts had been identified as promising – the besylate, tartrate and phosphate salts. Merck decided to proceed with the phosphate salt because of the flake-like morphology of the salt, which was believed to impart preferred formulation properties.

The decision was reported in a memorandum dated April 9, 2002, which reported on the physical characterization of the salt, its stability data, and its biopharmaceutical and mechanical properties. The memorandum indicated that at that time, it existed as “a single anhydrous polymorph”.

[229] In March 2002, the DHP salt of sitagliptin was formulated into tablets and used for clinical studies.

[230] In February 2002, the DPP-4 project team also began a polymorph study of the DHP salt. This was a multi-disciplinary team effort that involved the active participation of numerous scientists from several working groups. Merck understood that they were behind Novartis and others in the development timeline and took an “all hands on deck” approach. Dr. Wenslow estimated that the DPP-IV team conducted “over 1,000 polymorph experiments on the 1:1 DHP salt by exposing it to a vast array of different solvents, and reaction conditions”. He described this work in his affidavit as “challenging” because the polymorphs “exhibited very similar energies”. As a result, the analytical tools had difficulty distinguishing between the polymorphs.

[231] The initial polymorph screening work was conducted by scientist Chris Lindemann and included multiple crystallizations in a variety of solvents, including water. The results reported in May 2002, indicated a single anhydrous crystal phase as well as a potentially amorphous material that recrystallized to what was believed to be a hydrate and was later, in 2003, determined to be another anhydrous form.

[232] During 2002, two high throughput polymorph screens were conducted searching for possible polymorphs, each involving a variety of solvents, including water, in 96-well screens, followed by evaluation of the results by the Physical Measurements Group. This screening was described by Dr. Wenslow as being “atypical” and reflective of the significant investment Merck had made in the project.

[233] In addition to these high throughput screens, Dr. Wenslow referred to extensive additional testing to investigate the impact of different solvents conducted along with characterization of the crystal structure, using a variety of techniques, including XRPD, NMR, and Raman spectroscopy. On any given day, Dr. Wenslow described 10-15 members of the DPP-IV project team conducting or analysing polymorph experiments.

[234] By the end of 2002, a significant volume of solid state characterization data had amassed, suggesting a complex system of “four unique forms”, including a solvated form with ethanol and a form thought to be a hydrate (Type A). The DPP-IV team was able to isolate Type A in January 2003, and determined it to be another anhydrous polymorph.

[235] By January 2003, Merck had identified at least three primary anhydrous polymorphs, some of which interconverted under manufacturing conditions in the presence of solvent. Mixtures of different crystal forms were appearing in batches for use in the clinic and had to be controlled for clinical studies.

[236] Merck conducted a solvent screen to find a non-solvating solvent that could control the interconversion of its Form I anhydrous form. As explained by Dr. Wenslow "[t]o try and find different conditions to prepare a single crystalline form of pure anhydrous 1:1 DHP salt, our team surprisingly and unexpectedly discovered a completely novel crystalline monohydrate form in March 2003". On March 26, 2003, an experiment conducted by Stephen Cypes in isoamyl alcohol [IAA]/water (95/5%) yielded for the first time the crystalline monohydrate, which was confirmed by XRPD. Shortly after, another scientist, Dina Zhang, also prepared the monohydrate in a different lab using the same type of slurry experiment (Elitzin Report, Ex 66, paras 202, 215(a); Ex 4, F-17).

[237] Dr. Wenslow described the preparation of the monohydrate as a "serendipitous discovery that resulted in drastic and profound changes for Merck and the DPP-IV team." Through further research, Merck was able to develop conditions that could prepare the anhydrous forms as well as the crystalline monohydrate by controlling the reaction conditions and the water activity. At the same time, Merck, characterized the monohydrate's physical properties and behaviour in formulations. Merck concluded overall that the monohydrate displayed improved physical and chemical stability over the anhydrous forms, primarily as it did not exhibit form conversion upon compaction. The monohydrate also exhibited some improved sticking characteristics over the anhydrous forms.

[238] The long-term decision to proceed forward with the monohydrate over the mixture of anhydrous forms took place the week of May 12, 2003. While this did not mean that work

stopped on the mixture of anhydrous forms, the monohydrate became the priority and the anhydrous mixture took on a secondary role.

[239] As explained by Dr. Wenslow:

> 7. Quite fortuitously, the monohydrate's physical stability, chemical stability, and its improved pharmaceutical processability (notably, reduced stickiness) led the DPP-IV project team to select the monohydrate over the anhydrous forms for further development. We were very fortunate to discover that the crystalline monohydrate was bioequivalent with the previous anhydrous form used for Phase I and Phase II clinical trials because of its unexpectedly high solubility. This was a "game changer" for Merck. The monohydrate was not only superior to the anhydrous forms, but it was also a suitable replacement for Merck's upcoming Phase IIB trials.

[240] Dr. Elitzin asserts that Merck should have arrived at the monohydrate sooner, but did not take steps to characterize the hydrate form they saw initially in 2002, choosing instead to chase the anhydrous form and trying to exclude water. However, I do not view the experimentation in this way. Until Type A was isolated and confirmed to be an anhydrous form, Merck was of the view that it had a hydrate as one of its forms. Its initial screening included water as part of the solvent system.

[241] I interpret the work conducted by Merck as establishing that the journey to the monohydrate was not straight-forward or predictable.

[242] A further issue is how to put in context the timing taken to obtain the DHP salt and crystalline monohydrate form, in the face of an overall accelerated timeline for obtaining a final product that could be used in Phase II clinical trials.

[243] The evidence establishes that Merck had to leap-frog Novartis who was well ahead of Merck in the race to market a DPP-4 inhibitor. This required Merck to compress the amount of time typically taken to move to the clinic from 21 months to 6 months by conducting preformulation biopharmaceutical studies simultaneously with Phase I formulation development, overlapping Phase I formulation development with Phase I formulation development, and shortening the timing of steps. As described by Dr. Foley, this required both resource investment and taking on risks that steps might be missed and experiments might need to be repeated if unexpected results were received.

[244] In this case, Merck benefited from its experience with L-221869 and was able to accelerate the steps involved in its salt screening process, which involved the application of otherwise routine processes. Similarly, once the monohydrate was reliably formed and was determined to have a bioavailability profile similar to the anhydrous form, Merck was able to accelerate clinical testing by relying on its Phase I studies conducted with the anhydrous compound.

[245] From my review of the work completed, I do not consider the accelerated timeline to suggest that the monohydrate was arrived at readily or easily. Rather, the evidence indicates that the multi-disciplinary team took over a year to find the monohydrate and only found it by chance. While the route to the DHP salt was straightforward, a significant amount of work and effort was involved in arriving at the crystalline monohydrate without predictable results. The path of the inventors does not support an obviousness finding.

(4) Secondary Factors

[246] While not part of the obvious to try analysis, secondary factors have also been recognized as being relevant to the obviousness analysis.

[247] As set out earlier, JANUVIA® was the first DPP-4 inhibitor to come to market. Dr. Lewanczuk described JANUVIA® as a practice changing drug that satisfied an unmet need by being able to lower blood glucose when it was high but do nothing when it was normal, thereby avoiding hypoglycemia and other side effects typical of type 2 diabetes (TT V8, P: 734 L:15-P:735 L:6).

[248] While I do not consider this evidence as dispositive, in my view it further supports the inventiveness of identifying the DHP salt of sitagliptin in crystalline monohydrate form, with its advantageous properties, as becoming the medicine in JANUVIA®.

G. *Conclusion on Obviousness of the Asserted Claims*

[249] On the basis of the analysis above, it is my view that there was insufficient motivation to try to obtain the compound of claim 4 and that the work and effort required to obtain the crystalline monohydrate was extensive and not predicable. The compound, and a process for making it, would not have been self-evident to explore or arrive at, nor would its suitability for making medicaments or its capability of being used as a therapeutic. For all these reasons, I find that the Asserted Claims are not obvious.

