Federal Court  Cour fédérale

Date: 20220223

Docket: T-794-19

Citation: 2022 FC 260

Ottawa, Ontario, February 23, 2022

PRESENT: The Honourable Madam Justice Kane

BETWEEN:

ALLERGAN INC. AND ALLERGAN PHARMACEUTICALS INTERNATIONAL LIMITED

Plaintiffs

and

APOTEX INC.

Defendant

[redacted] **PUBLIC JUDGMENT AND REASONS**

Table of Contents

I. Background

[1] Osteoporosis is a common condition in women over 50, characterized by weakening of the bone, leading to fractures. Bisphosphonates are widely used in the treatment of osteoporosis. There are several bisphosphonates available for the treatment of osteoporosis in different formulations and with different dosing instructions. This patent infringement action [Action] focusses on one of the bisphosphonates – risedronate – taken weekly as a 35 mg dosage and known as ACTONEL DR® [ACTONEL DR]. ACTONEL DR is said to differ from other formulations of risedronate and from formulations of other bisphosphonates in that it can be taken either with food or without food, at the preference of the patient.

[2] The Plaintiffs have established (by way of the affidavit of Mr. FooLim Yeh) that Allergan Inc. holds a Notice of Compliance [NOC] or ACTONEL DR and that it lists Canadian Patent 2,602,188 [the '188 Patent, the '188 or the Patent] on the Patent Register for that product (granted on October 13, 2009).

[3] ACTONEL DR is a weekly oral dosage (tablet), the key ingredient of which is sodium risedronate, used for the treatment of osteoporosis in post-menopausal women. ACTONEL DR is an enteric-coated delayed release tablet at a strength of 35 mg risedronate and contains ethylene-daimine-tetraacetic acid [EDTA]. (Allergan also makes and markets ACTONEL, which is an immediate release dosage administered daily as a 5 mg dosage, weekly as a 35 mg dosage or monthly as a 150 mg dosage).

[4] The Plaintiffs have also established its ownership of the '188 Patent. The Patent was originally granted to Proctor and Gamble [P&G]. P&G assigned the Patent and its rights to WarnerChilcott in October 2009. Warner-Chilcott subsequently assigned the Patent to Allergan Pharmaceuticals International Limited in December 2015. The Plaintiffs have established that Allergan Inc. is an innovative pharmaceutical company. The Plaintiffs are collectively referred to as Allergan.

[5] Pursuant to section 42 of the *Patent Act*, RSC 1985, c P-4 [*Patent Act*], Allergan has the exclusive right, privilege and liberty of making, constructing, using and selling to others to be used the invention claimed in the '188 Patent.

[6] The ‘188 Patent (Dosage Forms of Risedronate) was filed in Canada on November 23, 2005 and claims a priority date of April 15, 2005. The Patent was issued on October 13, 2009. The Patent has 137 claims. The asserted claims are described more fully below.

[7] Apotex Inc. [Apotex] is a generic pharmaceutical company. In March 2019, Apotex submitted an Abbreviated New Drug Submission [ANDS] to Health Canada seeking an NOC for its generic product, an orally administered delayed release tablet containing 35 mg sodium risedronate [APO-RISEDRONATE DR or the Apotex product]. Apotex compares its product to ACTONEL DR.

[8] On May 16, 2019, Apotex served a Notice of Allegation [NOA] on Allergan in respect of ACTONEL DR regarding the ‘188 Patent.

[9] Allergan, now brings this Action pursuant to subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [*PMNOC Regulations*]. Allergan seeks a declaration that Apotex will infringe, directly or indirectly, at least one of the claims of the ‘188 Patent by making, constructing, using and selling the Apotex generic product.

[10] Apotex disputes that its product will infringe the ‘188 Patent. Apotex also alleges that the ‘188 Patent is invalid on the grounds of anticipation, obviousness, inutility, insufficiency of disclosure and overbreadth.

[11] The parties agree that relevant dates for the determination of the issues in this Action are: for claims construction, the date of the publication of the patent, October 26, 2006; for anticipation and obviousness, the priority date, April 15, 2005; and, for the assessment of utility, the Canadian filing date, November 23, 2005.

II. Overview

A. *Summary of Allergan's Position*

[12] Allergan submits that its product, ACTONEL DR, is unique among the several bisphosphonates currently available to treat osteoporosis because it overcomes the "food effect".

[13] Allergan notes that this "food effect" for bisphosphonates was known well before the 1990s and many pharmaceutical companies were grappling with how to solve this problem, but did not succeed.

[14] Allergan notes that the experts explained the scientific basis for the "food effect". In layman's terms, this means that the food in the stomach, which includes calcium and other cations, attaches to the bisphosphonate and prevents its absorption.

[15] Absorption relates to the availability of the drug to treat the underlying condition. Allergan notes (as do all the experts) that bisphosphonates are very poorly absorbed. This poor absorption (also referred to as bioavailability) is made even worse if the bisphosphonate is taken with food, to the extent that drug absorption is almost completely eliminated.

[16] Allergan submits that ACTONEL DR remains the only oral bisphosphonate "suitable" for use with or without food or beverage intake. The tablet provides "pharmaceutically effective absorption" in either state – fed or fasted – and will treat a patient's osteoporosis. Other oral bisphosphonates, including Allergan's earlier product, ACTONEL® [ACTONEL], must be taken before breakfast on an empty stomach, with only water and no food for at least 30 minutes. This fasted administration of ACTONEL (and other bisphosphonate products) is essential to ensure that a sufficient amount of the bisphosphonate is absorbed.

[17] Allergan submits that the rigid dosing requirements for the other bisphosphonates, including its own precursor, ACTONEL, were inconvenient for some patients and almost impossible to comply with for others. For example, patients who take several medications and/or rely on others to administer their medication may not be able to adhere to the proper dosing instructions. This inconvenience contributes to poor compliance in taking the medication and leads to impairment in the treatment of the patient's osteoporosis.

[18] Allergan notes that other pharmaceutical companies attempted to *reduce* the inconvenience of the food effect problem, but only Allergan overcame it. For example, some pharmaceutical companies developed a once weekly, or once monthly dose, to reduce the inconvenience of taking the medication in a fasted state daily. Others pursued intravenous administration. The inventors of the '188 Patent were the first to provide a direct solution to overcome the food effect as it discloses an oral dosage form of risedronate that provides pharmaceutically effective absorption (i.e., similar absorption in the fed or fasted state) whether taken with or without food.

[19] Allergan notes that the ‘188 teaches how the invention works to overcome the food effect and also clearly teaches what does not work. The ‘188 Patent provides targeted release of just the right amount of the chelating agent in the small intestine with risedronate. The amount is high enough to bind ions and minerals in food, but low enough not to significantly alter fasted absorption. The ‘188 Patent also teaches that slow or prolonged delivery of the chelating agent and risedronate in the small intestine does not overcome the food effect; rather, in addition to targeted release in the small intestine, that release must be immediate.

[20] Allergan submits that the ‘188 is not anticipated or obvious, meets the requirements of the *Patent Act* with respect to utility and sufficiency of disclosure, and is not overbroad.

[21] Allergan disputes that Brazilian Patent Application 0106601 [BR 601], cited by Apotex as prior art, anticipates the ‘188. Allergan submits that BR 601 would not have been found by the skilled person and, in the unlikely event that it did come to the attention of the skilled person, BR 601 does not disclose or enable a bisphosphonate suitable for use with or without food that provides pharmaceutically effective absorption in either the fed or fasted state.

[22] Allergan acknowledges that the ‘188 Patent cites BR 601, and as a result, it is an anticipatory reference but submits that it should not be considered as part of the mosaic of prior art for the purpose of analysis of the allegations of obviousness.

[23] Allergan asserts that the ‘188 Patent is inventive – i.e., not obvious. Allergan argues that the prior art taught away from the use of enteric coatings for risedronate as this was shown to

reduce absorption. With respect to the use of EDTA, Allergan notes that the prior art taught that the amounts of EDTA required to overcome the food effect were too high for clinical use. It was not obvious that the low amounts of EDTA used in combination with the enteric coatings, to provide for release of risedronate and EDTA in the small intestine (bypassing release in the stomach) as claimed in the '188 Patent, would overcome the food effect.

[24] Allergan argues that the prior art relied on by Apotex is so broad that it cannot be found to teach the invention claimed in the '188 Patent.

[25] Allergan submits that there was strong motivation to address the food effect, but other pharmaceutical companies did not pursue the inventive approach of the '188 Patent. Allergan notes that there remains no other oral dosage form that addresses the food effect. Allergan adds that if this invention were obvious, as Apotex alleges, it is curious that no other pharmaceutical company, despite their research efforts, has come up with this approach.

[26] Allergan also points to the work of the inventors, Drs. Richard Dansereau and David Burgio, over many years, which ultimately resulted in the invention.

[27] Allergan explains that the P&G researchers sought to develop a formulation to allow risedronate to be taken "anytime". The initial approaches were not successful and after several setbacks, the inventors arrived at the formulation disclosed in the '188 Patent; oral dosage forms of risedronate that are suitable for use with or without food or beverage intake because they provide pharmaceutically effective absorption either way.

[28] With respect to the allegation of inutility, Allergan submits that the evidence of Drs. Burgio and Dansereau, and that of the experts, Drs. Serge Cremers and Patrick Sinko, show that utility was demonstrated as of the Canadian filing date, November 23, 2005, by the P&G Pilot Bioavailability Study No. 2004132 [‘132 Study] results.

[29] Allergan further submits that there was sufficient disclosure of the invention. The evidence of Drs. Cremers and Sinko establishes that the skilled person could make and use the invention without undue burden and without exercising any inventive ingenuity based on the disclosure of the ‘188 Patent and their common general knowledge.

[30] Allergan submits that Apotex will infringe the asserted claims for the oral dosage forms by making and selling the Apotex product and will infringe the claims related to use given that the Apotex product is also intended to be used to treat osteoporosis.

[31] Allergan describes the first set of claims as product claims, which includes Claim 1 and several dependant claims. Allergan argues that Apotex’s intentions and how the proposed product will ultimately be used are irrelevant. The claims only require that Apotex’s proposed product be “suitable for” use with or without food or beverage intake.

[32] Allergan notes that the Apotex product has nearly identical ingredients, and its proposed product monograph is a copy of the ACTONEL DR product monograph. Allergan submits that the Apotex product has all the essential elements of the ‘188 Patent, noting that it is suitable for use

both with food and without food and will provide pharmaceutically effective absorption with or without food or beverage intake, therefore, it will infringe the ‘188 Patent.

[33] Allergan disputes Apotex’s argument that it will not infringe because its proposed product monograph and package insert instruct users not to take the tablet without food. Allergan submits that the dosing instruction to take the tablet with food is only to avoid a potential side effect of abdominal pain and has nothing to do with pharmaceutically effective absorption.

[34] With respect to the evidence, Allergan submits that its experts were candid and neutral and made concessions where called for and did not advocate for a particular interpretation or outcome.

[35] Allergan submits that, in contrast, Apotex’s experts – Drs. John Yates, Alan Parr, and John Dillberger – were evasive in some of their responses and aimed to support Apotex’s position. In addition, Allergan suggests that the prior art selected by Apotex and provided to its experts led their experts to rely on hindsight. Allergan notes that where the plain words in references conflicted with Apotex’s invalidity theory, the experts then disagreed with the prior art.

[36] Allergan also notes that Mr. Duane Terrill, Apotex’s Director of Regulatory Affairs (Canada and Caribbean), initially stated that Apotex sought [redacted] from Health Canada [redacted] due to concerns about the safety of its biostudy participants. Allergan alleges that this concern was [redacted]

B. *Summary of Apotex's Position*

[37] Apotex submits that it will not infringe the claims of the '188 Patent because its product is not for use with or without food, rather only for use with food. Apotex also submits that it will not infringe because the '188 Patent is invalid on the basis of anticipation, obviousness, inutility, insufficiency of disclosure and overbreadth.

[38] With respect to invalidity, Apotex submits that the subject matter of the '188 Patent was previously disclosed and enabled by BR 601. Apotex notes that BR 601 is cited in the '188 Patent, and as a result, Allergan cannot resile from BR 601 as prior art or that it was publicly available.

[39] Apotex argues that the '188 Patent does not claim anything new or inventive; all the essential elements were disclosed in BR 601. Apotex submits that BR 601 taught the combination of bisphosphonates (of which risedronate is one), a chelating agent (of which EDTA is one), and an enteric coating – all of which are the essential elements of the '188 Patent.

[40] Apotex further submits that BR 601 disclosed the solution to the problem of low bioavailability of bisphosphonates by the use of the chelating agent and an enteric coating to permit the bisphosphonate to bypass the stomach and release immediately in the small intestine. Apotex submits that BR 601 addresses the food effect and, if performed, would result in pharmaceutically effective absorption in both the fed and fasted states.

[41] Apotex further submits that BR 601 enabled the skilled person to make the formulations in the ‘188 Patent with the information from BR 601.

[42] Apotex also argues that the claims of the ‘188 Patent were obvious. Apotex adds that even if the claims are not anticipated by BR 601, BR 601 is part of the mosaic of prior art for the purpose of the obviousness analysis.

[43] Apotex notes that by April 2005, the prior art was well developed with respect to bisphosphonates, including risedronate, and it was well known that bisphosphonates had low absorption, which was even lower if taken with food.

[44] Apotex argues that there were no differences between the state of the art in 2005 and the subject matter of the claims. The only possible small gap between the prior art and the subject matter of the claims would be that the art did not specifically combine risedronate and EDTA in an enteric coating for use with or without food and explicitly teach that this dosage would provide pharmaceutically effective absorption. Apotex submits that this small gap would easily be bridged by the skilled person using their common general knowledge.

[45] Apotex submits that the invention was obvious to try and the relevant factors support this determination. Among other things, Apotex submits that there was a general motivation to overcome the food effect and a specific motivation to do so by combining EDTA and the bisphosphonate in an enteric-coated form.

[46] Apotex disputes that the work of the inventors was long or arduous. Apotex submits that the inventors identified the possible use of EDTA early in their project. However, the inventors wasted effort by pursuing colonic delivery that the skilled person would have known would fail. Apotex submits that once the inventors were on the right track, the invention came easily.

[47] Apotex adds that the comparable patent in the United States for the product ATELVIA® [ATELVIA] was found to be obvious in the United States.

[48] Apotex also argues that the ‘188 Patent is invalid for inutility, insufficiency of disclosure and overbreadth.

[49] With respect to infringement, Apotex submits that Allergan’s allegations are based on distorting the plain words of the claims and of Apotex’s proposed product monograph for APO-RISEDRONATE DR.

[50] Apotex focuses on the clear requirement in the claims of the ‘188 Patent that the oral dosage form of risedronate is for use “with or without food or beverage intake” at the preference of the person taking the medication. Apotex disputes that the asserted claims are product claims, rather characterizes the asserted claims as “product for use” claims.

[51] Apotex argues that the essential element of Claim 1, “for use with or without food or beverage intake”, will not be satisfied by Apotex because APO-RISEDRONATE DR is not an oral dosage form for use with or without food. It is only for use with food.

[52] Apotex submits that the evidence is clear; the proposed product monograph for APO-RISEDRONATE DR (which is identical to that of ACTONEL DR) instructs persons taking the medication to take it with food and to not take it while fasting as it *may* cause abdominal pain. Therefore, Apotex does not infringe and does not induce others to infringe the claims of the '188 Patent.

[53] Apotex notes that it obtained [redacted] from Health Canada [redacted] because of the safety concerns of testing the product on human subjects who may experience abdominal pain.

[54] Apotex submits that, to the extent physicians prescribe the product without food or beverage, this would be an off-label use and would not be based on any guidance from Apotex's label.

C. *Summary of the Court's Findings*

[55] The parties have tendered a vast amount of evidence and have extensively cited passages in the jurisprudence to support their respective arguments. It is important to focus on the principles established in the jurisprudence rather than the application of the principles to the particular facts of the cases cited. No two cases are identical; the facts differ, the evidence differs, and the allegations made and arguments advanced differ. I have not addressed every case cited by the parties in these Reasons. I have considered the key cases and I have focussed on the well established principles and how they relate to the issues in this case. I have considered all the

evidence, some of which is applicable to more than one issue, but I have not referred to every aspect of the evidence in these Reasons.

[56] For the reasons that follow I find that Apotex has not established on a balance of probabilities that the asserted claims of the ‘188 Patent are invalid. I find that the asserted claims are not anticipated by BR 601 and are not obvious in light of the prior art, including BR 601. I also find that the asserted claims are not invalid due to lack of demonstrated utility, insufficiency of disclosure or overbreadth.

[57] I also find that Allergan has not established on a balance of probabilities that Apotex will infringe the asserted claims of the ‘188 Patent either directly or indirectly. The Apotex product is only for use with food. It is not for use with or without food, which is an essential element of the asserted claims.

III. The ‘188 Patent

[58] The title of the Patent is “Dosage Forms of Risedronate”.

[59] The Abstract states:

> Oral dosage forms of risedronate comprised of a safe and effective amount of a pharmaceutical composition comprising risedronate, a chelating agent, and, means for effecting delayed release of the risedronate and the chelating agent in the small intestine provide immediate release of the pharmaceutical composition to the small intestine of the mammal subject and pharmaceutically effective absorption of the bisphosphonate with or without food or beverages. The present invention substantially alleviates the interaction between risedronate and food or beverages, which

> interaction results in the bisphosphonate active ingredient not being available for absorption. The resulting oral dosage may thus be taken with or without food. Further, the present invention effects delivery of risedronate and the chelating agent to the small intestine, substantially alleviating the upper GI irritation associated with the bisphosponate (*sic)* therapies. These benefits simplify previously complex treatment regimens and can lead to increased patient compliance with bisphospanate (*sic*) therapies.

[60] The Patent describes the field of invention in the same manner as the Abstract, adding that "the invention further relates to a method of treating or preventing diseases characterized by abnormal calcium and phosphate metabolism comprising administering to a human or other mammal in need thereof the oral dosage form described herein".

[61] In the *Background to the Invention*, the Patent notes that bisphosphonates were first developed to improve the performance of detergents in hard water. They were subsequently found useful in the treatment and prevention of conditions characterized by abnormal calcium and phosphate metabolism. These conditions fall into two categories: those which cause or result from deposition of calcium and phosphate in the body, referred to as pathological calcifications, which includes osteoporosis; and, those which are manifested by anomalous calcium and phosphate deposition, which include arthritis, neuritis, bursitis and other inflammatory conditions.

[62] The Patent describes osteoporosis as a condition in which bone hard tissue is lost disproportionately to the development of new hard tissue. Bone strength is weakened and bone becomes less dense and fragile.

[63] The Patent notes that bisphosphonates tend to inhibit the resorption of bone tissue. However, the administration of bisphosphonates sometimes results in heartburn, esophageal burning, pain or difficulty swallowing or pain in the mid-sternum. The Patent notes that this is thought to be due to the bisphosphonate adhering to mucosal tissues, which leads to their irritation. To avoid this irritation, patients were instructed to take the medication with a full glass of water and to remain upright for a half hour.

[64] The Patent states that oral bisphosphonates are poorly absorbed in the gastrointestinal [GI] tract. The Patent also notes that absorption enhancers, such as EDTA, were proposed to increase absorption of bisphosphonates, but were thought to be impossible due to their effect on mucosal integrity. The Patent cites a publication by Ezra, Aviva et al, "Administration Routes and Delivery Systems of Bisphosphonates for the Treatment of Bone Resorption" (2000) Advanced Drug Delivery Reviews 42:175-195 [Ezra] (discussed in these Reasons in the context of prior art). The Patent also cites Janner, Marco et al, "Sodium EDTA enhances intestinal absorption of two bisphosphonates" (1991) Calcified Tissue International 49:280-283 [Janner] (also discussed in the context of prior art) for its conclusion that the high amount of EDTA required to increase absorption excludes EDTA as a candidate for use with oral bisphosphonates.

[65] The Patent notes that the primary site of absorption of bisphosphonate is in the small intestine and that similar absorption occurs throughout the small intestine regardless of where the bisphosphonate is delivered (citing Mitchell, David Y et al, "Risedronate gastrointestinal absorption is independent of site and rate of administration" (1998) Pharmaceutical Research

15(2):228-232 [Mitchell 1998]). The Patent notes that for this reason, delivery of the bisphosphonate alone to the small intestine would not increase absorption or efficacy.

[66] The Patent further notes that "others have attempted to increase the absorption of bisphosphonates by increasing the permeability of the intestinal mucosa through delivery of microparticles of chelating agents and bisphosphonate to the reported site of absorption" (citing BR 601).

[67] The Patent further notes that, although bisphosphonates have been approved by some regulatory agencies as effective for the treatment of various bone pathologies, interactions with foods and minerals cause less of the bisphosphonate to be available for absorption. This is referred to as the "food effect". The Patent cites Mitchell, David Y et al, "The effect of dosing regimen on the pharmacokinetics of risedronate" (1999) Br J Clin Pharmacol 48:536-542 [Mitchell 1999] as demonstrating that administration of risedronate within 30 minutes of a meal reduced its absorption by 50% compared to administration in a fasted state. The Patent explains that as a result of the food effect, dosing instructions direct the patient to take the medication at least 30 minutes prior to the first food of the day. The Patent adds that dosing instructions can be complex and inconvenient, resulting in poor compliance.

[68] The Patent then notes the ongoing need to develop an oral dosage form of bisphosphonate that can be taken with or without food or beverages (i.e., having the same pharmaceutically effective absorption regardless) at the preference of the patient and which does not produce upper GI irritation.

[69] The Patent asserts that:

> …it has been found that a pharmaceutical composition comprising risedronate, a sufficient amount of a chelating agent to bind the ions and minerals in food, and a means for effecting delayed release of risedronate and the chelating agent in the small intestine is useful in providing an oral dosage form which provides immediate release of risedronate to the small intestine, as well as pharmaceutically effective absorption of risedronate when administered with or without food or beverage intake.

[70] The Patent adds that the oral dosage forms of the invention can be taken with or without food or beverages, which simplifies the treatment and increases patient compliance and convenience. In addition, the oral dosage form provides for delayed release in the small intestine, which may alleviate upper GI tract irritation experienced with other oral bisphosphonates and the need to remain upright after ingestion.

[71] The *Summary of the Invention* describes several aspects. One broad aspect is the oral dosage form of risedronate for use with or without food or beverage intake. This includes a pharmaceutical composition comprising: from 1 mg to 70 mg of bisphosphonate (which includes risedronate), EDTA, wherein the EDTA is at least 50% as soluble in water as the bisphosphonate, and an enteric coating.

[72] In the *Detailed Description of the Invention* the relevant terms are defined. Of note, "pharmaceutically effective absorption" is defined as "an amount of a chelating compound high enough to significantly bind the metal ions and minerals in food but low enough not to significantly alter absorption of risedronate as compared to absorption in the fasted state. That is, absorption is

similar with or without food. Given the high variability of bisphosphonate absorption, fed exposure within about 50% of fasting exposure is expected to be pharmaceutically effective absorption".

[73] With respect to "kits", the Patent states that the invention comprises kits that are useful for administering the oral dosage forms according to a continuous dosing schedule of daily, weekly, three times per month, twice per month or monthly. The kits include instructions, packaging and dispensing means and other memory aids.

[74] The Patent includes 12 examples. Examples I-VIII are of enteric-coated tablets containing risedronate and EDTA. Example IX is of a soft gel capsule containing risedronate and EDTA. Examples X-XII describe patients who take dosage forms of Examples I and IV.

[75] The '188 Patent has 137 claims. There are two independent claims, Claims 1 and 98. Other dependent claims narrow the ranges of the bisphosphonate or EDTA or other elements, address use and treatment and the kits.

[76] Allergan has narrowed the asserted claims, described more fully below. The key claim is Claim 1, as other claims depend on it via other dependant claims.

[77] Claim 1 of the 188 Patent states:

> 1. An oral dosage form of a bisphosphonate for use with or without food or beverage intake, comprising a pharmaceutical composition comprising:
>
> > (a) from about 1 mg to about 70 mg of the bisphosphonate, the bisphosphonate being risedronate, an acid, salt, ester,

> hydrate, polymorph, or solvate thereof, or a combination of two or more of the foregoing;
>
> (b) EDTA wherein the EDTA is at least 50% as soluble in water as the bisphosphonate; and
>
> (c) an enteric coating,
>
> wherein the enteric coating provides for release of the bisphosphonate and the EDTA in the small intestine and the molar ratio of EDTA to bisphosphonate is at least 2, to provide for pharmaceutically effective absorption of the bisphosphonate with or without food or beverage intake.

[78] Other claims: Claims 1-63 and 98-132 are to oral dosage forms; Claims 64-77 and 133-136 are to use to treat with those oral dosage forms; Claims 79 and 137 are to a kit.

IV. The Evidence

A. *Expert Witnesses for Allergan*

[79] **Dr. Jonathan Adachi** is a Canadian practicing medical physician and expert in the diagnosis, treatment and care of patients suffering from osteoporosis, including with the use of bisphosphonates. Dr. Adachi is the only expert qualified as a Canadian physician. He has treated patients with osteoporosis for over 35 years and was the past president of Osteoporosis Canada, the only national organization dedicated to osteoporosis. His evidence in chief focused on claims construction and infringement from the perspective of a skilled physician. He also responded to Dr. Yates invalidity report.

[80] Dr. Adachi described the common general knowledge of the skilled physician as of April 2005, including that bisphosphonates were a well-known class of drugs to treat osteoporosis

and several were on the market. He explained that bisphosphonates suffered from low oral bioavailablity, which was significantly reduced if taken with food. He also noted that the strict dosing requirements – to take the drug on an empty stomach, with a full glass of water, to avoid food or beverages for at least 30 minutes and to remain upright – posed challenges to patients and doctors. He noted that patients did not always follow the dosing instructions which impaired their treatment.

[81] In Dr. Adachi's opinion, the claims of the '188 Patent will be infringed by Apotex because the Apotex product is for use both with and without food. Dr. Adachi explained that the Apotex product ponograph must be read holistically and would inform physicians that whether taken with or without food, the product would provide pharmaceutically effective absorption. Dr. Adachi stated that the skilled physician would understand that the dosing instructions that state that the product should be taken with food is only to minimize the risk of abdominal pain, and would know that the product would be effective whether taken with food or without food. Dr. Adachi explained that in his experience, only a minority of patients experienced abdominal pain.

[82] In Dr. Adachi's opinion, the Apotex product infringes the claims of the '188 Patent and the Apotex product monograph will induce physicians to prescribe the Apotex product to patients in a manner that will infringe the asserted claims.

[83] Dr. Adachi stated that the instruction that ACTONEL DR "should" be taken with food is to minimize the risk of upper abdominal pain, which is noted in the product monograph. Dr. Adachi stated that the skilled physician would understand that taking it with food may lower

the risk of abdominal pain, but it will still be effective if taken without food. He reiterated that only a minority of patients, in his experience, suffered from upper abdominal pain to the extent that they discontinued treatment. The most important thing is that the patient takes the medication. Dr. Adachi stated that taking it with or without food are both "on label" uses.