[250] I note that while I have not considered each of the dependent claims separately, as I have found that claim 4 of the 400 Patent is not obvious and each of claims 5-7, 19, 20, 22, 24 and 26 depend on the compound of claim 4, or include it within its scope, it is also, as set out in the preceding paragraph, my view that these dependent claims are not obvious too.

VI. Insufficiency

[251] Pursuant to subsections 27(3)(a) and (b) of the *Patent Act*, the specification of an invention must:

Specification	**Mémoire descriptif**
(3) The specification of an invention must	**(3)** Le mémoire descriptif doit :
(a) correctly and fully describe the invention and its operation or use as contemplated by the inventor;	**a)** décrire d'une façon exacte et complète l'invention et son application ou exploitation, telles que les a conçues son inventeur;
(b) set out clearly the various steps in a process, or the method of constructing, making, compounding or using a machine, manufacture or composition of matter, in such full, clear, concise and exact terms as to enable any person skilled in the art or science to which it pertains, or with which it is most closely connected, to make, construct, compound or use it;	**b)** exposer clairement les diverses phases d'un procédé, ou le mode de construction, de confection, de composition ou d'utilisation d'une machine, d'un objet manufacturé ou d'un composé de matières, dans des termes complets, clairs, concis et exacts qui permettent à toute personne versée dans l'art ou la science dont relève l'invention, ou dans l'art ou la science qui s'en rapproche le plus, de confectionner, construire,

composer ou utiliser
l'invention;

[252] The skilled person must be able to produce the invention using only the instructions contained within the disclosure and the skilled person's common general knowledge: *Teva v Pfizer*, 2012 SCC 60 [*Teva*] at para 50, 70-71; *Teva Canada Ltd v Leo Pharma Inc*, 2017 FCA 50 [*Leo Pharma*] at para 43-44. A disclosure is insufficient if it necessitates the working out of a problem: *Idenix Pharmaceuticals Inc v Gilead Pharmasset LLC*, 2017 FCA 161 [*Idenix*] at para 19. The disclosure must teach the skilled person how to put all embodiments of the invention into practice, without the need for exercising inventive ingenuity or undue experimentation, although some non-inventive trial and error experimentation may be required: *Seedlings Life Science Ventures LLC v Pfizer Canada ULC*, 2021 FCA 154 at para 68; *Leo Pharma* at para 59.

[253] The party challenging the sufficiency of the patent (here, PMS) bears the burden of proof: *Whirlpool Corp v Camco Inc*, 2000 SCC 67 at para 75. Sufficiency is a question of fact (*Leo Pharma* at para 44), to be determined as of the date the application was filed; in this case, June 18, 2004: *Teva* at para 90. PMS must establish by way of evidence, on a balance of probabilities, that the patent is insufficient as of that date: *Merck Sharp & Dohme Corp v Wyeth LLC*, 2021 FC 317 at para 135.

[254] As a preliminary matter, I note that in oral argument PMS asserted that the filing date of the 400 Patent was in 2003. However, June 24, 2003 refers to the claim date of the 400 Patent,

not its filing date. The filing date as identified on the face of the 400 Patent is its PCT filing date of June 18, 2004.

[255] As confirmed in oral submissions, PMS' only argument on the issue of insufficiency is whether the process details disclosed in the 400 Patent for making the crystalline monohydrate are sufficient. Despite evidence led on the *d*-spacings relating to claims 5-7, it does not advance any further arguments on a claim specific basis.

[256] The 400 Patent provides both general and specific methods for preparing the crystalline monohydrate. The general methods are set out at pages 7 and 8 of the patent and provide seven methods for crystallizing the monohydrate of the non-stereospecific DHP salt of structural formula I. The general methods refer to several different processing conditions, including using ethanol/water at 25ºC, with crystallization at a water concentration of 31 wt% (method A); isoamyl alcohol [IAA]/water at 25ºC, 40ºC and 60ºC, with crystallization at a water concentration of 2.9 wt%, 3.6 wt% and 4.5 wt% (methods B, C and D, respectively); and isopropyl alcohol [IPA]/water at 25ºC, 40ºC and 75ºC, with crystallization at a water concentration of 7.0 wt%, 8.1 wt% and 20 wt% (methods E, F and G, respectively). Each of the methods requires the further steps of "recovering the resultant solid phase" and "removing the solvent therefrom".

[257] A more detailed method for making the crystalline monohydrate of the DHP salt of sitagliptin (the *R*-enantiomer depicted as structural formula II) is set out at page 15 of the 400 Patent. This process describes preparation of the crystalline monohydrate using an IPA/water

solvent system and involves first preparing the DHP salt from the free base of sitagliptin and phosphoric acid.

[258] As admitted by Dr. Hollingsworth, if the PSA had the 400 Patent and wanted to make the crystalline monohydrate of the DHP salt of sitagliptin, a logical method to follow would be the detailed method at page 15 of the 400 Patent (TT V3, P:305 L:26-P:306 L:8; P:308 L:15-23). Dr. Elitzin acknowledged that the PSA would have no difficulty in understanding or following the instructions given at page 15 (TT V2, P:219 L:17-23; TT V2, Conf, P:20 L:15-20).

[259] In its written argument, PMS advanced an argument that the PSA would not be able to produce the crystalline monohydrate because the 400 Patent does not teach the nucleation step that was necessary for Stephen Cypes to make the monohydrate in March of 2003, and the PSA would not have the seed crystals of monohydrate necessary to coax the crystallization of the monohydrate out of solution.

[260] In oral argument, PMS indicated that it was not relying on its seeding theory. Rather, it asserted that this had only been raised in rebuttal to Merck's evidence and the expectation of arguments that Merck might raise. Instead, PMS indicated that its sufficiency argument was based on Merck's failure to make the monohydrate in 2002 using what it asserts were similar methods; its further failure to make the monohydrate for a period of time after the Cypes experiment in March 2003; and the purported insufficient details in the 400 Patent. PMS argues that the disclosure does not direct the PSA to the critical conditions required for the initial nucleation step and as such, the PSA would not be able to make the monohydrate. PMS argues

there is nothing in the 400 Patent that would alert the PSA to the pitfalls Merck faced or how to escape them.

[261] Merck asserts that PMS' argument is speculative. It asserts that the experiments Merck conducted in 2002 and in April 2003 were not the same as the methods set out in the 400 Patent. Further, Merck contends that these experiments are of no moment as Merck was able to reliably make the crystalline monohydrate after April 2003 following the conditions set out in the patent. Merck asserts that there is no evidence to suggest that the crystalline monohydrate would not be made by the methods set out in the 400 Patent, if followed by the PSA at the filing date.

[262] Dr. Elitzin considered the experiments conducted in 2002 to be similar in nature to the experiments that yielded the monohydrate in 2003. He opined that the reason that the experiments in 2002 did not yield the monohydrate could be because of contamination within the experiment or because some parameter of the experiment did not allow for formation of the monohydrate (Elitzin Report, Ex 66, para 202). Dr. Elitzin acknowledged that there were some differences between the 2002 experiments and those that led to the monohydrate in 2003 and that could explain why the same results were not achieved (Elitzin Report, Ex 66, para 204). He could not identify from looking at the inconsistencies what was missing from the 2002 experiments to explain why the monohydrate was not formed (TT V2, P:211 L24-P:212 L:20).

[263] Dr. Wenslow explained that the critical step that took place on March 26, 2003 was the initial nucleation event for the monohydrate (Wenslow Affidavit, Ex 17, para 91; TT V4, Conf, P:126 L:5-20). He explained that Merck still does not fully understand why the solvent system

and conditions used by Stephen Cypes triggered the nucleation for the first time (Wenslow Affidavit, Ex 17, para 63).

[264] PMS argues that the PSA needs to be told how they can avoid the problems that befell Merck. There is no dispute that certain details of the Cypes experiment are not disclosed in the 400 Patent. However, PMS has not shown that any of the additional details from the Cypes experiment that are not in the 400 Patent are necessary to make the crystalline monohydrate.