[84] Dr. Adachi opined that physicians treating osteoporosis would know that ACTONEL DR can be taken with or without food, despite the dosing instructions, as this is what the ACTONEL DR product monograph instructs when read as a whole. Dr. Adachi stated that the skilled physician would be confident that the same formulation can be taken with or without food and it will provide similar absorption either way.

[85] **Dr. Fakhreddin Jamali** is an expert in pharmacokinetics in human clinical studies and the assessment and approval of generic drug submissions, including for enteric-coated dosage forms and related Health Canada guidance documents. Dr. Jamali holds a PharmD and PhD. He was a member of the Scientific Advisory Committee on Bioavailability & Bioequivalence for Health Canada's Therapeutic Products Program. He has acted as a consultant for both brand and generic pharmaceutical companies. His evidence focussed on Apotex's submissions to Health Canada on bioequivalence of the Apotex product as compared to ACTONEL DR.

[86] Dr. Jamali explained that Health Canada would not simply accept a generic drug manufacturer's statement that a drug "should" be taken with food as justification for not conducting a bioequivalence study in the fasted state, given the strict requirements of Health Canada's bioequivalence guidance document. Dr. Jamali first stated that it was likely that Apotex

did, in fact, conduct bioequivalence testing between the two drugs in both the fasted and fed states. Following his review of additional documents, Dr. Jamali confirmed that Apotex sought [redacted] on the basis of safety concerns when the product is taken in fasted state.

[87] **Dr. Serge Cremers** is a pharmacologist with expertise in the clinical and translational pharmacology of bisphosphonates, including for treatment of metabolic bone diseases such as osteoporosis. Dr. Cremers received his PharmD and PhD in the Netherlands. He has published extensively and is currently a professor at the Columbia University Irving Medical Center in New York. His evidence focused on claims construction and infringement from the perspective of a pharmacologist. He also responded to the reports of Dr. Yates and Dr. Parr regarding the allegations of invalidity.

[88] Dr. Cremers noted that it has long been known that oral formulations of many bisphosphonates suffered from a "food effect." Failure to follow the strict dosing instructions resulted in lowered absorption and poorer clinical outcomes. Dr. Cremers noted that many patients found it difficult to follow the dosing regime.

[89] Dr. Cremers emphasized that the '188 Patent was focussed on tackling the food effect which relates to the absorption of the bisphosphonate and that the bioavailability was the most important factor.

[90] Dr. Cremers stated that the skilled person would understand that the ‘188 Patent relates to a solution to the food effect problem with bisphosphonate drugs: pharmaceutical compositions comprising risedronate, a sufficient amount of chelating agent to bind the ions and minerals in food, and a means for effecting delayed release of risedronate and the chelating agent in the small intestine. The skilled person would understand the Patent to be disclosing that these oral dosage forms overcome the food effect problem because they provide for “pharmaceutically effective absorption of risedronate when administered with or without food or beverage intake.”

[91] Dr. Cremers compared the Apotex product to the reference product ACTONEL DR and concluded that the Apotex product contains all the essential elements of the asserted claims of the ‘188 Patent and would infringe those claims.

[92] Dr. Cremers acknowledged that the dosing instructions for ACTONEL DR and also for APO-RISEDRONATE DR were specific but added that a product monograph should be read holistically.

[93] In Dr. Cremers’ opinion the ‘188 Patent was not anticipated by BR 601 and was not obvious.

[94] With respect to the allegation of obviousness, Dr. Cremers stated that as of April 15, 2005, to his knowledge, the prior art contained no direct solution to the food effect problem for oral bisphosphonate formulations.

[95] Dr. Cremers stated that the state of the art did not provide the claimed risedronate dosage forms that overcame the food effect and also provided similar absorption when taken with or without food. Inventive ingenuity would be required to bridge the differences and arrive at the invention.

[96] **Dr. Patrick Sinko** is an expert in pharmaceutics, including the pharmacokinetics of pharmaceutical products, drug formulation, drug delivery systems, and toxicology. He received his PhD in the United States and has been a professor in the Department of Pharmaceutics at Rutgers University, New Jersey, since 1991. He has published extensively and has served as editor and reviewer for many scientific journals. He is also a member of the Society of Toxicology. His evidence responded to the reports of Dr. Parr and Dr. Dillberger on the allegations of invalidity. Counsel for Apotex objected to Dr. Sinko's qualification as an expert in toxicology, however the Court is satisfied, based on Dr. Sinko's curriculum vitae and his explanation of his expertise, including his role at Rutgers University, that he is indeed an expert in toxicology.

[97] Dr. Sinko stated that the invention of the '188 Patent overcomes the food effect and has the additional benefit of not significantly increasing small intestinal membrane permeability when taken without food. Dr. Sinko notes that this is important because significantly altering the small intestine membrane can lead to irreversible damage. In his view, the '188 Patent achieves two things: it provides for an oral dosage form of risedronate that can be taken with or without food, and it does so in a safe way.

[98] In Dr. Sinko's opinion, the '188 Patent is not anticipated by BR 601 and is not obvious.

[99] With respect to obviousness, Dr. Sinko stated that none of the prior art taught to combine a specific amount of risedronate, a specific amount of EDTA, or a specific enteric coating that could achieve "pharmaceutically effective absorption", as defined in the '188 Patent.

[100] **Ms. Maria Margarida Rodrigues Mittelbach** is the former Director of the Patents Registry of the Brazilian patent office (i.e., National Institute of Industrial Property) with expertise in its practice and procedures including as of 2005. She is a lawyer and legal consultant in Brazil. From 1970 to 1999, she was employed by the Brazilian patent office as a patent examiner and then as the Director of the Patents Registry for over 12 years. In 2002, she started her own intellectual property law firm. Ms. Mittelbach continues to be familiar with patent practice and procedures in Brazil. She explained how a patent application could be found, in particular, the likelihood that BR 601 would be found and accessed.

[101] Ms. Mittlebach explained the process to search for a patent or patent application in Brazil. Ms. Mittelbach acknowledged that the Brazilian patent office's online database was publically available in 2005, but noted that it was not as reliable or accurate as it is today. Ms. Mittlebach opined that experienced practitioners could not rely solely on the database to search for published patent applications because of the substantial delay in the first publication of the application in the Brazilian Gazette. She also noted that the Gazette was not available digitally until June 14, 2005 (two months after the relevant date). Ms. Mittlebach explained that the Brazilian Gazette is published weekly and includes hundreds of abstracts which would require review of the whole document. Ms. Mittlebach noted that a search for a patent must be conducted in Portuguese and only the title, application number and abstract could be searched by key words. The full text of the

patent application is not searchable by key words. Requesters must attend in person at the Brazilian patent office to obtain a copy of a patent.

[102] Ms. Mittlebach also noted that the database shows that the first time a copy of BR 601 was requested from the Brazilian patent office was in April 2013, although she agreed that a simple (unofficial) copy could have been obtained previously by an in-person request.

B. *Fact Witnesses for Allergan*

[103] **Dr. David Burgio** is one of the inventors of the ‘188 Patent. He is the current senior vice president of Research and Development for Global Personal Health Care at P&G. Dr. Burgio was the pharmacokineticist and pharmacologist on the team that developed ACTONEL DR. Dr. Burgio attached to his affidavit confidential documents related to the development of the invention at P&G.

[104] Dr. Burgio described his work and that of Dr. Dansereau which, after five years, resulted in the invention of an oral dosage form to overcome the food effect. He described, among other things, the obstacles faced, the concern about the use of EDTA, increasing intestinal permeability, the Enterion studies which led to a new strategy to target release in the small intestine, the testing of prototype formulations and the clinical development of the formulation. Dr. Burgio also explained various P&G documents that chronicled their project.

[105] Dr. Burgio explained that he did not recall how he became aware of BR 601, but noted that this occurred after he and Dr. Dansereau had developed their invention. He opined that BR 601 was likely provided by someone in P&G's patent prosecution team.

[106] **Dr. Richard Dansereau** is one of the named inventors of the '188 Patent. Prior to retirement, he was employed by P&G as a scientist and research fellow for 35 years. He was the lead formulator on the team that developed ACTONEL DR. Dr. Dansereau attached to his affidavit confidential documents related to the development of the invention at P&G.

[107] Dr. Dansereau described the work he conducted with Dr. Burgio and others at P&G to address the food effect of risedronate, which had inconvenient dosing instructions, particularly for elderly women, who are the main patient population for osteoporosis. He noted that P&G had identified the food effect as the biggest unmet need for bisphosphonates. He explained that it was not known at that time, what caused the food effect, and various hypotheses were identified along with various options to address the food effect.

[108] Dr. Dansereau described the work of the inventors in a similar manner as Dr. Burgio, including the setbacks and challenges, the Enterion studies and the testing of prototype formulations. He explained that the original hypothesis of colonic delivery was not successful. With respect to the use of chelating agents, he noted that he focussed on EDTA due to its strong binding characteristics compared to risedronate. At that time, EDTA had been used as a stabilizer or preservative, not for this type of pharmaceutical application.

[109] With respect to BR 601, Dr. Dansereau did not recall how this came to his attention but, like Dr. Burgio, opined that it may have been provided by the patent department at P&G. Dr. Dansereau stated that his impression upon reviewing BR 601 was that one of its objectives was to use a chelating agent to increase the permeability of the intestinal mucosa and thus increase the capacity to absorb the bisphosphonate. He explained that he and Dr. Burgio did not want to alter intestinal permeability. In his view, BR 601 was about providing lower doses of the bisphosphonate active ingredient, not about solving the food effect.

[110] **Mr. Foo-Lim Yeh** is the Director of Regulatory Affairs at Allergan, responsible for overseeing the regulatory approval and maintenance of Allergan's pharmaceutical products with Health Canada. Mr. Yeh attested to Allergan's NOC for ACTONEL DR.

C. *Expert Witnesses for Apotex*

[111] **Dr. John Yates** is an expert in pharmacology, including the pharmacology and chemistry of bisphosphonates, bone and mineral metabolism, the development of pharmaceutical products for treating disorders of the bone, including osteoporosis, and the use of bisphosphonates to treat disorders of the bone, including osteoporosis. He holds degrees in the United Kingdom, which are equivalent to an MD and PhD in Canada. Dr. Yates led a team of researchers at Merck & Co Inc. [Merck] from 1990 to 2003, which focussed on the development of alendronate, a bisphosphonate. Dr. Yates addressed the allegations of invalidity of the '188 Patent, including the state of the art as of April 15, 2005, from the perspective of a pharmacologist. Dr. Yates also responded to Dr. Adachi's opinion on the infringement allegations.

[112] Dr. Yates' view is that the Apotex product will not infringe the '188 because it is not a product that can be taken with or without food or beverage.

[113] Dr. Yates stated that the claims of the '188 Patent require that the oral dosage form provides "pharmaceutically effective absorption" regardless of whether the dosage form is administered in the fed or fasted state. Dr. Yates notes that the patent provides that it is at the preference of the patient whether to take the dosage fed or fasted, and the intention is to simplify the treatment therapy and lead to increased compliance.

[114] In Dr. Yates' opinion, the '188 Patent is anticipated by BR 601 and it is obvious based on the prior art, including BR 601.

[115] With respect to obviousness, Dr. Yates stated that there were no differences between the state of the art in 2005 and the subject matter of the claims. Dr. Yates adds that any possible differences would have been bridged by the skilled person using their common general knowledge and would have readily combined several other prior art references to develop the subject matter of the asserted claims.

[116] Dr. Yates emphasized the teaching of BR 601, which in his view teaches every element of the claims. He opined that BR 601 disclosed an enteric-coated bisphosphonate and EDTA that will provide pharmaceutically effective absorption because it does not require that it must be taken fasted or must be taken fed. Dr. Yates added that even without BR 601, the claims of the '188 Patent would be obvious. Dr. Yates provided his opinion of the teaching of several prior art

references. Among other things, he did not agree with the Allergan experts that the prior art discouraged the use of EDTA.

[117] **Dr. Alan Parr** is an expert in pharmaceutical formulation, including pre-formulation of solid dosage forms (both conventional and delayed/controlled release) and the biopharmaceutics of pharmaceuticals, including their design and evaluation and including for drugs having poor absorption and/or solubility. He received his PharmD and PhD in the United States. He has 30 years of experience in the pharmaceutical industry, of which 28 years were with GlaxoSmithKline. Dr. Parr is currently an independent consultant in biopharmaceutics. Dr. Parr addressed the validity issues, including the teaching of the state of the art as of April 15, 2005, and the common general knowledge from the perspective of a pharmacologist.

[118] Dr. Parr's view is that the '188 Patent is anticipated by BR 601 and is obvious based on BR 601 and the teaching of the prior art.

[119] Dr. Parr explained the teaching of the prior art from his perspective, noting among other things that formulations of EDTA and bisphosphonates had been described in the prior art and that EDTA was known to be safe at particular levels, including those exceeding the amounts set out in the '188 Patent. Dr. Parr disagreed with Dr. Sinko's opinion regarding possible adverse impacts of EDTA on the intestine.

[120] Dr. Parr also opined that BR 601 enables the skilled person, using the common general knowledge, to prepare the subject matter of the claims. He pointed to the example of the

alendronate formulation in BR 601. Dr. Parr noted that a pharmaceutical formulator would have experience using the excipients and enteric coatings set out in BR 601 and the dosage forms claimed in the ‘188 Patent would not be difficult to prepare. Dr. Parr added that the prior art included disclosure of this combination (citing BR 601, PCT Patent Application WO 00/61111 [WO 111], U.S. Patent 5,462,932 [the ‘932 Patent] and U.S. Patent 5,730,715 Patent).