[265] As noted by Dr. Wenslow (Wenslow Affidavit, Ex 17, paras 74, 76):

> 74 ... following the appearance of the crystalline monohydrate, processes we had previously employed that never made the monohydrate, now reliabl[y] did. Specifically, after its first creation (nucleation), slurrying the 1:1 DHP salt in water would reliably result in the formation of the crystalline monohydrate. This was unexpected because, prior to the initial creation of the crystalline monohydrate (i.e., the first nucleation event), such slurr[y]ing experiments only yielded anhydrous 1:1 DHP salt forms.
>
> ...
>
> 76. ...It seems the crystalline monohydrate was extremely difficult to nucleate. But once this happened for the very first time, there [was] no problem making this crystal grow using the process of claim 24. We determined this scientifically by measuring the solubility of each form at various conditions, and then prepared "Van't Hoff'plots, which show the inflection point as to when the monohydrate crystallizes out. For example, in the case of isopropyl alcohol and 25^{o}C (i.e. the conditions of claim 24 of the 400 Patent), we determined through our experimentation that as long as the water concentration was higher than 6.8%, the crystalline monohydrate could be prepared. ...

[266] There is a live debate between the parties as to whether there are any experiments conducted by Merck subsequent to March 26, 2003 that followed the process of the 400 Patent and did not make the crystalline monohydrate.

[267] Drs. Elitzin and Hollingsworth pointed to two experiments conducted in April 2003 by Dr. Hansen, after the crystalline monohydrate was formed by Stephen Cypes, that used IAA/water but did not make the monohydrate. In each of these experiments, the solvent was removed from the compounds by drying the compounds in an oven. In one of the experiments, the temperature at drying was 70ºC and the other was at 45ºC under nitrogen flow. On cross-examination, Drs. Elitzin and Hollingsworth were taken to page 18 of the 400 Patent, which states that the crystalline monohydrate converts to a dehydrated monohydrate if heated above 40ºC under very dry nitrogen flow. It was acknowledged by Dr. Hollingsworth that in view of this teaching, the PSA would not heat a sample above 40ºC under dry nitrogen flow if they wanted to make the crystalline monohydrate (TT V3, P:311 L:16-P:312 L:3).

[268] Merck argues that the April 2003 experiments accordingly cannot be considered to follow the protocol of the patent. They assert that the differences in drying method and temperature explain why the monohydrate did not form.

[269] At trial, Dr. Wenslow sought to introduce evidence that the Hansen experiments from April 2003 did not produce the monohydrate because they were not complete. However, I have held these comments cannot be accepted on the basis of hearsay as there are no contemporaneous documents to support these facts.

[270] PMS asserts that an adverse inference should be drawn because neither Mr. Hansen nor Mr. Cypes, both of whom are inventors on the 400 Patent, appeared at the trial to provide testimony about the 2003 experiments. As noted above, some explanation for this may be because of the agreement between the parties entered into in advance of discovery that Dr. Wenslow would be the sole inventor examined for discovery and the sole inventor to appear at trial. There was no evidence indicating that PMS was dissatisfied with Dr. Wenslow's testimony on the inventorship issues on discovery. There would be no basis for Merck to anticipate that an objection would be raised for the trial. While I agree that Dr. Hansen's testimony would have assisted with understanding these 2003 experiments, nothing turns on the details of these experiments.

[271] Indeed, irrespective of whether the experiments conducted in April 2003 produced the monohydrate, PMS has not identified any evidence to suggest that after April 2003, and as of the filing date of the 400 Patent, which was over one year thereafter, the crystalline monohydrate could not be made following the methods set out in the patent. Dr. Elitzin acknowledged in cross-examination that he had found no examples of any of the general methods at pages 7 and 8 of the 400 Patent (methods A-G) being followed after April 2003 that did not produce the monohydrate (TT V2, Conf, P:29 L:8-P:30 L:8). Similarly, Dr. Elitzin acknowledged in cross-examination that there were no examples of Merck having performed the detailed method set out at page 15 of the patent after April 2003 and producing a product other than the monohydrate (TT V2, Conf, P:30 L:9-17).

[272] Even if seeding were to be considered as a possible explanation for Merck's reliable production of the crystalline monohydrate after April 2003, it is undisputed that in three of four experiments that were run by Merck after April 2003, following the method set out in the 400 Patent, no seed crystals were used and crystalline monohydrate was still made (Wenslow Affidavit, Ex 17, para 92; Elitzin Report, Ex 4, F44, pp. MRK21629, 32, 36, MRK21646, 49, 52 and MRK21708, 10, 14; TT V4, Conf, P:121 L:21-P:122 L:18).

[273] Crystalline monohydrate was also made by Dina Zhang outside the laboratory where Stephen Cypes conducted his experiment, making it further unlikely that this could be explained by unintentional seeding through contamination of the equipment in the laboratory with the monohydrate (Dunitz, Ex 9, p. 194). While Dina Zhang's notebook was not produced in the action, the success of her experiment was reported in several documents, accepted by PMS for the truth of their contents and was accepted by Dr. Elitzin in his analysis (TT V2, Conf, P:15 L:1-5).

[274] As noted by Merck, it is not necessary for an inventor to provide a theory of why the invention works to support the sufficiency of the patent: *Valeant Canada LP/Valeant Canada SEC v Generic Partners Canada Inc*, 2019 FC 253 at para 115; *Eurocopter* at para 150.

[275] As highlighted by Merck, there is no evidence that the methods of the 400 Patent would not produce the crystalline monohydrate if followed by a skilled person. Indeed, Dr. Elitzin admits that he does not know what the outcome would be if the PSA were to try to make the crystalline monohydrate without seed crystals (TT V2, P:220 L:10-17).

[276] Merck argues that PMS' experts should have done their own experiments to show that the disclosure was not sufficient but chose, to their detriment, not to introduce any such testing. Both Dr. Elitzin and Dr. Hollingsworth confirmed that they could have followed the methods had they chosen to do so (TT V2, P:222 L:2-10; TT V3, Conf, P:70 L:27-P:71 L:2). PMS relies on the comments made by the FCA in *Idenix* to suggest that current tests cannot be used to inform the issue. In *Idenix*, the issue of sufficiency turned on whether the skilled person would be able to synthesize the claimed compound when one of the steps in the synthesis (fluorination) was not taught by the patent. The plaintiff sought to rely on evidence that showed, after the filing date, that all three possible synthetic pathways that worked could have been chosen by the skilled person. However, the FCA found these results benefited from hindsight. They were not relevant to the issue of sufficiency as they did not reflect the knowledge of the skilled person at the relevant date. I do not read this case, however, as suggesting the opposite to be true. If the PSA could not make the crystalline monohydrate in 2022 following the instructions of the patent, there would be no basis to suggest that the PSA could have made the crystalline monohydrate with those same instructions, and without the benefit of hindsight, at the filing date in 2004.

[277] Without some evidence that any early difficulties at Merck would behold the PSA, there is no basis to conclude that the PSA would not have been able to make the crystalline monohydrate at the filing date following the methods set out in in the 400 Patent. There is similarly no basis to conclude that the public would not be able to make the same successful use of the teachings of the patent when it expires in 2024. PMS' burden has not been met.

[278] I accordingly cannot conclude that the 400 Patent is invalid for insufficiency.

VII. Conclusion

[279] For the reasons set out above, the Asserted Claims of the 400 Patent are not invalid for either obviousness or insufficiency and judgment in favour of Merck shall accordingly issue.

VIII. Costs

[280] Despite the Court's request, the parties did not provide any substantive submissions as to directions for costs. However, they did agree that a lump sum award of costs would be appropriate for the successful party, provided that the party was able to support the quantum claimed.

[281] The Court will accordingly provide a schedule for cost submissions based on a lump sum award as part of its Judgment.