[121] Dr. Parr’s view is that there is no difference between the state of the art in April 2005 and the subject matter of the ‘188 Patent. The only possible difference is that there was no specific example in the prior art of making an enteric-coated tablet containing risedronate and EDTA. Dr. Parr stated that this difference would be easily bridged without inventive ingenuity.

[122] **Dr. John Dillberger** is an expert in toxicology and the application of toxicology, pathology and pharmacology to the safety evaluation of drugs and the preparation of safety evaluation packages for regulatory submissions. He received his Doctor of Veterinary Medicine degree and PhD in pathology and environmental toxicology in the United States. He has been certified as an expert in veterinary pathology and toxicology by American professional bodies and is a fellow in the International Academy of Toxicologic Pathology. Dr. Dillberger’s evidence focussed on the safety of EDTA and its use in food and pharmaceuticals as of April 15, 2005.

[123] Dr. Dillberger disagreed that the prior art noted in the ‘188 Patent and other prior art taught away from the use of EDTA. He disagreed with Dr. Sinko that EDTA, particularly together with a bisphosphonate, has a toxic effect on the intestinal membrane. Dr. Dillberger stated that there was extensive use of EDTA in food and pharmaceuticals as of April 15, 2005.

[124] **Dr. Lélio Denicoli Schmidt** is an expert in Brazilian intellectual property law, including patent law and practice, including before the Brazilian patent office. He holds a PhD in intellectual property. Dr. Schmidt is currently a senior partner at a Brazilian intellectual property law firm, and is a patent and trademark agent enrolled at the Brazilian Patent and Trademark Office. He has acted as an expert to assist Brazilian judges in several intellectual property cases. His evidence focussed exclusively on the filing and publication of BR 601 and whether and how it could be found and accessed.

[125] Dr. Schmidt confirmed that BR 601 was filed on December 21, 2001 and published on the Brazilian patent office's Official Gazette No. 1705 on September 9, 2003. He noted that the Gazette provided the application number, application filing date, title of the invention, abstract of the invention, applicant name, inventor name, and patent agent name.

[126] Dr. Schmidt opined that prior to April 2005, BR 601 would have been publicly available on the online database of the Brazilian patent office, created in 1997, which includes Brazilian issued patents and published patent applications. He explained that to obtain a complete copy of BR 601, a person must attend at the Brazilian patent office; the request cannot be made in writing or online.

[127] With respect to how he had located BR 601, Dr. Schmidt acknowledged that he was provided with the application number by counsel for Apotex. He explained that he found BR 601 in the database by inputting the application number, which led him to Official Gazette No. 1705.

He also acknowledged that he had never searched for BR 601 prior to April 2005 and, in fact, the first time he did so was in 2020.

[128] Dr. Schmidt acknowledged that over 300 patent applications are published in each weekly edition of the Official Gazette and that BR 601 was published in a volume of that length.

D. *Fact Witnesses for Apotex*

[129] **Mr. Duane Terrill** is the Director of Regulatory Affairs Canada and Caribbean at Apotex. He has been employed by Apotex since 1990 with a focus on Regulatory Affairs since 2005. Among other responsibilities, he oversaw the regulatory submissions to Health Canada for the Apotex product. Mr. Terrill attached to his affidavit documents filed with Health Canada in relation to the Apotex product.

[130] Mr. Terrill explained that Apotex submitted a Supplemental Abbreviated New Drug Submission [SANDS] for APO-RISEDRONATE DR to Health Canada. He noted that Apotex only conducted a comparative bioavailability study on the APO-RISEDRONATE DR tablets and ACTONEL DR tablets [redacted]. Apotex sought [redacted] from Health Canada [redacted], submitted to Health Canada, cited the safety concerns associated with administration of the product in the fasted state (i.e., upper abdominal pain), the position of the United States Food and Drug Administration [U.S. FDA], which conducted only a fed study, and the labelling instructions that ACTONEL DR be consumed after breakfast. Health Canada granted [redacted].

[131] On cross examination, when presented with [redacted] a [redacted] study conducted in 2016 at the request of Apotex, Mr. Terrill testified that he was not aware that Apotex had conducted [redacted] studies with 35 mg delayed-release risedronate tablets. Mr. Terrill acknowledged that it appeared that Apotex had conducted such a [redacted] study in 2016.

[132] Mr. Terrill stated that Apotex did not conduct a [redacted] study on the specific formulation which was ultimately submitted to Health Canada.

[133] Mr. Terrill did not dispute the suggestion by counsel for Allergan that Apotex sought to [redacted] pursue a course of action for other reasons [redacted]

[134] **Dr. Martin Bonenfant** is the Director of Legal and Intellectual Property at Medicago Inc., a biopharmaceutical company. He holds a PhD in Reproductive Biology. Between 2002 and 2005, he was employed as a scientific analyst by Chemical Abstracts Service, a division of the American Chemical Society and a provider of scientific information. Between 2005 and 2008, Dr. Bonenfant was employed by Canadian law firm Ogilvy Renault as a technical advisor in patents.

[135] Dr. Bonenfant explained that during his time at Chemical Abstracts Service he was responsible for reviewing scientific documents and inputting the relevant information into the "STN" database, a database that provides worldwide coverage of scientific documents including international journals, patents, and patent applications. He noted that given the team of over 800

analysts, who spoke various languages, publications in a foreign language were reviewed and the relevant information was put into the database, including the title, abstract, date of publication, type of publication (scientific or patent), language and entry date.

[136] Dr. Bonenfant was retained by Apotex to carry out a search on the STN search engine for scientific documents, including patent applications, which included the words “composition” and “bisphosphonates” in their titles. Dr. Bonenfant attested that on January 21, 2021 he conducted a search on the STN database for publications using specific search terms that had “composition” and “bisphosphonates” in the title. This yielded 27 scientific documents, one of which was information about BR 601.

On cross examination, Dr. Bonenfant agreed that access to the STN database requires a paid subscription.

E. *Observations Regarding the Experts’ Evidence*

[137] Both parties submit that the evidence of their experts is more credible and based on greater or more relevant experience. Both parties cast aspersions on the opposing experts for various reasons, including their participation in analogous litigation in the United States, their advocacy for a particular position, and their sometimes contrived and other times vague answers.

[138] Allergan submits that the Apotex experts had predetermined views about the teaching of the art. Allergan notes that Dr. Yates and Dr. Dillberger had both testified in the U.S. litigation for

the analogous product and both acknowledged that they were confirming the same opinions from the previous litigation.

[139] Allergan also cautions against relying on opinions based on hindsight by the Apotex experts, noting that Apotex selected the prior art and provided it to the experts. Allergan adds that the Apotex experts did not conduct any further searches for relevant prior art that would support a different view.

[140] As I stated at the hearing, I review all the evidence, including the testimony of the experts in its entirety. I am sceptical of being pointed to extracts of examination and cross examination which points in a particular direction to support a particular argument without the full context being considered.

[141] The experts all brought their expertise and perspectives to bear on the issues and mandates given to them and provided detailed evidence and responses to questions.

[142] However, despite that all the experts were highly qualified and some had similar expertise, their opinions differed on several key issues. They interpreted the prior art differently and some disagreed with the underlying statements in some of the art, while taking other statements at face value, without any scrutiny or based on assumptions. For example, despite his considerable expertise and the high regard that other experts expressed, Dr. Yates' evidence was not persuasive on several issues due to his interpretations, assumptions and rigidity.

[143] With respect to Allergan's submission that Dr. Parr's blinded evidence is not deserving of any greater weight given the contrived manner his opinion was procured, I note that the jurisprudence is mixed on the treatment of blinded evidence. I favour the approach noted in *Janssen Inc v Apotex Inc*, 2019 FC 1355 at paras 58-59 [*Janssen 2019*], that blinded opinions are not necessarily given greater weight just because they are blinded. As noted by the Court:

> [58] There is some authority in this Court that favours blinded witnesses. However, I am of the view that blinding can be overrated. It may be a factor in giving weight but the Court is more interested in the substance of the opinion and the reasoning behind the conclusions. In that respect my conclusion is similar to that in *Shire Canada Inc v Apotex Inc*, 2016 FC 382, 265 ACWS (3d) 456.
>
> [59] Blinding may in some cases be unhelpful because the opinion lacks proper context. In other cases blinding will produce a less cluttered opinion. In the present case I do not favour Apotex's experts simply because they were blinded. I would favour their opinions on the POS and common general knowledge because they offered stronger reasons for their position. Some of Apotex's witnesses, Nam for example, provided confusing and at times contradictory statements on utility and non-infringement.

[144] Similar reasoning applies here. I have considered the opinions of Dr. Parr in their overall context, including his responses on cross examination.

[145] The weight attached to particular evidence and my preference for the opinion of one expert over that of another is addressed in the analysis of the issues.

V. The Person of Skill in the Art

[146] The person of skill in the art [the skilled person] is not a real person, rather a notional person or team of persons with an amalgamation of different skills and attributes. The skilled

person provides the lens or perspective through which the patent is construed, the teaching of the prior art is considered, and the allegations, in this case, of invalidity and infringement are assessed (*Pfizer Canada Inc v Pharmascience Inc*, 2013 FC 120 at para 28; *Teva Canada Limited v Janssen Inc*, 2018 FC 754 at para 66, aff'd 2019 FCA 273; *Teva Canada Innovation v Pharmascience Inc*, 2020 FC 1158 at para 232).

[147] There is an abundance of jurisprudence about the skilled person.

[148] In *Janssen Inc v Teva Canada Ltd*, 2020 FC 593 at para 98 [*Janssen 2020*], the Court considered the jurisprudence and summarised the skilled person as follows:

> The POSITA is a worker of ordinary skill to which the invention relates who possesses the ordinary amount of knowledge incidental to the particular trade (*Consolboard Inc v Macmillan Bloedel (Saskatchewan) Ltd*, [1981] 1 SCR 504 at 523). The POSITA may be a team of persons with different skills (*Teva Canada Limited v Janssen Inc*, 2018 FC 754 at para 66 [*Teva Canada*], aff'd 2019 FCA 273).

[149] In *Valeant Canada LP/Valeant Canada SEC v Generic Partners Canada Inc*, 2019 FC 253 at para 44 [*Valeant*], the Court described the skilled person in much the same way:

> The PSA is unimaginative and uninventive, but reasonably diligent in keeping up with advances (*Pfizer Canada Inc v Teva Canada Ltd*, 2017 FC 777 at para 185). The PSA is not incompetent, and brings background knowledge and experience to the workbench (*AstraZeneca Canada Inc v Apotex Inc*, 2015 FC 322 at para 276). The PSA is not stripped of the ability to pursue reasonable and logical enquiries, and can make deductions based on the information available (*Jay-Lor International Inc v Penta Farms Systems Ltd*, 2007 FC 358 at para 75 [*Jay-Lor*], citing *Beloit Canada Ltd v Valmet Oy* (1986), 8 CPR (3d) 289 at 294 (FCA) [*Beloit*]).

A. *Allergan's Position on the Skilled Person*

[150] Allergan submits that for this Patent, some aspects are directed to a skilled physician and others to a skilled person having a range of experience, including pharmacology (and formulation).

[151] With respect to the aspects of the '188 Patent directed to a skilled physician, Allergan submits that this person is a physician with actual experience treating patients with osteoporosis.

[152] Allergan submits that with respect to the aspects of the '188 Patent directed to a skilled pharmacologist (a part of the "skilled person" team) – as opposed to the skilled physician – the level of expertise expected is that of the ordinary pharmacologist. Allergan submits that Dr. Yates' perspective and evidence was based on the skill set of an entire drug development team, such as the team he led at Merck, a leading industry player in the bisphosphonates field. Allergan submits that the opinions of Dr. Yates and Dr. Parr reflect their view that the skilled pharmacologist would possess skills superior to those of the person of ordinary skill and should be considered in this light.

B. *Apotex's Position on the Skilled Person*

[153] Apotex submits that there is no real disagreement about the attributes of the skilled person. Apotex submits that the '188 Patent is directed to a team familiar with the oral dosing of bisphosphonates, including their side effects, bioavailability when fasting and fed, and how bisphosphonates are administered. The team includes a drug formulator having a graduate degree in a relevant discipline and at least a few years experience developing oral formulations, including

delayed-release formulations. The team also includes clinical researchers with relevant scientific backgrounds, such as an MD, and several years experience designing, conducting and interpreting clinical trials, and with familiarity with animal studies, including toxicology and pharmacology.

C. *The Experts' Evidence regarding the Skilled Person*

[154] Allergan's expert, Dr. Cremers, opined on the attributes of the skilled person or team taking into account the subject matter of the '188 Patent.

[155] Dr. Cremers stated that the '188 Patent is directed to a team that includes a skilled physician and a skilled person. The skilled person could have a PhD degree in pharmacy, pharmaceutical sciences, or pharmacology, and some related work experience; or a master's degree in such disciplines and more related work experience (about 3 years); or a bachelor's degree in such disciplines and a greater amount of related work experience (about 5 years). This skilled person would have a general understanding of formulations, including dosage forms and coatings, and a general understanding of the clinical pharmacology of bisphosphonates.

[156] Dr. Cremers added that the skilled physician would have an MD in a relevant field for the treatment of diseases described in the '188 Patent along with some practical work experience in the treatment of such diseases.

[157] Allergan's expert, Dr. Adachi, also considered the subject matter of the Patent in setting out his opinion on the attributes of the skilled physician. Dr. Adachi agreed that the Patent is directed to a team of skilled individuals.

[158] In Dr. Adachi's view, the aspects of the Patent relating to the treatment of osteoporosis and other bone diseases would be directed to a skilled physician with experience in diagnosing and treating diseases characterized by abnormal calcium and phosphate metabolism, including osteoporosis. The skilled physician would have an MD and clinical and practical experience using bisphosphonates, including risedronate, to treat diseases characterized by abnormal calcium and phosphate metabolism such as osteoporosis.

[159] Apotex's expert, Dr. Yates, described his view of the skilled person noting his own extensive qualifications and his own experience, including his 13 years as clinical researcher at Merck, where he led teams that included scientists in many different disciplines, including drug formulation, drug manufacturing, and basic and clinical research. Dr. Yates opined that "[i]t is to just such a team that the 188 Patent is directed."

[160] Dr. Yates elaborated, based on the qualifications of the team he had led at Merck, that the skilled person would include a drug formulator with a PhD or master's degree in a relevant discipline, such as formulation science, and at least a few years of experience in developing oral formulations, including delayed-release formulations. The team would also include a clinical researcher with an MD, a strong scientific background and several years of experience in designing, conducting and interpreting the results of clinical trials. Dr. Yates added that the same clinical researcher or another scientist on the team would also be familiar with relevant studies conducted in animals, including toxicology and pharmacology studies. All members of the team would be familiar with the oral dosing of bisphosphonates, including their side effects,

bioavailability under fasting and fed conditions, and conditions under which bisphosphonates were administered.

[161] Dr. Parr stated that the skilled person is a team that would include a formulator, with a graduate degree (e.g., MSc or PhD), such as a pharmaceutical formulator with several years of experience developing pharmaceutical dosage forms in industry. The team would also include clinicians, preclinical pharmacologists, and toxicologists.

D. *The Skilled Person for the Purpose of this Application*

[162] With respect to Allergan's submission that the Apotex experts elevated the attributes and expertise of the skilled person beyond that of the ordinary skilled person, this view is reflected to some extent in Dr. Yates' evidence. Dr. Yates stated that the skilled person or team is the type of team he led at Merck. However, Dr. Yates disputed that his team members were more expert or knowledgeable than those that other pharmaceutical companies would hope to retain for similar projects.

[163] There is really not much disagreement on the attributes of the skilled person or team of persons. Whether the Apotex experts applied a higher than ordinary standard of knowledge, skill and experience to their perspective as a skilled person or skilled physician will be assessed in the context of their opinions and evidence. For example, in several instances, Dr. Yates disagreed with statements in the prior art, noting that the skilled person would not agree. Dr. Yates also was reluctant to praise the inventors or members of his own team for their knowledge and expertise. Whether his opinion of others or on the teaching of the prior art is due to an application of a higher

standard will be considered in that context. In my view, this does not change the characterization of the skilled person. As noted in the jurisprudence, the skilled person is not imaginative or inventive and possesses ordinary knowledge and skill in their field, albeit that the field may be highly specialized. The skilled person or team of persons, given the attributes and experience required, is hardly "ordinary" as that term is generally understood, but among their peers, they are just that; neither exceptionally brilliant nor dull.

[164] I find that the skilled person is a two part team: a skilled physician and a skilled person (other than the skilled physician), that is also a team.

[165] The skilled physician is a physician with experience in diagnosing and treating diseases characterized by abnormal calcium and phosphate metabolism, including osteoporosis. The skilled physician would have practical experience using bisphosphonates, including risedronate, to treat diseases characterized by abnormal calcium and phosphate metabolism such as osteoporosis. The skilled person would, of course, have an MD and several years experience in a clinical practice which includes the diagnosis and treatment with bisphosphonates of such conditions. The skilled person would include family physicians, endocrinologists, rheumatologists, geriatricians, or a resident in those fields where they meet these criteria.

[166] The skilled person, or team of persons (apart from the skilled physician) would be familiar with the oral dosing of bisphosphonates, including their side effects, bioavailability when fasting and fed, and how bisphosphonates are administered. The team includes a drug formulator or other scientist with a master's or PhD degree in pharmacy, pharmaceutical sciences, or pharmacology,

and related work experience, with an understanding of or experience with formulations, including dosage forms, coatings and the clinical pharmacology of bisphosphonates, including delayed-release formulations. The team also includes clinical researchers with relevant scientific backgrounds, and experience designing, conducting and interpreting clinical trials, including familiarity with animal studies, including toxicology and pharmacology.

VI. The Invention

[167] With respect to the disclosure of the ‘188 Patent, the experts described the invention in a similar manner, basically reiterating the words in the Patent as set out above and offering little in the way of a layman’s explanation.

[168] For example, Apotex’s expert, Dr. Yates, noted that the invention pertains to a solid dosage form of risedronate, which also contains EDTA in an enteric-coated dosage form that is designed to remain intact in the stomach. Once the intact dosage form passes through the pylorus (the exit valve of the stomach) and into the higher pH environment of the small intestine the enteric coating dissolves allowing the contents of the dosage form to become available for absorption. Dr. Yates explained that enteric-coated dosage forms are also referred to as delayed-release dosage forms because the release is delayed until the dosage form is in the small intestine.

[169] Dr. Yates added that the ‘188 Patent states that once the dosage form is in the small intestine, it is designed to release both the risedronate and the EDTA rapidly, with consequent absorption of the risedronate. Dr. Yates explained that this approach differs from the earlier immediate-release formulations of bisphosphonates, including alendronate and risedronate, which

were required to be taken after an overnight fast and without any food for at least 30 minutes after dosing.

[170] Dr. Yates noted that the interaction of bisphosphonates with food was referred to as the "food effect". The binding of the bisphosphonates to multivalent cations, particularly calcium, impaired the absorption of the bisphosphonate. Dr. Yates stated that EDTA was known to bind strongly to such cations and was known to have the potential to overcome the food effect.

[171] The experts agreed that all the elements of the claims are essential elements. They also agree that the inventive concept of each claim is the subject matter of the claim, i.e., with all the elements set out as essential.

A. *The Construction of the Claims*

[172] The '188 Patent has 137 claims. Claims 1 and 98 are independent claims. The other claims depend from Claim 1 and from other dependant claims. The experts opined on the meaning of all the claims, noting several groupings of claims. Allergan subsequently narrowed its allegations of infringement to three sets of claims.

[173] The first set, which Allergan characterizes as "product claims", is composed of Claim 63, as it depends on Claim 60, as it depends on Claim 54, as it depends on Claim 36, as it depends on Claim 6, as it depends on Claim 5, as it depends on Claim 4, as it depends on Claim 3, as it depends on Claim 1. This covers the following claims:

Claim 1. An oral dosage form of a bisphosphonate for use with or without food or beverage intake, comprising a pharmaceutical composition comprising:

a) from about 1 mg to about 70 mg of the bisphosphonate, the bisphosphonate being risedronate, an acid, salt, ester, hydrate, polymorph, or solvate thereof, or a combination of two or more of the foregoing;

b) EDTA wherein the EDTA is at least 50% as soluble in water as the bisphosphonate; and

c) an enteric coating, wherein the enteric coating provides for release of the bisphosphonate and the EDTA in the small intestine and the molar ratio of EDTA to bisphosphonate is at least 2, to provide for pharmaceutically effective absorption of the bisphosphonate with or without food or beverage intake.

Claim 3. The oral dosage form of claim 1, wherein the composition contains from about 10 to about 70 mg of the bisphosphonate.

Claim 4. The oral dosage form of claim 3, wherein the composition contains from about 15 to about 55 mg of the bisphosphonate.

Claim 5. The oral dosage form of claim 4, wherein the composition contains from about 35 mg to about 50 mg of the bisphosphonate.

Claim 6. The oral dosage form of claim 5, wherein the composition contains about 35 mg of risedronate sodium.

Claim 36. The oral dosage form of claim 6, wherein the composition contains about 100 mg of disodium EDTA.

Claim 54. The oral dosage form of any one of claims 3 to 7, 10 to 13, 16 to 20, 23 to 26, 29, 30, 33 to 36, 39, 42, 45, 48 and 51, wherein the enteric coating dissolves at about pH 5.5.

Claim 60. The oral dosage form of any one of claims 3 to 7, 10 to 13, 16 to 20, 23 to 26, 29, 30, 33 to 36, 39, 42, 45, 48, 51, 54 and 57, wherein the enteric coating is a methacrylic acid copolymer.

Claim 63. The oral dosage form of any one of claims 3 to 7, 10 to 13, 16 to 20, 23 to 26, 29, 30, 33 to 36, 39, 42, 45, 48, 51, 54, 57 and 60, wherein the composition weighs no greater than 1 gram.

[174] The second set, which Allergan characterizes as “use claims”, is composed of Claim 77, as it depends on Claim 72, as it depends on Claim 69, as it depends on Claim 66, as it depends on the product claim set above. The relevant claims are:

Claim 66. Use of an oral dosage form of any one of claims 3 to 7, 10 to 13, 16 to 20, 23 to 26, 29, 30, 33 to 36, 39, 42, 45, 48, 51, 54, 57, 60 and 63 for the treatment or prevention of a disease characterized by abnormal calcium and phosphate metabolism.

Claim 69. Use according to claim 66 wherein the disease is osteoporosis, Paget’s disease, hyperparathyroidism, hypercalcemia of malignancy, osteolytic bone metastasis or a combination of any of the foregoing.

Claim 72. Use according to claim 69, wherein the disease is osteoporosis.

Claim 77. Use according to any one of claims 66, 39 and 72, wherein the composition is for weekly use.

[175] The third set is the "kit claim", which is Claim 79 as it depends on the product claim set. Claim 79 states:

> Claim 79. A kit comprising:
>
> (a) one or more oral dosage forms according to any one of claims 1 to 63; and
>
> (b) means for facilitating compliance for use of the one or more oral dosage forms.

B. *The Issue in Dispute Regarding the Construction of the Claims*

[176] The claims appear to be clearly worded and the meaning of "for use with or without food or beverage intake" *per se* is not contentious. However, the parties disagree about how these words, as they are used in the context of "an oral dosage form of a bisphosphonate for use with or without food or beverage intake" in Claim 1, affect the construction of the claim.

[177] As noted above, Allergan characterizes the first set of claims as "product claims". Apotex disputes this characterization and argues that this overlooks the clear wording that the product must be for use with or without food or beverage intake. Apotex characterizes the claims as "products for use" claims. The submissions of both parties on the construction of the claims are related to their positions on infringement. The Court's role is to construe the claims in a purposive manner before considering the allegations and engaging in an analysis of the issues. The Court's construction guides the analysis of all allegations; there is one construction for all purposes.

C. *Allergan's Submissions*

[178] Allergan submits that the first set of claims are "product claims" all of which depend from independent Claim 1, which defines an oral dosage form – a physical thing – with specific ingredients and a specific coating. Allergan submits that Claim 1 relates only to the product, i.e., the oral dosage form and what it will achieve. Allergan disputes Apotex's characterization that Claim 1 is a "product for use" claim, i.e., that how it is intended to be used is part of the construction.

[179] Allergan adds that the product claim set is not a use claim set. The claims do not claim a new use for an old product. Claim 1 does not state what the dosage form is to be used for (i.e., for what treatment or condition). Other claims (the use claim set) deal with the product's use for the treatment of osteoporosis. Use is not a requirement in the product claim set. The term "for use with or without food…" is an option or a capability. A patient need not use the oral dosage at all.

[180] Allergan submits that Claim 1 should be interpreted to reflect that the patient has the choice to take the products with food or without food because either way the product will provide pharmaceutically effective absorption and will treat their osteoporosis. The claim should not be interpreted to require the actual use of the product.

[181] With respect to the meaning of the term "oral dosage form … for use with or without food or beverage intake", Allergan submits that "for use…" means "suitable for use…". Allergan explains that because the oral dosage forms will provide pharmaceutically effective absorption

whether taken with or without food or beverage intake, they are "suitable for use" with or without food or beverage intake, or in other words capable of use in both states.

[182] Allergan submits that the jurisprudence has established that the word "for" in a product claim is normally construed to mean that the claimed product is "suitable for" the use stated in the claim, citing *Fox on the Canadian Law of Patents* (Donald MacOdrum, *Fox on the Canadian Law of Patents*, 5th ed (Toronto: Carswell, 2021), ch 8.9(c) [*Fox*]).

[183] Allergan further submits that the effect of interpreting the product claim as meaning "suitable for use", as stated by *Fox,* is that the claim extends to any product that is suitable for that stated purpose, whether it is used for that purpose or not. Allergan notes that the jurisprudence has established exceptions to this rule of construction, but none of the exceptions are at play in this case. Allergan submits that the jurisprudence cited by Apotex, including *AB Hassle v Canada (Minister of National Health & Welfare)*, 2001 FCT 1264 [*AB Hassle*] and *Bristol-Myers Squibb Canada v Apotex Inc*, 2017 FC 1061 [*BMS 2017*], dealt with claims that were drafted as product for use claims, but in fact dealt with the new use of an old product. In the present case, the first set of asserted claims, which depend on Claim 1, are new product claims.

[184] Allergan notes that as set out in Apotex's written submissions, Apotex agreed that an oral dosage form that is for use with or without food or beverage intake is an oral dosage form that is suitable for use and/or capable of use with or without food or beverage intake.