APPENDIX

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
1.	17. **After sitagliptin was found to have biological activity, the DPP-IV project team initially studied the free base of sitagliptin for potential development.** The team's work is recorded in a memorandum from December 2001 entitled "Preliminary Pharmaceutical Assessment of L-224715" authored by Dr. Shultz. As the memorandum indicates, the DPP-IV project team conducted numerous analyses to assess the free base's suitability for further development as a drug candidate, including its physical and chemical stability, as well as hygroscopicity. This research unfortunately revealed an unexpected degradation problem with the free base that was previously unknown. **In light of this finding, the DPP-IV project team determined sitagliptin free base was unsuitable for further development and made finding a suitable salt form for sitagliptin a priority.**	**1. TT V4, Conf, P:84 L:17-20** **2. TT V4, Conf, P:84 L:26-P:85 L:1** **3. TT V4, Conf, P:85 L:2-6** **4. TT V4, Conf, P:85 L:23-P:86 L:14** **8. TT V4, Conf, P:88 L:19-24**	Hearsay, Opinion, Rules 232 and 248, Beyond the Pleadings	Objections to para 17 dismissed as the statements arise from the memorandum which has been accepted for the truth of its contents. It is also supported by the April 9, 2002 memorandum (Wenslow Affidavit, Ex 17, Exhibit J). The statements are relevant to the invention story. Rule 232/248 objection lacks sufficient connection. Oral objection 1 dismissed – This testimony does not relate to the objection at paragraph 17. The date of sitagliptin's first synthesis is the subject of two PMS read-ins (Ex 65, Items C9 and A4), was acknowledged by PMS in response to Merck's Request to Admit (Ex 62) and was already accepted without objection as part of paragraph 16 to Dr. Wenslow's Affidavit. Remaining oral objections are after the fact and should have been raised during testimony. Further, this testimony relates to information supported by the document.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
2.	18. **At the time, the DPP-IV project team already had significant knowledge and experience working with previous DPP-IV inhibitor compounds. This included a compound having the internal code "L-221869", which was a structural analog of sitagliptin having a near identical chemical structure to sitagliptin, differing only in a single fluorine (F) atom:**	**1. TT V4, Conf, P:84 L:17-20**; see Item 1. **4. TT V4, Conf, P:85 L:23-P:86 L:14;** see Item 1. **6. TT V4, Conf, P:86 L:27-P:87 L:11**	Hearsay, Opinion, Rule 232 and 248, Beyond the Pleadings	Objections dismissed. Statements reflect documentary evidence accepted as being admissible for their truth. Rule 232/248 objection lacks foundation. The statements are relevant to the invention story, which was put in issue by PMS' pleading. The reference to "we" in the oral testimony is understood to mean the DPP-IV project team.
3.	19. **In considering potential salts of sitagliptin to try, we knew that weakly basic compounds, like sitagliptin, were commonly formulated as the hydrochloride salt. We also knew that the hydrochloride salt of sitagliptin could be made according to the process used by the team back in June 2001. Therefore, we believed the "natural" salt candidate to evaluate was the hydrochloride salt. However, the DPP-IV team had previously made salts of L-221869 in an effort to find a form that would be suitable (L- 221869 free base had issues), having no idea what salts might form as a solid or which (if any) would have properties making them suitable as a development candidate for further study. As a**	**1. TT V4, Conf, P:84 L:17-20;** see Item 1. **4. TT V4, Conf, P:85 L:23-P:86 L:14;** see Item 1. **5. TT V4, Conf, P:86 L:19-24** **6. TT V4, Conf, P:86 L:27-P:87 L:11;** see Item 2. **7. TT V4, Conf, P:87 L:27-P:88 L:11** **8. TT V4, Conf, P:88 L:19-24;** see Item 1. **9. TT V4, Conf, P:89 L:1-8** **11. TT V4, Conf, P:89 L:14-20**	Hearsay, Opinion, Rule 232 and 248, Beyond the Pleadings	Oral objection 12 sustained; this evidence was successfully objected to at the hearing. Oral objections 7, 9 and part of 13 (91:2 – 92:2) sustained as they relate to specific details of the salt formation work before Dr. Wenslow was on the project that do not clearly arise from the documentary evidence. Oral objection 11 dismissed as it is uncontroversial and explains a comment made during testimony. The remaining objections are dismissed. The reliability of these statements arise from the

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
	memorandum issued by Dr. Shultz in December 2001 on L- 226189 states, it was determined that the hydrochloride salt of this closely related compound was "eliminated as a development candidate due to its hygroscopicity and propensity [to] hydrate reversibly".[4] As it turned out, investigation of L-226189 led the team to conclude that the tartrate and besylate salts of L-226189 showed good solubility, and slight to no hygroscopicity.[5] In fact, they were superior to the phosphate salt of L-226189.	**12. TT V4, Conf, P:89 L:23-24** **13. TT V4, Conf, P:90 L:20 - P:92 L:2**		documentary evidence accepted as being admissible for its truth. The statements otherwise reflect Dr. Wenslow's experience in drug development generally, or are uncontroversial statements. Although these statements contain some of the "gloss" PMS impugns, this does not mislead the Court and otherwise directly relates to the content of the documents. The statements about the 869 compound relate to Merck's course of conduct, which was put in issue by PMS' pleading. The rule 232/248 objection is not borne out by the cross-examination referenced for the remaining items.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
4.	20. **When it came to deciding what we should with sitagliptin, we relied on our past experience with DPP-IV inhibitor compounds, and in particular, L-221869.** By December 2001, our colleagues had already made the sitagliptin hydrochloride salt described above. **Even though it had not yet been evaluated, our experience with the hydrochloride salt of L-221869 led us to worry that the hydrochloride salt of sitagliptin might potentially suffer from the same issues since the compound structures were near identical. Similarly, we thought tartrate and besylate salts might be possible for sitagliptin as well. This would, of course, need to be evaluated. But since we were under significant time pressures, we decided not to focus on the sitagliptin hydrochloride salt. Instead, based on our experience with DPP-IV inhibitors, we decided to conduct a broad salt selection project looking for any solid sitagliptin salts that might have suitable properties. Given the team's work on L-221869, it was hypothesized that we should be able to make salts with improved solubility over sitagliptin free base.** This decision is reflected in the memorandum summarizing the analyses conducted on sitagliptin free base.[6]	**1 . TT V4, Conf, P:84 L:17-20;** see Item 1. **2. TT V4, Conf, P:84 L:26-P:85 L:1;** see Item 1. **3. TT V4, Conf, P:85 L: 2-6;** see Item 1. **4. TT V4, Conf, P:85 L:23-P:86 L:14;** see Item 1. **5. TT V4, Conf, P:86 L:19-24**; see Item 3. **6. TT V4, Conf, P: 86 L:27-P:87 L:11;** see Item 2. **8. TT V4, Conf, P:88 L:19-24;** see Item 1.	Hearsay, Rule 232 and 248, Beyond the Pleadings	The objection to sentences 3 to 6 of paragraph 20 are upheld. The remaining statements from paragraph 20 reflect the cited report from Leigh Shultz, admitted for its truth.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
5.	21. **Drawing on this in-house knowledge, the DPP-IV project team attempted a broad salt screen on sitagliptin instead of solely focusing on the hydrochloride sitagliptin salt that had initially been made, despite it being the otherwise natural candidate.** The team conducted salt experiments in December 2001, attempting to form various salts of sitagliptin.[7] The various acids and solvents that were used are depicted below:[8]	**5. TT V4, Conf, P:86 L:19-24;** see Item 3 **7. TT V4, Conf, P:87 L:27-P:88 L:11;** see Item 3. **9. TT V4, Conf, P:89 L:1-8;** see Item 3. **11. TT V4, Conf, P:89 L:14-20;** see Item 3 **12. TT V4, Conf, P:89 L:23-24;** see Item 3. **13. TT V4, Conf, P:90 L:20-P: 92 L: 2;** see Item 3	Hearsay, Opinion	Objections dismissed. Statements reflect the documentary evidence admitted for its truth.
6.	23. **We did not know if any of these solids obtained were crystalline, however, until they were analyzed by XRPD. As reflected from the below snapshot, we were only able to obtain crystalline salts with less than half (four of the eleven acids attempted): phosphate salt, sulfate salt, tartrate salt, and besylate salt:[10]**		Hearsay, Opinion	Objection dismissed. Statements supported by documentary evidence accepted as being admissible for their truth. Facts relating to these statements also admitted through PMS read-ins (e.g., Ex 65; Item C22). Dr. Wenslow was also asked about details of the Vydra salt screen during cross-examination.
7.	24. Interestingly, we did not obtain a crystalline hydrochloride salt in these salt experiments using hydrochloric acid, even though Merck had previously made a hydrochloride salt back in June 2001 using	**10. TT V4, Conf, P:89 L:9-12**	Opinion	Objection allowed

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
	different reaction conditions. **This result reflects the unpredictability our team faced with salt formation, and the importance of finding the right reaction conditions that could potentially drive salt formation.**			
8.	25. **We did not yet know if any of these crystalline salts were suitable for further development either.** In January 2002, the DPP-IV development team set out to investigate which, if any, of the crystalline salts were suitable for further development. As recorded in a memorandum from Dr. Hansen on January 7, 2002, the besylate and tartrate salts would be pursued first.[11] **While we did not know if either would be suitable, we hoped based on our experience with L-226189 [*sic*] that these two salts would also have promising properties.** In an e- mail dated January 11, 2002, Dr. Schultz instructed Dr. Hansen to try the tartrate salt of sitagliptin first, **as that was looking to be the best salt for the near identical compound, L-221869.[12]**	**4. TT V4, Conf, P:85 L:23-P:86 L:14;** see Item 1. **6. TT V4, Conf, P:86 L:27-P:87 L:11;** see Item 2.	Hearsay, Beyond the Pleadings	Objections dismissed. These statements reflect the documentary evidence accepted as being admissible for its truth. The evidence goes to the invention story and is responsive to the issue of obviousness.
9.	29. **Thereafter, we studied these salts with the hope that one would be our lead development candidate. Based on the results of our experimentation,** the phosphate salt was ultimately selected as the most promising and was recommended for Phase I clinical development and safety assessment studies.[14]		Hearsay	Objection dismissed. Statement supported by documents admitted for their truth.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
10.	33. **This experimentation revealed that the 1:1 DHP salt possessed distinct advantages over the other sitagliptin salts. We did not know of these advantages until we had synthesized the sitagliptin salts and conducted experimentation on them. For example, the team found the 1:1 DHP salt to be significantly more chemically stable than the sitagliptin free base, besylate salt and tartrate salt, which were all prone to undesirable degradation, as illustrated in the below graph:**[17]	**1. TT V4, Conf, P:84 L:17-20;** see Item 1. **2. TT V4, Conf, P:84 L:26- P:85 L:1;** see Item 1. **3. TT V4, Conf, P:85 L:2-6;** see Item 1. **8. TT V4, Conf, P:88 L:19-24;** see Item 1.	Hearsay, Opinion, Beyond the Pleadings	Objections dismissed except for last sentence of paragraph 33.
11.	34. In the above graph, "Salt A" (aqua) is the tartrate salt, and "Salt B" is the besylate (green) salt of sitagliptin. Following 4-week stability studies, the 1:1 DHP salt (royal blue) demonstrated significantly lower levels of hydrolysis and deamination, **meaning lower amounts of degradation products. This indicated to the team that the 1:1 DHP salt had superior chemical stability.**	**3. TT V4, Conf, P:85 L:2-6;** see Item 1.	Hearsay, Opinion, Beyond the Pleadings	Objections dismissed. Dr. Wenslow has the experiential background to explain the meaning of these scientific terms, which do not appear controversial. The last sentence flows from the remainder of the paragraph to which there is no objection.
12.	35. My team also conducted DSC and TGA analysis of the salts, **which revealed the 1:1 DHP salt had superior physical stability in terms of its stability to stress, high temperature and humidity. The team also looked carefully at the morphology, or the shape and appearance, of the crystalline salts. To do this, we relied on specialists at**	**14. TT V4, Conf, P:92 L:16 - P:93 L: 9**	Opinion, Beyond the Pleadings	Objections dismissed except for oral testimony excerpt 92:16-22. The statements reflect the team's understanding at the time and are supported by documents accepted as being admissible for their truth. PMS' qualification raised in argument about Ex L is not accepted in view of the parties' document agreement and PMS' own reliance