[185] Allergan points to the evidence of Apotex's expert, Dr. Yates, in his report responding to Dr. Adachi's opinion on infringement, where he stated that the term "with or without food…" must be read together with "pharmaceutically effective absorption" and noted that "according to the 188 Patent, the solution to the food effect problem is a risedronate dosage form that is capable of being taken either with food or without food (or beverage), based on the preference of the patient."

[186] Allergan adds that Dr. Parr also noted that the oral dosage can be taken with food or without food so long as pharmaceutically effective absorption is achieved.

[187] Allergan also made extensive submissions in the context of its allegations of infringement, including the distinction between product claims, use claims and product for use claims with reference to the jurisprudence on infringement.

D. *Apotex's Submissions*

[188] Apotex notes that there is no dispute that the term "for use with or without food or beverage intake" is an essential element of the asserted claims. Apotex submits that this term is used in distinct elements of Claim 1.

[189] Apotex disputes Allergan's position that the phrase "oral dosage form … for use with or without food or beverage intake" means that the claimed dosage form is "suitable for" or "capable of" use with or without food or beverage intake if this interpretation suggests that it is suitable for use in both states if, when used in either state, it results in pharmaceutically effective absorption. Apotex appears to agree that "use with or without food…" could mean "suitable for use…" if that

interpretation applies only to the oral dosage form, i.e., how it is to be taken and not with regard to the result it will achieve.

[190] Apotex submits that the Court should not read in or read out words in the claims.

[191] Apotex submits that Claim 1 is not simply a product claim, as argued by Allergan with a view to shoring up their infringement allegations, rather a "product for use" claim.

[192] Apotex submits that Allergan's proposed construction duplicates the use of the same phrase later in Claim 1 – that the dosage form is "to provide pharmaceutically effective absorption … with or without food or beverage intake". Apotex submits that this is a distinct and separate element from the earlier reference to an "oral dosage form for use with or without food…", which defines the purpose of the oral dosage and the use for the oral dosage form. The second part of the claim sets out what comprises the oral dosage form. Apotex submits that pharmaceutically effective absorption is the result of the oral dosage form and this is achieved when taken with or without food. Apotex submits that each distinct element must be given meaning, which Allergan's construction does not.

[193] Apotex submits that the words of the claims are clear, but if guidance is needed from the disclosure, the '188 Patent clearly describes the invention as a means to overcome the food effect. Apotex notes that the '188 Patent describes the food effect problem with bisphosphonates, the inconvenience of the strict dosing requirements while fasted, and its impact on patient compliance and, in turn, treatment. The '188 Patent describes its invention as an oral dosage form that can be

taken at the preference of the patient, either with or without food. The construction of the claims must be "tethered" to the invention as disclosed.

[194] Apotex also points to the evidence of Dr. Cremers who explained that "for use with or without food or beverage intake" defines the purpose of the oral dosage form, i.e., its intended use, while the phrase "to provide for pharmaceutically effective absorption of the bisphosphonate with or without food or beverage intake" defines the pharmacological result of the dosage form.

[195] Apotex submits that this means that the oral dosage form is for use with food or beverage and also for use without food or beverage. An oral dosage form that is limited to use in only one state, with food, but not without food, or without food but not with food would not meet this essential element.

E. *The Relevant Jurisprudence Regarding Construction of the Claims*

[196] Claims construction is for the Court to determine guided by expert evidence if needed. The construction of the claims precedes consideration of the allegations of invalidity. The claims are construed as of the publication date, which in this case is October 26, 2006.

[197] In *Valeant*, the Court noted the "canons of claim construction" at para 42:

> [42] The canons of claims construction are found in the Supreme Court of Canada's decisions in *Whirlpool* at paragraphs 49 to 55 and *Free World Trust v Électro Santé Inc*, 2000 SCC 66 [*Free World Trust*] at paragraphs 44 to 54. They are the following:
>
> (a) claims are to be read in an informed and purposive way with a mind willing to understand, viewed through the eyes

> of the person skilled in the art as of the date of publication having regard to the common general knowledge;
>
> (b) adherence to the language of the claims allows them to be read in the manner the inventor is presumed to have intended, and in a way that is sympathetic to accomplishing the inventor's purpose, which promotes both fairness and predictability; and
>
> (c) the whole of the specification should be considered to ascertain the nature of the invention, and the construction of claims must be neither benevolent nor harsh, but should instead be reasonable and fair to both the patentee and the public.

[198] The parties do not dispute the applicable principles.

F. *Overview of the Experts' Evidence on the Construction of the Claims*

[199] The wording of the claims is clear and when read in conjunction with the disclosure of the Patent, the claim language reflects the inventors' intentions. There should be no need to turn to the opinions of the experts for guidance. However, the meaning of "for use with or without food…" is in dispute, particularly as that term is used in the context of "oral dosage form … for use with or without food…." There is no disagreement about what "with or without food or beverage intake" means on its own. To the extent that Allergan and Apotex disagree, their disagreement is about the characterization or labelling of the claims, in particular, whether the first set of claims for oral dosage forms are product claims or "product for use" claims.

[200] Given this disagreement and the need for the claims to be read through the eyes of the skilled person, the experts' opinions have been considered.

[201] Dr. Adachi described the disclosure of the ‘188 Patent and the essential elements of the claims. From the perspective of the skilled physician, Dr. Adachi described the goal of the Patent as addressing the ongoing need to develop an oral dosage form that can be taken with or without food. This takes into account patient preference, which improves adherence to therapy. Dr. Adachi noted that the biggest obstacle had been taking the medication correctly.

[202] Dr. Adachi noted that from his perspective, the skilled physician would understand that the ‘188 Patent relates to a solution to the food effect problem with bisphosphonate drugs. He explained that the skilled physician would understand that these oral dosage forms overcome the food effect problem because the combination of the elements (risedronate, a sufficient amount of a chelating agent and a means for effecting delayed release in the small intestine) result in pharmaceutically effective absorption of the drug regardless of whether the drug is administered with or without food or beverage.

[203] With respect to Claim 1, Dr. Adachi noted that the skilled physician would understand that “for use with or without food or beverage intake” describes “oral dosage form of a bisphosphonate,” and means an oral dosage form which may be used either with or without food or beverage intake. The skilled physician would be confident that the same formulation can be taken with or without food and it will provide similar absorption either way.

[204] Dr. Adachi noted that the term “with or without food or beverage intake” as used at the end of Claim 1 would have a consistent meaning. The skilled physician would understand this to mean that effective absorption could be achieved either with or without food or beverage intake.

[205] Dr. Cremers provided a description of the ‘188 Patent referring to the language of the Patent, noting the definitions of terms, and opined on the meaning of the claims using the language used in the claims (as did the other experts).

[206] Dr. Cremers stated that the skilled person would understand that the ‘188 Patent relates to a solution to the food effect problem with bisphosphonate drugs. The skilled person would understand the Patent to be disclosing that the oral dosage forms overcome the food effect problem because they provide for “pharmaceutically effective absorption of risedronate when administered with or without food or beverage intake.”

[207] Dr. Cremers explained that “for use with or without food or beverage intake” defines the purpose of the “oral dosage form of a bisphosphonate” (e.g., risedronate). The phrase means that the oral dosage form is for use with “or” without food or beverage intake, meaning that the claim encompasses both uses within its scope as alternatives. Dr. Cremers stated that this is consistent with the description in the Patent.

[208] Dr. Cremers opined that the choice of taking the product either with or without food at their preference is an integral part of the invention and an essential element of the claims.

[209] Dr. Yates offered his opinions on the meaning of the dependant claims, in a similar manner to the other experts and using the same words used in the Patent.

[210] Dr. Yates stated that the ‘188 Patent discloses enteric-coated formulations of risedronate plus EDTA that can be taken with or without food and overcomes the food effect.

[211] Dr. Yates stated that Claim 1 and the dependant claims require that the dosage form provides pharmaceutically effective absorption “regardless of whether the dosage form is administered in the fed or fasted state”. Dr. Yates noted that the problem solved by the ‘188 is described as meeting the need for an oral dosage form of a bisphosphonate “which can be taken with or without food or beverages (i.e. has pharmaceutically effective absorption regardless of food or beverage intake) at the preference of the patient, and which does not produce upper gastrointestinal irritation.” Dr. Yates added that the intention is to simplify the treatment therapy and lead to increased compliance.

[212] In his report responding to that of Dr. Adachi on infringement, Dr. Yates reiterated that the ‘188 Patent “describes an oral dosage form that does away with restrictive dosing requirements …” and that “the claimed oral dosage form is one that gives patients the option of taking it “with or without food or beverage intake”, whatever the patients’ preference may be.”

[213] Dr. Yates added with respect to the use of the term “for use with or without food…” at the end of Claim 1:

> … Claims 1 and 98 conclude in the same manner: the dosage forms of claims 1 and 98 must release sufficient EDTA in the small intestine “to provide for pharmaceutically effective absorption of the bisphosphonate with or without food or beverage intake.” The term “pharmaceutically effective absorption” is defined on page 6 of the 188 Patent to mean that the absorption of risedronate in the fed state must be within 50% of the absorption in the fasted state. Thus, the skilled person would understand that the

> words “with or without food or beverage intake” in claims 1 and 98 are to be read together with “pharmaceutically effective absorption” and mean that the dosage form will provide similar absorption of risedronate (within 50%) whether taken in the fed or fasted state “at the preference of the patient”.

[214] Dr. Parr noted that Claims 1 to 63 of the ‘188 Patent are claims to an oral dosage form of a bisphosphonate for use with or without food or beverage intake. He explained that the dosage form provides for pharmaceutically effective absorption of the bisphosphonate with or without food or beverage intake; in his words, “that permits the absorption of the bisphosphonate compounds to be consistent irrespective of being given under fed or fasted conditions.”

[215] Dr. Parr stated that:

> The term “for use with or without food or beverage intake” [in claim 1] would be understood to mean that the oral dosage form can be taken with or without food or beverage; that is, there is no limitation on the timing, amount or type of food or beverage so long as pharmaceutically effective absorption is achieved.

[216] Dr. Parr noted that the skilled person would understand that it is essential that the oral dosage form is able to be administered with or without food or beverage intake.

G. *The Court’s Construction of the Claims*

[217] The experts’ opinions focussed on the invention of the ‘188 Patent as providing the choice to the patient to take the oral dosage with food or without food to overcome the food effect and to achieve pharmaceutically effective absorption, not on whether “an oral dosage form … for use

with or without food…" means "suitable for" such use. The experts appear to be of the view, as am I, that it is clear what "for use with or without food…" means.

[218] None of the experts stated that "for use…" means "suitable for use" nor did they opine on whether the claims were "product claims" or "product for use" claims. All the experts interpreted the claims as reflecting the purported invention of a bisphosphonate that could be used with or without food, at the choice of the patient, because either way pharmaceutically effective absorption would be achieved.

[219] Dr. Cremers stated that "for use…" defines the purpose of the oral dosage form, which is to overcome the food effect. Dr. Yates stated that the '188 Patent's solution to the food effect is an oral dosage "capable of" being taken with or without food. Dr. Parr stated that the oral dosage form can be taken with or without food or beverage "so long as pharmaceutically effective absorption is achieved" and that it is essential that the dosage form is "able" to be administered with or without food.

[220] Although the parties each submit that the experts supported their respective views on construction, the experts were fairly consistent. No one suggested that two different meanings applied to the same term used in two parts of the claim.

[221] The term "with our without food or beverage intake" does not require interpretation – it clearly signals that the patient has a choice to take the oral dosage form either with food or without food.

[222] The experts emphasized the purpose of the invention and that the oral dosage form is for use both with and without food because this reflects and achieves that goal – to overcome the food effect and to result in similar absorption whether taken with food or without.

[223] The parties made very extensive submissions on their interpretation of the claims and the characterization of the first claim set, pointing to specific jurisprudence and/or distinguishing it. The case law which distinguishes product claims and claims for new uses of existing products does not assist in the construction of clearly worded claims. This case law is more relevant in the context of the allegations of infringement and will be considered in that context.

[224] There is a distinction between a use claim – as in a specified use of the formulation to treat or prevent a condition – and how to use a product. The ‘188 Patent includes use claims that indicate for what disease the invention is to be used (i.e., osteoporosis). The issue now raised, however, is about the manner of use of the oral dosage form (i.e., to be used either with or without food).

[225] For the ‘188 Patent, the ability to use the oral dosage form either with food or without food is set out in the claim because its purpose is to overcome the food effect (which is the problem of the extremely low absorption of the bisphosphonate when taken with food as opposed to when taken fasted). The oral dosage can be taken either with food or without food at the choice of the patient and the treatment effect will be similar (i.e., pharmaceutically effective absorption). The invention of the ‘188 Patent signalled a significant change in the administration of oral bisphosphonates, hence the emphasis on this feature.

[226] The jurisprudence guides that "[t]he entire patent specification should be considered in order to ascertain the nature of the invention, however adherence to the claim language allows the claims to be read in the way in which the inventor is presumed to have intended, promoting fairness and predictability" (*Biogen Canada Inc v Taro Pharmaceuticals Inc*, 2020 FC 621 at para 78 [*Biogen*]).

[227] In my view, there is no need to read in "suitable for" into the construction of the claims. The addition of these words to "oral dosage form… for use with or without food or beverage intake" as "oral dosage form … *suitable for use* with or without food or beverage intake" adds nothing.

[228] The term "for use with or without food or beverage intake" means what it says and reflects the disclosure of the Patent and the intention of the inventors – that the oral dosage of the bisphosphonate (risedronate) can be consumed, administered, taken (i.e., used) either with food or without food or beverage at the preference of the patient. When used either way, at the preference of the patient, pharmaceutically effective absorption will result. The purpose is important, otherwise there would be no need to state that it is for use with or without food. The inclusion of "for use with or without food…" is an essential element and integral part of the claim. As noted by Apotex, the construction is "tethered" to the invention.