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
	Merck who were trained in conducting and analyzing electron microscope images. Based on this work, we discovered the DHP to possess better morphology than the tartrate and besylate salts.[18]			on Ex L in their written argument [same note applies to items 13, 19, 26, 27, 32, 33, 35, 37 and 38 below]. The statements are responsive to the obviousness issue.
13.	36. **As reflected in the above images, the tartrate and besylate salts all exhibited "needle-like" morphology.** Our analysis of the hydrochloride salt prepared in January 2002 also revealed that it suffered from similar "needle-like" morphology.[19] **Through our research, needle-like morphology was found undesirable for solid dosage formulations due to flow issues and a propensity for sticking. By being "sticky", we observed certain salts would stick to our manufacturing equipment during tableting. We understood this to be a problematic formulation issue because if the material sticks to the equipment, there is the potential for unequal amounts of the active ingredient being formulated into dosage forms.**	**14. TT V4, Conf, P:92 L:16 - P:93 L:9;** see item 12. **33. TT V4, Conf, P:124 L:21-23**	Hearsay, Opinion, Beyond the Pleadings	Objections dismissed. These statements are supported by Ex L accepted as being admissible for its truth. The statements reflect the team's understanding during the sitagliptin project.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
14.	38. **At the time the 1:1 DHP salt was promoted to clinical development, the DPP-IV project team understood that it existed as a single anhydrous crystalline form. We commenced our polymorph experiments on the 1:1 DHP salt in early 2002 (see e.g., Dr. Hansen e-mail of February 7, 2002, indicating "Chris [Lindemann] will try to find other polymorphs and further characterize this salt").**[20] On February 15, 2002, Dr. Lindemann informed the team that he had conducted multiple crystallizations in variety of solvents, including water, and only found a single crystal phase (the anhydrous form), as well as potentially amorphous material:[21]		Hearsay, Rules 232 and 248	Objection to Exhibit N dismissed as the information in the document is not controversial or prejudicial in light of the admission into evidence of the remainder of the paragraph and the details of the experiment. The additional facts in the objection are within Dr. Wenslow's direct knowledge and are also supported by contemporaneous documents accepted as being admissible for their truth.
15.	41. **We came to this eventual understanding by extensively and systematically investigating the impact of different solvents on the formation of the 1:1 DHP salt, thus evaluating it for polymorphism. Each time we exposed the solid 1:1 DHP salt to solvent, it would dissolve, and its crystal structure would be destroyed. Every time we recrystallized it, the 1:1 DHP salt had the opportunity to exist as a new solid form. We considered each such test to be a polymorph experiment or polymorph screen, as some might describe it. Following the variability we observed in April 2002, on any given day, at least**	**7. TT V4, Conf, P:87 L:27 - P:88 L:11;** see Item 3. **9. TT V4, Conf, P:89 L:1-8;** see Item 3. **11. TT V4, Conf, P:89 L: 14-20**; see Item 3. **12. TT V4, Conf, P:89 L:23-24;** see Item 3. **13. TT V4, Conf, P:90 L:20 - P:92 L:2;** see Item 3. **15. TT V4, Conf, P:94 L:6 – 21**	Hearsay, Opinion, Rules 232 and 248	Objections dismissed. These statements reflect Dr. Wenslow's knowledge and understanding during the sitagliptin project. The statements explain the sentence to which there is no objection and is consistent with it. Oral objection 15 sustained on the basis of hearsay. Rule 232/248 objection is not sufficiently particularized.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
	10-15 members of the DPP-IV project team were conducting or analyzing polymorph experiments to gain insight into the complex sitagliptin polymorph system. This additional experimentation, over and above the systematic polymorph screens we conducted, allowed the team's scientists to use their own creativity in searching for additional polymorphs. **This creative and unconstrained search for polymorphs is not the sort of experimentation we had done before and was also only made possible because of the immense resources Merck devoted to this project. Our directive at the time and throughout the program was to leave no stone overturned. I will return to this work below.**			
16.	42. **During the 2002 time, I conservatively estimate that the DPP-IV project team performed over a 1,000 polymorph experiments on the 1:1 DHP salt as a part of this systematic polymorphism evaluation.** My group was responsible for then analyzing the crystal structure of the resulting experiments by not only XRPD but also F-ssNMR, and Carbon ssNMR ("C- ssNMR"). **The DPP-IV project team also employed Raman Spectroscopy to assist our analysis. During the 2002 time, and in addition to the polymorph experiments, I**	**16. TT V4, Conf, P:96 L:21 - P:97 L:5** **18. TT V4, Conf, P:97 L:13 – 18** **21. TT V4, Conf, P:102 L:2 – 3**	Hearsay, Opinion, Rules 232 and 248, Beyond the Pleadings	Objections dismissed. These statements reflect Dr. Wenslow's knowledge of what occurred during the sitagliptin project. The first sentence of paragraph 42 refers to the estimate found in paragraph 3 of the affidavit to which there is no objection.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
	conservatively estimate that we performed over 1,000 XRPD, F-ssNMR, C-ssNMR, and Raman spectroscopy analyses on the 1:1 DHP salt. This amount of experimentation reflects our desire to gain a deep and exceptional understand the polymorph system, and the significant resources invested in the experimentation necessary to achieve this objective.			
17.	43. As part of our experimentation, we conducted **not one but two** high throughput polymorph screens – **one in May 2002,[25] and another in November 2002[26]** – searching for possible polymorphs. This systematic screening involved crystallizing the 1:1 DHP salt with a variety of different solvents in 96-well plates, and then evaluating any resulting solids for their crystal form. The use of 96-well plates allowed numerous samples to be tested simultaneously. This high throughput screening **was expensive and not common to Merck at the time** and represents another example of the atypical level of investigation and significant investment Merck made into the 1:1 DHP salt project.	**7. TT V4, Conf, P:87 L:27 - P:88 L:11;** see Item 3. **9. TT V4, Conf, P:89 L:1-8;** see Item 3. **11. TT V4, Conf, P:89 L:14-20;** see Item 3. **12. TT V4, Conf, P:89 L:23-24**; see Item 3. **13. TT V4, Conf, P:90 L:20 - P:92 L:2;** see Item 3. **20. TT V4, Conf, P:100 L:10 - P:101 L:10**	Opinion, Rules 232 and 248	Objections to the affidavit dismissed. The first and second underlined portions arise from the documentary evidence accepted as being admissible for its truth and repeat facts contained in other paragraphs of the affidavit to which there is no objection. The third statement reflects Dr. Wenslow's understanding at the time. The oral testimony does not relate to the objections to the affidavit. Rule 232/248 objection not sufficiently explained and lacks sufficient connection to the objected to portions of the affidavit.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
18.	56. **The complex phase relationships between the anhydrous forms and the shear-sensitive conversion of Form I to Form III posed a problem for the DPP-IV project team. Because these anhydrous forms readily interconverted under normal manufacturing and processing conditions, a high degree of control of both the manufacture of the 1:1 DHP salt, and its pharmaceutical processing during formulation, would have been required to control the identity and proportion of the polymorphic forms in the final drug product.**	**24. TT V4, Conf, P:105 L:21 – 26**	Hearsay, Opinion	Objections dismissed. These statements reflect Dr. Wenslow's knowledge and understanding at the time. Dr. Wenslow was cross-examined on the interconversion of the anhydrous forms and the comparison of the anhydrous forms to the monohydrate (TT V4, P: 381 L:27-P:382 L:11).
19.	57. **To avoid having to implement these controls, the DPP-IV project team hypothesized that it might be possible to obtain pure Form I directly—without having to go through the metastable de-solvated Form II—by recrystallizing the 1:1 DHP salt in a non-solvating solvent and then maintained by adequate storage controls.**	**24. TT V4, Conf, P:105 L:21 – 26;** see Item 18.	Hearsay	Objection dismissed. The statement reflects Dr. Wenslow's knowledge and understanding and are supported by Ex L, which has been accepted as being admissible for its truth.
20.	59. **On February 7, 2003, Dr. Cypes discovered that a non-solvated crystal of the 1:1 DHP salt could be crystallized in a rather obscure solvent that we did not often use, isoamyl alcohol ("IAA"). Based on XRPD analysis, it was determined that this form was anhydrous Form I.**		Hearsay, Rules 232 and 248	Objection sustained.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
21.	60. This was promising. **However, it was also discovered that the needle-like morphology of the Form I crystals made in this manner was poor for processability.** As a result, efforts were made to try to improve the morphology of the Form I crystals. During the February to March 2003 time, the team performed experiments using a mixture of IAA/water at different temperatures to see it the crystal structure would have better morphology.[40] **The resulting particles had a more favorable rod morphology.**	**14. TT V4, Conf, P:92 L:16 - P:93 L:9;** see Item 12. **27. TT V4, Conf, P:111 L:23 – 28**	Hearsay, Opinion	Objections dismissed. These statements reflect Dr. Wenslow's factual understanding of the results of the work conducted by the team and arises from documentary evidence accepted as being admissible for its truth. PMS also cross-examined Dr. Wenslow on the differences in morphology between the monohydrate and the anhydrous forms (TT V4, P:379 L:9-27). Facts relating to the morphology and stickiness of the monohydrate and differences between the forms are the subject of PMS read-ins (Ex 65; Items C27, C28, C39, E9, and E18).
22.	63. **To give some sense of how lucky we ended up, I can say that in my 25-year career as a scientist, including my time at Merck on the DPP-IV project team, this is the only time I am personally aware of isoamyl alcohol being used in crystallization experiments. To this day, we do not fully understand why this solvent system, and the conditions used, triggered the nucleation of the crystalline monohydrate for the very first time.**		Opinion	Objection dismissed. The first sentence reflects Dr. Wenslow's personal experience. The second sentence reflects Dr. Wenslow's factual understanding and was relied on by PMS in their closing argument (TT V10, P:869 L:16-22).

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
23.	64. The creation of the crystalline monohydrate was a highly surprising development **to the DPP-IV project team as a whole—and** to me **and the Physical Measurements group.** Over a year of development on the 1:1 DHP salt had taken place, including extensive experiments with the 1:1 DHP salt in both water and aqueous solvent mixtures, as well as significant systematic efforts to identify any polymorphs, including hydrates and solvates. Despite this, the DPP-IV project team had not observed an actual hydrated form of the 1:1 DHP salt until the surprising and unexpected creation of the crystalline monohydrate using the odd mixture of IAA and water, very late in the development cycle. **It was a serendipitous discovery that resulted in drastic and profound changes for Merck and the DPP-IV team. The discovery of the crystalline monohydrate was initially met with panic.**	**25. TT V4, Conf, P:109 L:19 – 20**	Hearsay	Objection to first part of paragraph 64 and oral objection 25 sustained as it speaks to the state of mind of others. Objection to last sentence of paragraph 64 dismissed. This statement reflects Dr. Wenslow's factual recollection of events and the team's understanding at the time. PMS also relies on parts of the last statement in their closing argument (TT V10, P:869 L:16-22).