[229] The first set of claims is construed as claims for an oral dosage form that can be used (i.e., can be consumed, administered or taken) at the choice of the user/patient either with or without food or beverage intake. This oral dosage form contains about 35 mg of risedronate sodium (Claim

6) and about 100 mg of disodium EDTA (Claim 36) in a core coated with a methacrylic acid copolymer enteric coating (Claim 60) that begins to dissolve at about pH 5.5 (Claim 54). This oral dosage form also weighs less than 1 gram (Claim 63). Claim 1 requires that this oral dosage form provides targeted release of EDTA and risedronate in the small intestine in an immediate release fashion. Claim 1 also requires that this oral dosage form provides pharmaceutically effective absorption whether it is used (i.e., consumed, administered, taken) with or without food or beverage intake.

[230] The second set of claims are "use" claims; i.e., the use of the products as claimed and construed to treat osteoporosis. The use claim set is directed to the weekly use of the claimed oral dosage forms (Claim 77) for the treatment or prevention of osteoporosis (Claim 72).

[231] The kit claims are for the oral dosage forms claimed along with some means of facilitating patient compliance (Claim 79), including packaging.

VII. The State of the Art

[232] The key art cited by Apotex and/or referred to by the Apotex and Allergan experts is set out in summary form below. The expert's opinions on the teaching of the art is described in the context of the anticipation and obviousness analysis at Parts IX and X.

A. BR 601

[233] BR 601 is a Brazilian patent application, filed in December 2001 and published in September 2003 but never issued by the Brazilian patent office. BR 601 is entitled "Pharmaceutical composition containing bisphosphonate for the treatment of diseases related to calcium and/or phosphate metabolism…." The inventor is Alcebiades de Mendonga Athayde and the applicant is Libbs Pharmaceutical Company Ltda. (BR/SP). BR 601 discloses that the "invention pertains to a pharmaceutical composition containing bisphosphate and a chelating agent for the treatment of diseases related to calcium and/or phosphate metabolism, for example osteoporosis, Paget's disease, heterotopic ossification, and cancer-related hypercalcemia." Apotex submits that the '188 Patent is anticipated by BR 601. BR 601 is described in more detail below.

B. *Food Effect in Small Intestine*

[234] Mahé, S, "Gastroileal nitrogen and electrolyte movements after bovine milk ingestion in humans" (1992) Am J Clin Nutr 56:410-416 [Mahé], studied the digestion and absorption of proteins, including milk proteins, in the small intestine of humans. Seven human subjects participated in the study. The report revealed that after milk ingestion, "[42%] of milk nitrogen was absorbed before the jejunum and 93% was absorbed before the end of the ileum." [these are parts of the intestine]. Based on these results, the authors concluded that "for the completion of the absorption of dietary proteins such as milk proteins, the lower part of the intestine is necessary."

[235] Fordtran, John S et al, "Ionic Constituents and Osmolality of Gastric and Small-Intestinal Fluids After Eating" (1996) Am J Digestive Diseases 11(7):503-521 [Fordtran], performed a series of experiments in human subjects to study the normal absorptive processes in the small intestine following the ingestion of food, specifically after eating a meal of steak (which contains a lower

amount of calcium) and a meal of milk and a doughnut (which contains a higher amount of calcium). Twenty-two studies were carried out in 10 participants with the steak meal and six studies were carried out in one participant with the milk and doughnut meal.

[236] Fordtran noted in its introduction that "the electrolyte composition and osmolality [i.e., the measure of the number of dissolved particles in a fluid] of post-prandial [i.e., occurring after a meal] fluid in the … small intestine are not known" and "are of interest". Fordtran noted that "the concentration of calcium in proximal duodenal fluid depends to a large extent on dietary intake." Fordtran found that calcium concentration was much higher after ingestion of the milk and doughnut meal relative to the steak meal. In the concluding paragraph of the publication, the authors summarized that, "[f]rom the results, osmotic constituents of postprandial gastric and intestinal fluid, and the pattern of electrolyte, volume, and osmotic pressure changes at different levels of the small intestine were determined."

[237] Other art cited but not addressed by the experts includes Davis 1984, Noach 1993, Berne 1998, Lee 1998, and Farhadi 2003.

C. *Bisphosphonates*

[238] Mitchell 1998: The '188 Patent cites Mitchell 1998 in support of the statement that bisphosphonates, such as risedronate, have similar absorption throughout the small intestine. Mitchell 1998 reported on the comparison of the absorption of risedronate administered as a solution to three different GI sites. Mitchel 1998 concluded that the study indicated that the rate

and extent of risedronate absorption are independent of the site of administration along the GI tract.

[239] Mitchell 1999: This study was funded by P&G to "examine the effect of timing of a risedronate dose relative to food intake on the rate and extent of risedronate absorption following single-dose, oral administration". Mitchell 1999 reported that the extent of risedronate absorption was comparable in subjects dosed two hours after dinner and 30 minutes before breakfast, however, a "significantly greater extent of absorption" occurred when risedronate was given one or four hours before a meal. Mitchell 1999 is cited in the '188 Patent as demonstrating that the administration of risedronate within 30 minutes of a meal reduced absorption of risedronate by 50% compared to the fasted state (i.e., the food effect).

[240] Twiss, Irene M et al, "The Sugar Absorption Test in the Evaluation of the Gastrointestinal Intolerance to Bisphosphonates: Studies with Oral Pamidronate" (2001) Clinical Pharmacology & Therapeutics 69(6):431-437 [Twiss] found that enteric-coated 150 mg pamidronate tablets increased small intestinal permeability in human participants. Dr. Cremers cites Twiss in support of his statements that bisphosphonates had the potential to cause GI toxicity in the small intestine.

[241] PCT Patent Application WO 2004/065397 A1 [WO 397] is an international patent application published on August 5, 2004, entitled "Risedronate Sodium Having a Very Low Content of Iron". The invention relates to a method of making risedronate sodium substantially free of iron including the steps of refluxing, especially with mechanical agitation, a combination

of risedronic acid, a sodium base and an iron-reducing amount of EDTA in a liquid, and isolating risedronate sodium substantially free of iron from the combination.

[242] Other art cited but not addressed by the experts includes Ebrahimpour 1995, Gertz 1995, Van Beek 1998, Powell 1999, Fleisch 2000 and Ogura 2004.

D. *Absorption Enhancers, including EDTA*

[243] Poiger, H & Schlatter, Ch, "Compensation of Dietary Induced Reduction of Tetracycline Absorption by Simultaneous Administration of EDTA" (1978) Europ J Clin Pharmacol 14:129-131 [Poiger], investigated the effects of milk and the counteracting effects of EDTA on absorption of tetracycline, an antibiotic used to treat bacterial infections and acne. Four dosage regimens were tested in five human subjects: (1) tetracycline alone; (2) tetracycline with 500 mg EDTA; (3) tetracycline with milk; and (4) tetracycline with milk and 2.3 g EDTA. Poiger concluded that the negative effect of milk can be overcome by simultaneous administration of EDTA. Poiger noted that using a combination of EDTA and tetracycline, the bioavailability of the tetracycline remained constant regardless of the diet. Poiger concluded that it was not necessary to take the drug in the fasted state, noting that this may lead to gastric irritation in many patients. Poiger also noted that EDTA is used as a food additive and its toxicology had been reviewed by JECFA, the Joint Food and Agriculture Organization of the United Nations and World Health Organization Expert Committee on Food Additives, in 1974 [JECFA 1974]. Poiger concluded that the combined administration of tetracycline and EDTA "might be worthy for further consideration."

[244] Van Hoogdalem, EJ et al, "3-Amino-1-hydroxypropylidene-1,l-diphosphonate (APD): a novel enhancer of rectal cefoxitin absorption in rats" (1989) J Pharm Pharmacol 41:339-341 [Van Hoogdalem] states at the outset that, "[t]he enhancing effects of calcium-binding agents, in particular disodium EDTA, on intestinal drug absorption have been reported in various studies. […] However, the promoting effect of EDTA on intestinal drug absorption appears to be accompanied by a damaging effect on mucosal integrity. Concentrations of 0.8 to 1% induced a reversible loss of rectal epithelial cells (Nakanishi et a1 1983) and severe damage of small intestinal epithelium in rats (Nadai et al 1972). Furthermore, jejunal blood loss was observed in dogs (Tidball & Lipman 1962). These observations indicate that other compounds with a similar mechanism of action as EDTA but with a more benign effect on mucosal integrity are required." Van Hoogdalem conducted a study on another calcium-binding agent (APD) to evaluate its effects on rectal cefoxitin absorption in rats.

[245] As previously noted, Janner is cited in the '188 Patent for the statement that the high amount of EDTA required to effect an increase in gastrointestinal absorption excludes EDTA as a candidate for use with oral bisphosphonates. Given that bisphosphonates are poorly absorbed when given orally and absorption is highly variable, Janner investigated whether the calcium chelator, EDTA, could improve intestinal absorption of two bisphosphonates in fasted rats. The authors found that EDTA increased absorption of bisphosphonates when given at least a 10 mg/kg dose of EDTA (100 mg/kg and 500 mg/kg doses were also tested). Janner concluded that "EDTA enhances the absorption of AHBuBP (alendronate) and Cl2MBP (clodronate). However, the absorption still remains variable and occurs only at EDTA concentrations that make this chelator unsuitable for clinical use."

[246] Lin, Jiunn H et al, "On the absorption of alendronate in rats" (1994) J Pharm Sci 83(12):1741-46 [Lin] studied alendronate absorption in rats. Lin concluded that "co-administration of alendronate with EDTA improve the absorption; however, the clinical use of EDTA is limited." The doses of EDTA tested included 1.2, 2.4, 4.8, 9.6, and 18.6 mg/kg. The abstract of the publication further noted that "whereas food markedly impaired the absorption of alendronate, EDTA enhanced absorption in a dose-dependent manner." Lin also noted that "the enhanced absorption of alendronate…was attributed to the alteration of the integrity of the intestinal membrane."

[247] Ezra reviewed the existing literature on improved bioavailability and safety of bisphosphonates. The Ezra article first reviewed the literature on the bioavailability of bisphosphonates, the effect of food on the absorption of bisphosphonates, the mechanism of the absorption of bisphosphonates and the adverse gastrointestinal effects. The second part of the article described methods that have been used for improving the bioavailability of bisphosphonates. With respect to absorption enhancers, Ezra concluded that "[d]espite the strong absorption enhancing properties of EDTA, the applicability of this agent in human pharmacotherapy is impossible, considering its damaging effects on mucosal integrity. Janner et al have shown that EDTA enhances the absorption of alendronate and clodronate. However, the absorption still remains variable and occurs at EDTA concentration that make this chelator unsuitable for clinical use." As previously noted, Ezra is cited in the '188 Patent for the statement that oral doses of bisphosphonates are poorly absorbed in the GI tract and that the use of EDTA "as an agent in human pharmocotherapy has been thought to be 'impossible' in light of the effects of EDTA on mucosal integrity".

[248] The ‘932 Patent, as previously mentioned, is entitled “Oral liquid alendronate formulations” and was published in 1995. The invention of the ‘932 Patent “relates generally to the use of oral liquid formulations of alendronate … to inhibit bone resorption in human patients who have difficulty in swallowing.” More specifically, the invention “provides a method for treating and/or preventing bone loss in a subject who has difficulty in swallowing by the administering to said patient a pharmaceutically effective amount of alendronate, in an oral liquid formulation. The liquid formulation can be in the form of a syrup, an aqueous solution or a reconstituted alendronate powder in a water solution and contains a buffer to regulate the pH of the solution and a complexing agent to prevent the formation of insoluble complexes of alendronate.” The ‘932 Patent notes: “[c]omplexing agents include the citrate buffer … or EDTA. When EDTA is used, it is used in an amount of 0.005-0.1% by weight of the composition and 0.005-2 parts of EDTA to 1 part by weight alendronate and preferably 10 about 0.01% by weight of the composition. Preferred is where citrate buffer is used alone.” Claims 11 and 12 claim EDTA as the complexing agent.

E. *Safety of EDTA*

[249] Dr. Dillberger referred to several publications in his report which addressed the use and safety of EDTA.

[250] As noted above, JECFA 1974 determined that the acceptable daily intake of EDTA for humans was up to 2.5 mg/kg (or 150 mg of EDTA per day for a 60 kg adult). JECFA defines “acceptable daily intake” as the amount of food additive that can be taken daily in the diet, even over a lifetime, without risk.

[251] The 1993 Review of the U.S. FDA confirmed that the acceptable daily intake of EDTA is 2.5 mg/kg.

[252] Yonezawa, Michio, "Basic Studies of the Intestinal Absorption I. Changes in the Rabbit Intestinal Mucosa after Exposure to Various Surfactants" (1977) Nihon Univ J Med 19: 125-141 [Yonezawa] reported that EDTA did not damage intestinal epithelium of rabbits when it was directly and continuously exposed for an hour to a high concentration of EDTA.

[253] Dr. Dillberger also cited other publications in support of his view that EDTA was safe, including: Heimbach J et al, "Safety Assessment of Iron EDTA [Sodium Iron (Fe3+) Ethylenediaminetetraacetic Acid]: Summary of Toxicological, Fortification and Exposure Data" (2000) Food and Chemical Toxicology 38: 99-111; Bothwell, Thomas H et al, "The Potential Role of NaFeEDTA as an Iron Fortificant" (2004) Int J Vitam Nutr Res 74(6): 421-434; and Oser, Bernard L et al, "Safety Evaluation Studies of Calcium EDTA" 1963 Toxicology and Applied Pharmacology 5: 142-162.