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
24.	65. **The sudden appearance of a hydrate so late in the development cycle was concerning, to say the least. I and other members of the team knew of cautionary tales discussed in the literature of polymorphs suddenly appearing in similar situations with very negative consequences. For example, I was keenly aware of and immediately thought of the well-known story of Abbott's experience with ritonavir, where the sudden emergence of a new polymorph during commercial manufacture turned out to be disastrous. It ended up being the most stable form but was problematic because it did not have the properties of the form that had been clinically approved and marketed. As a result, Abbott had to withdraw from the market.** I panicked because the monohydrate was also very stable, and I expected it would be less soluble than the anhydrous form and we might have to start over in the clinic. As a result, we worked intensely and quickly to study this new crystalline monohydrate.	**19. TT V4, Conf, P:99 L:28 - P:100 L:6** **28. TT V4, Conf, P:113 L:5 – 7** **29. TT V4, Conf, P:113 L:24 – 25**	Opinion	Objections dismissed. The statements reflect Dr. Wenslow's factual recollection of events and the team's understanding at the time. Oral objection 19 sustained. Oral objection 29 unrelated to initial objection.
25.	70. We were fortunate. The monohydrate ended up being very amenable to formulation. **Ultimately, and serendipitously, the monohydrate's physical stability, chemical stability, high solubility, and improved pharmaceutical processability (notably, reduced stickiness) led the DPP-IV project team**		Beyond the Pleadings	Objection dismissed. Statements are relevant to the invention story and the issue of obviousness. Further, these statements arise from documentary evidence accepted as being admissible for its truth and

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
	to select the monohydrate over the anhydrous forms for further development. These data are summarized in an April 9, 2003 memorandum[43] co-authored by me and other scientists from Physical Measurements, PR&D, and CERD, as well as an internal presentation, "Parallel Development of Multiple Crystal forms for M-0431," I delivered with Cindy Starbuck on or around June 2003.[44] The work reported in the April 2003 memorandum and my June 2003 presentation accurately capture the work the DPP-IV project team conducted to characterize the crystalline monohydrate. **Below, I describe the superior properties of the crystalline monohydrate, with reference to the slides from the 2003 presentation.**			repeat facts stated elsewhere in the affidavit to which there is no objection. Dr. Wenslow was cross-examined on the properties of the anhydrous forms compared to the monohydrate and the reasons it was selected (TT V4, P:379 L:28-P: 382 L:11). Facts relating to the properties of the monohydrate are also the subject of various PMS read-ins (see Ex 65; Items C28, E9-12, E18, and E19).
26.	71. **Merck's worked showed that the crystalline monohydrate a) does not exhibit form conversion, an issue that Merck saw with the anhydrous forms[45]; (b) had favorable rod-like morphology;[46] (c) is non-hygroscopic[47]; (d) has no potential for dehydration;[48] and (e) showed reduced tablet sticking[49] as compared to anhydrous forms.[50]**	**14. TT V4, Conf, P:92 L:16 - P:93 L:9;** see Item 12.	Beyond the Pleadings, Rules 232 and 248	Objections dismissed. Statements arise from a document separately relied on by PMS and accepted as being admissible for its truth. Dr. Wenslow was cross-examined on the properties of the anhydrous forms compared to the monohydrate and the reasons it was selected (TT V4, P:379 L:28-P: 382 L:11).

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				The properties of the monohydrate are also the subject of various PMS read-ins (see Ex 65; Items C28, E9-12, E18, and E19).
27.	72. **The monohydrate was shown to be stable against dehydration under ordinary conditions through dynamic vapor sorption experiments conducted at 25°C and 40°C.**		Beyond the Pleadings	Objection dismissed. The statement arises from a document accepted as being admissible for its truth and is relevant to the teachings of the 400 Patent.
28.	73. **The monohydrate's stability was also demonstrated by DSC and TGA, which are reported in the 400 Patent.**		Beyond the Pleadings	Objection dismissed. The statement is factual, non-contentious information that is relevant background to the patent

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
29.	75. These data indicated that, **unlike the anhydrous forms**, it was possible to maintain a single polymorphic form of the 1:1 DHP salt in its crystalline monohydrate form at ambient conditions. This was an extremely positive result that overcome a critical challenge in the development of sitagliptin – adequate control of crystal polymorphism and the overall properties of the drug substances – **and one that was not predictable even after the creation of the monohydrate.** The **surprising** stability of this crystalline monohydrate at ambient conditions is also reported in the 400 Patent.		Opinion, Beyond the Pleadings	Objection to the first passage dismissed. The statement is factual and reflects the belief of the team at the time. Objections to the remaining passages sustained as being opinion.
30.	76. **Following the creation of the crystalline monohydrate in 2003, we also determined that if water concentration was above a certain threshold (around 6.8%), the process conditions reported in the 400 Patent and claimed by claim 24 would reliably make the crystalline monohydrate, and not the anhydrous 1:1 DHP salt.** It seems the crystalline monohydrate was extremely difficult to nucleate. But once this happened for the very first time, there is no problem making this crystal grow using the process of claim 24. We determined this scientifically by measuring the solubility of each form at various conditions, and then prepared "Van't Hoff" plots, which show the inflection point as to when the monohydrate		Hearsay, Opinion, Beyond the Pleadings	Objection dismissed. This statement is factual and arises from documentary evidence that is accepted as being admissible for its truth. The statement is consistent with the remainder of the paragraph to which there is no objection. The statement reflects Dr. Wenslow's knowledge and understanding of the project at the time.

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	crystallizes out. For example, in the case of isopropyl alcohol and 25°C (i.e. the conditions of claim 24 of the 400 Patent), we determined through our experimentation that as long as the water concentration was higher than 6.8%, the crystalline monohydrate could be prepared. This work is summarized in an email from Dr. Ferlita to me dated May 6, 2003:[55]			
31.	77. **Additionally, unlike the anhydrous forms, the monohydrate did not convert to another crystal form under shear or pressure. As shown below, compression of an anhydrous lot ("L- 224715-006F024" or "Lot 24") at 200 MPa resulted in a material with different XPRD pattern, while compression of the new crystalline monohydrate did not.[56] This property was another unexpected benefit of the monohydrate over the previous anhydrous forms.**		Hearsay, Opinion, Beyond the Pleadings	Objections dismissed except for last sentence (opinion). Statements reflect documentary evidence accepted as being admissible for its truth and are responsive to PMS' evidence. The statements are responsive to the issue of obviousness. These properties of the monohydrate are also the subject of PMS read-ins (see Item E12).
32.	78. **The monohydrate was also unexpectedly found to have improved chemical stability as compared to the anhydrous forms (already determined to be superior to other salt forms, including the hydrochloride salt) by having lower degradation, as shown below:[57]**	**5. TT V4, Conf, P:86 L:19-24;** see Item 3.	Hearsay, Beyond the Pleadings	Objections dismissed, except for parenthesis. Statements arise from a document accepted as being admissible for its truth, and repeat statements already made in the affidavit to which there is no objection. The statements are responsive to the issue of obviousness.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
33.	79. **In probe stability studies conducted at 40°C and 75% relative humidity, formulations using the monohydrate were found to generate fewer impurities than comparable formulations using anhydrous forms.[58] Additionally, in formaldehyde stress tests, the bulk monohydrate was shown to resist discoloration as compared to the bulk anhydrous forms.[59]**		Hearsay, Beyond the Pleadings	Objection sustained.
34.	80. **Both the bulk monohydrate active ingredient and formulations of the monohydrate were also unexpectedly found to have reduced sticking compared to the bulk anhydrous active ingredient and comparable formulations, as can be seen in the image below. Using a Carver press with a punch surface embossed with "MSD," a sample of the monohydrate ("L-224715-66839- 113") was determined to produce less sticking compared a sample of anhydrous forms ("Lot24"), with only about 150 µg of monohydrate remaining on the punch surface, as compared to over 300 µg of the anhydrous forms.[60]**		Hearsay, Opinion, Beyond the Pleadings, Rules 232 and 248	Objection dismissed. These statements arise from documentary evidence that Dr. Wenslow co-authored and that has been accepted as being admissible for the truth of its contents. Rule 232/248 objection not particularized by PMS. The statement is responsive to the issue of obviousness The reduced stickiness is also the subject of a PMS read-in (Ex 65, Item E18).
35.	81. **Comparable formulations of the monohydrate and anhydrous forms were additionally subjected to a 5-minute compression run using a Korsch tablet press applying approximately 9 kN of force. As shown below, a smaller amount of the monohydrate formulation was left**		Hearsay, Opinion, Beyond the Pleadings, Rules 232 and 248	Objections dismissed. The statement arises from a document accepted as being admissible for its truth. The statement reflects Dr. Wenslow's understanding of the team's work at

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
	on the surface of the tablet punch.[61] This result was a further surprising and unexpected property of the monohydrate that led to it selection over the anhydrous forms for further development.			the time and also repeats conclusions found elsewhere in the affidavit to which there is no objection. Rule 232/248 objection not particularized by PMS. The statement is responsive to the issue of obviousness
36.	82. **Another fortunate and unexpected benefit of the crystalline monohydrate was its high solubility. This was of crucial importance because up** until the creation of the crystalline monohydrate, the clinical studies were being conducted with the anhydrous forms of the 1:1 DHP salt, and we had received positive clinical data. **If the crystalline monohydrate turned out be the most predominant polymorph but had lower bioavailability (due to lower solubility) and thus, lower therapeutic efficacy than the anhydrous form, our team would have faced nothing short of a disaster.**	**26. TT V4, Conf, P:111 L:2- 5**	Hearsay, Opinion, Beyond the Pleadings, Rules 232 and 248	Objection to the affidavit dismissed. These statements reflect Dr. Wenslow's knowledge and understanding of the team's work at the time. Rule 232/248 objection not particularized by PMS. These statements are responsive to the issue of obviousness. Oral objection sustained on the basis of hearsay
37.	83. **As a result, the DPP-IV project team conducted bioequivalence studies in mice, rats, and dogs.** As indicated in the below slide, this "disaster check" confirmed that the crystalline monohydrate was bioequivalent to the anhydrous form, meaning that we could expect the monohydrate to confer the same therapeutic effectiveness as the anhydrous forms, and could rely on the data already generated in		Hearsay, Opinion, Beyond the Pleadings, Rules 232 and 248	Objection dismissed. The statement is factual and is supported by documentary evidence that has been admitted for its truth. The statement relates to the invention story and is not beyond the pleadings. Rule 232/248 objection not particularized by PMS.

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	the clinic using the anhydrous forms without having to start over again.[62]			
38.	84. **Given the crystalline monohydrate's improved physical stability, chemical stability, pharmaceutical processing, and high solubility that rendered it bioequivalent to the anhydrous form, the DPP-IV project team decided to switch from the anhydrous form to the crystalline monohydrate in clinical studies, as summarized by the below slide.[63]**		Hearsay, Beyond the Pleadings	Objections dismissed. Statement arises from documentary evidence that has been accepted as being admissible for its truth and reflects Dr. Wenslow's knowledge, and understanding of the work and team's objectives at the time. The paragraph is repetitive of content that appears elsewhere in the affidavit to which there is no objection. The statement is responsive to the issue of obviousness. The properties of the monohydrate are also the subject of various PMS read-ins (see Ex 65, Items C28, E9-12, E18, and E19).
39.	85. During this period, my group also conducted XRPD, TGA, and DSC analysis on a new hydrated crystalline hydrochloride salt the DPP-IV project team prepared. Our TGA analysis showed that the hydrochloride salt (which was a hydrate, and superior to the original hydrochloride salt that our team made back around June 2001) began to lose water at room temperature. **This property is**	**5. TT V4, Conf, P:86 L:19-24** – see Item 3. **30. TT V4, Conf, P:114 L:20-P:115 L: 5**	Hearsay, Opinion, Beyond the Pleadings	Objections dismissed. Statements reflect Dr. Wenslow's knowledge and understanding of the work at the time and arise from documentary evidence accepted as being admissible for its truth. The statements are responsive to the issue of obviousness.

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	disadvantageous for solid dosage formulations since the loss of water can lead to a phase change involving loss of crystallinity or formation of less-desirable amorphous forms. As such, we learned the crystalline monohydrate has superior physical stability versus the hydrochloride salts. We also learned that sitagliptin's chemical stability varied as a function of pH.[64] Through this experimentation, we determined that the crystalline monohydrate has superior chemical stability to the sitagliptin hydrochloride salts.			

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40.	87. **Merck's criteria for selecting the monohydrate: At paragraph 209, Dr. Elitzin states "it appears the key criterion used by Merck in selecting the monohydrate was the fact that it was less susceptible to polymorphic form interconversion" and that it did not have "any other significant advantages over other forms". This is not correct. As I explain above, the crystalline monohydrate exhibited several surprising and unexpected advantages, including improved physical and chemical stability, its high solubility and bioequivalence to the anhydrous form, stability at ambient conditions, and improved chemical and pharmaceutical processability.**		Opinion	Objection sustained.

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41.	94. Dr. Elitzin references two experiments in April 2003 conducted by Karl Hansen that led to the formation of Form I.[73] Dr. Hansen's notebook indicates the solvent ratio he used was "95:5 IAA/H2O", meaning he used approximately 5% by weight water, but he obtained Form I and not the monohydrate.[74] As I discuss above, Dr. Cypes initially prepared pure monohydrate by using 95:5 IAA/H2O at 60°C, with the XRPD pattern of the resulting monohydrate matching Figure 1 of the 400 Patent. **The reason Karl Hansen got Form I when he used these conditions, instead of the monohydrate, is that his reaction was incomplete.**	**35. TT V4, Conf, P:128 L:25-P:129 L: 9**	Hearsay, Opinion	Objections sustained on both grounds.
42.	97. **Merck's approach to polymorph screening: At paragraph 179, Dr. Elitzin states "Merck did not begin systematically investigating sitagliptin phosphate polymorphism until late 2002 or early 2003". This is also incorrect. In the 2002 time, the DPP-IV project team systematically conducted over a 1,000 polymorph experiments on the 1:1 DHP salt. These efforts included two formal high throughput polymorph screens in May 2002 and November 2002. Both used Merck's most advanced 96-well plate screening technology, and neither resulted in the crystalline monohydrate.**[77]		Rules 232 and 248	Objection dismissed. The statements are repetitive of other passages in the affidavit to which there is no objection and reflect facts set out in the documents admitted for the truth of their contents.

Item	Objections to Wenslow Affidavit (bolded and underlined)	Objections to Oral Testimony Asserted to be Related	Objection	Ruling
43.	102. Both Drs. Foley and Elitzin observe that the "original" and "fasttrack" sitagliptin timelines both begin with salt selection, but do not include the "physiochemical characterization' step from the EDT paradigm.[79] **This is not correct. The "salt selection" step in these sitagliptin timelines is just shorthand and conveys the same work as the "physiochemical characterization". As I discuss above, this work was in fact conducted, and it was comprehensive. For this reason, if anything, Merck mitigated its risk (not increased it) by its immense investment of money, scientific expertise, and technology into the project.**		Rules 232 and 248	Objection sustained The last sentence is also inadmissible as being opinion evidence.

JUDGMENT IN T-419-20

THIS COURT'S JUDGMENT is that

1. The Defendant's allegation that claims 4-7, 19, 20, 22, 24 and 26 of Canadian Patent No. 2,529,400 are invalid for obviousness and/or insufficiency is dismissed and such claims are accordingly found to be valid.

2. In view of the finding in paragraph 1 and pursuant to the agreement of the parties, the Court declares that the making, constructing, using or selling by Pharmascience Inc. of sitagliptin phosphate tablets in strengths of 25 mg, 50 mg and 100 mg in accordance with the Abbreviated New Drug Submission bearing Submission No. 233922 will directly or indirectly infringe at least one of claims 4-7, 19, 20, 22, 24 or 26 of Canadian Patent No. 2,529,400.

3. Costs of the action, including the motion determined herein, are reserved. Should the parties be unable to come to an agreement on costs, the costs shall be awarded in an amount to be determined after further submissions from the parties according to the following schedule:

    (a) the Plaintiffs submissions, which shall not exceed 10 pages, shall be served and filed within 30 days from the date of this Judgment;

(b) the Defendant's submissions, which shall not exceed 10 pages, shall be served and filed within 30 days after receiving the Plaintiffs' submissions; and

(c) any reply submissions from the Plaintiffs, which shall not exceed 5 pages, shall be served and filed within 15 days of step (b).

"Angela Furlanetto"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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