[254] Other art regarding EDTA cited but not referred to or only briefly mentioned includes Windsor 1961, Tidball 1962, Yamashita 1985, Noach 1993, Hochman 1994 and Quan 1998.

F. *Enteric Coating/Delayed Release*

[255] PCT Patent Application WO 1993/21907 [WO 907] is an international patent application entitled "Pharmaceutical preparation and process for its manufacture". The invention concerns a pharmaceutical preparation for oral use containing clodronate (a type of bisphosphonate).

According to the invention, the preparation is a drug delivery form which is enteric-coated with a film which dissolves at a pH-value of from 5 to 7.2.

[256] Canadian Patent 2,122,479 (1993) [the '479 Patent] was filed by P&G and is entitled "Risedronate delayed-release compositions". Dr. Dansereau is one of the listed inventors. The invention is directed to a novel enteric-coated oral dosage form of risedronate that is insoluble at a pH below 5.5 (i.e. stomach) but soluble at pH 5.5 or above (i.e. small intestine).

[257] Mitchell, DY et al, "Bioavailability of Immediate-Release and Delayed-Release Risedronate Formulations Upon Oral Administration To Healthy Male Subjects In Fasted And Fed State" (1996) Pharmaceutical Research 13(9) (Supp): S-458 [Mitchell 1996] is an abstract that describes a randomized, three-way crossover study that determined the relative bioavailability of delayed-release and immediate-release risedronate formulations with 14 male subjects in fasted and fed states. The subjects were given one of three formulations: three 10 mg immediate-release [IR] capsules; one capsule containing delayed-release [DR] micropellets; or one delayed-release [DR] tablet. Mitchell 1996 noted that bioavailability was not significantly different among the three formulations when administered in the fasted state. However, administration of food half hour after dosing the DR tablet and DR micropellets reduced the median relative bioavailability of each formulation by 80-100% while the IR capsule was reduced by 50%. Mitchell 1996 concluded that the results indicate that changes from IR to DR formulations "should not only assess bioequivalence, but should further assess the influence of dosing relative to meals."

[258] PCT Patent Application WO 00/61111 (2000) [WO 111] is entitled "A pharmaceutical formulation comprising an (*sic*) bisphosphonate and an additive agent providing an enhanced absorption of the bisphosphonate". The invention provides pharmaceutical formulations comprising at least one bisphosphonate and an additive consisting of one or more absorption enhancing agents for the treatment and prevention of osteoporosis. WO provides a long list of absorption enhancers, additives and bisphosphonates. WO 111 noted the drawbacks of taking bisphosphonates fasted. WO 111 also noted that the invention will allow a patient to take the medication with food, however WO 111 refers to various administration routes and is not limited to oral administration. Claims 1-34 are for other than oral administration. Claim 35 claims a formulation of claims 1-34 that is adapted for oral administration. Claim 36 claims a formulation of claims 1-35 adapted for non-colonic delivery. The WO 111 provides several examples of alendronate.

[259] U.S. Patent 6,468,559 B1 (2002) [the '559 Patent] is entitled "Enteric coated formulation of bisphosphonic acid compounds and associated therapeutic methods". The invention notes, among other things, that "the oral dosage forms are provided for the administration of a bisphosphonic acid compound in the prevention and treatment of conditions associated with bone resorption such as osteoporosis, Paget's disease, [etc.]. The dosage forms are either enterically coated capsules housing the drug in a liquid or semi-solid carrier, or enterically coated osmotically activated drug delivery devices." Though the '559 Patent refers to many examples of bisphosphonic acids, it specifically notes that "[a]lendronate…, risedronate, tiludronate, and zoledronate are preferred compounds for administration using the present dosage forms." Regarding risedronate, the '559 Patent notes that, "for administration of risedronate…, a daily

dosage of about 20 mg to 40 mg, optimally 30 mg, is indicated for the treatment of Paget's disease." Claim 4 sets out several bisphosphonates, including risedronic acid. Claim 6 refers specifically to risedronic acid as the active agent.

[260] Blümel, JE et al, "Alendronate daily, weekly in conventional tablets and weekly in enteric tablets: preliminary study on the effects in bone turnover markers and incidence of side effects" (2003) J Obstet Gynaecol 23(3):278-81 [Blümel], conducted a randomised, double-blind, three-month trial involving 75 participants. The objective of the study was to compare side effects and bone turnover markers in postmenopausal women who had received alendronate daily (10 mg/day) or weekly (70 mg/week) in tablets with or without enteric coating. The main finding reported by Blümel is that weekly alendronate administration tends to be associated to less digestive disturbance compared with daily use. Blümel also reported that the response of bone turnover markers was similar in patients who took standard and enteric alendronate, suggesting that enteric coating does not impact the efficiency of alendronate. Blümel noted, however, "further well-designed studies are warranted" in part because the size of the study was small.

[261] Other patents on enteric-coated dosage forms of bisphosphonates include those that Dr. Dansereau and others from P&G had patented: PCT Patent Application WO 1993/009785; PCT Patent Application WO 95/08331; U.S. Patent No. 5,431,920; and U.S. Patent No. 5,622,721.

G. *Post Art – Publications after 2005*

[262] As mentioned above, the '132 Study, led by Dr. Dansereau, was conducted in the spring/summer of 2005. The results showed that 100 mg EDTA in an enteric-coated 35 mg

risedronate formulation when delivered to the small intestine worked to overcome the food effect while not significantly increasing absorption in the fasted state. The formulation with an immediate-release core and an enteric coating with a pH 5.5 trigger and 10% coating had similar risedronate absorption in fed versus fasted conditions.

[263] McClung, MR et al, "Treatment of postmenopausal osteoporosis with delayed-release risedronate 35 mg weekly for 2 years" (2013) Osteoporos Int 24:301-310 [McClung] reports on a 2-year, randomized, controlled, non-inferiority study that assessed the efficacy and safety of a delayed-release 35 mg weekly oral formulation of risedronate when taken before or immediately after breakfast. The three treatment groups included: 5 mg IR daily, 35 mg DR FB (following breakfast) weekly, and 35 mg DR BB (before breakfast) weekly. McClung concluded that, "[r]isedronate 35 mg DR weekly is as effective and as well tolerated as risedronate 5 mg IR daily, and will allow subjects to take their weekly risedronate dose immediately after breakfast." Under the section on safety assessments, the author concluded, "[t]he incidence of upper and lower gastrointestinal adverse events was similar across groups. However, the incidence of events related to upper abdominal pain was higher in the DR BB group than in the other two groups; most of these events were judged to be mild or moderate." Furthermore, "[u]pper abdominal pain occurred somewhat more frequently in DR BB groups while slightly more subjects experienced diarrhea with the DR FB regimen, but these differences did not result in more subjects discontinuing from study medication."

VIII. The Common General Knowledge

[264] Allergan notes that the properties of bisphosphonates were known, the food effect was known, the strict dosing required to overcome the food effect was an obstacle to compliance, several bisphosphonates were on the market, and some weekly and monthly dosages were aimed to reduce the inconvenience of fasted dosing by limiting the frequency of administration.

[265] Apotex submits that in addition to common general knowledge noted by Allergan, the use of enteric coatings and EDTA was known to address the food effect. Apotex further submits that EDTA was known to be safe for humans, and not toxic at the doses at issue in the '188 Patent.

[266] As noted in *Janssen 2020* at para 109:

> [109] Common general knowledge is the knowledge generally known at the relevant time by the person skilled in the field of art or science to which the patent relates. It does not include all information in the public domain (*Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at para 37 [Sanofi]; *Bell Helicopter Textron Canada Limitée v Eurocopter*, société par actions simplifiée, 2013 FCA 219 at paras 63-65).

A. *Overview of the Experts' Evidence on the Common General Knowledge*

[267] Dr. Cremers noted that the skilled person would have knowledge related to the pharmacology of oral dosage forms, pharmaceutical compositions, and pharmacological principles. The skilled person would know that bisphosphonates are a class of drugs that decrease bone resorption and are used for the treatment of osteoporosis and other metabolic bone diseases.

The skilled person would also know that, as of 2005, several bisphosphonates were approved for treatment, including alendronate and risedronate.

[268] In addition, the skilled person was aware of the strict dosing requirements for oral bisphosphonates.

[269] Dr. Cremers noted that coatings were known to be used in pharmaceutical compositions for several purposes including stability and to affect dissolution rates or the site of dissolution. Enteric coatings were known to prevent the contents of a medication from dissolving in the esophagus and stomach.

[270] Dr. Adachi described the common general knowledge of the skilled physician, noting that this included the use of bisphosphonate drugs available, the obstacle of the “food effect”, which resulted in the poor absorption of these drugs when taken with food or beverage, and the need to prescribe bisphosphonates to be taken alone before breakfast with water on an empty stomach and that this strict dosing regimen was known to be inconvenient and not always complied with by patients.

[271] Dr. Yates agreed that it was known that bisphosphonates exhibit poor oral bioavailability, especially when consumed with food or calcium-containing beverages (i.e., the food effect) because of the formation of insoluble bisphosphonate-calcium complexes. He added that chelating agents were known to also bind to calcium ions, and some, such as EDTA, in preference to bisphosphonates.

[272] Dr. Parr noted, as did Dr. Cremers, that the common general knowledge included: the properties of bisphosphonates, gastrointestinal physiology, and the use of enteric coatings. Dr. Parr added that enteric-coated dosage forms with bisphosphonates were also known, as was the purpose of chelators, including EDTA and the acceptable daily intake of EDTA.

B. *The Court's Finding on the Common General Knowledge*

[273] I find that the common general knowledge as of April 2005 was that:

- The workings of the GI tract, including residence times, pH of different sections, and absorption within different sections were known;
- Osteoporosis was a well-known disease, characterized by a progressive weakening of the bone;
- Bisphosphonates were a known class of drug used to treat osteoporosis;
- Oral bisphosphonates marketed in Canada by April 2005 included alendronate (FOSAMAX®) and risedronate (ACTONEL);
- Bisphosphonates suffered from low oral bioavailability. When taken with food, there was a significantly lower absorption; this is the "food effect";
- To avoid the food effect problem, patients were required to take bisphosphonate drugs on an empty stomach with a full glass of water, remain upright and abstain from food or other beverages for at least 30 minutes;
- The cause of the food effect was thought to be due, at least in part, to bisphosphonates forming complexes with ions, such as calcium and magnesium, from the food in the stomach;

- Bisphosphonates were known to be absorbed in the small intestine;
- EDTA was a well-known chelator;
- The use of enteric coatings for several purposes was known, including: to reduce irritation to the upper GI tract (mouth, esophagus, stomach) from some oral dosage forms and to prevent dissolution in the stomach, allowing the dosage forms to dissolve in the intestine; and,
- The skilled person knew how to develop dosage forms, including with enteric coatings.

IX. Is the '188 Patent Anticipated by the BR 601?

A. *Apotex's Submissions*

[274] Apotex submits that BR 601 was made available to the public prior to April 15, 2005 and as such it is a prior art reference. Apotex submits that because BR 601 is cited in the background of the '188 Patent, Allergan cannot dispute that BR 601 is prior art for the purpose of obviousness and anticipation.

[275] Apotex notes that BR 601 was published on September 9, 2003 and its entire contents (description and claims) were readily obtainable from the Brazilian patent office. Apotex disputes that BR 601 would not have been capable of being located by the skilled person, noting that the Brazilian patent office's online database was operational at the relevant time. Apotex notes that Ms. Mittelbach acknowledged that a "simple copy", as opposed to an official copy, could have been provided to a requester before the date noted on the record for the provision of an official copy.

[276] Apotex further notes that the inventors acknowledged that they had been provided with BR 601. Apotex submits that some explanation about how the inventors came to have BR 601 should have been provided by Allergan but was not. Apotex submits that an adverse inference should be drawn that documents held by P&G would have shown that BR 601 was readily accessible.

[277] Apotex submits that BR 601 discloses formulations that have all of the essential elements of the asserted claims of the '188 Patent. Apotex argues that the formulations of BR 601 inherently possess all of the attributes of the formulations claimed in the '188 Patent. Apotex points to *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 at paras 23-27 [*Sanofi*], for the proposition that the subject matter defined by the claims is disclosed where the elements of the claim were explicitly or inherently available to the public before the claim date. Apotex submits that disclosure is sufficient if the element was inherent in the teaching of the prior art. Apotex adds that whether it would be apparent to the skilled person that they were performing the invention and infringing is not relevant.

[278] Apotex notes that BR 601 disclosed an oral composition containing a bisphosphonate, which includes risedronate. Apotex further notes that the amount of the bisphosphonate in BR 601 overlaps with the amount of risedronate in the '188 Patent. In addition, both provide for delivery to the small intestine, both have similar dissolution ranges, the enteric coatings overlap, and BR 601 provides for immediate release, delayed and prolonged release.

[279] Apotex submits that BR 601 discloses the essential elements of the claims of the '188, including "about 35 mg of risedronate". First, Apotex notes that BR 601 discloses that a range of

1 mg to 150 mg of a bisphosphonate can be included in the oral pharmaceutical composition, and risedronate is one such bisphosphonate. Second, Apotex adds that in 2003 (the publication date of BR 601) it was known that risedronate was prescribed for 35 mg weekly dose, therefore this amount was an "effective quantity" of a bisphosphonate as disclosed by BR 601. Third, Apotex notes that Claim 11 of BR 601, which is dependent on Claim 1, claims an oral pharmaceutical composition that contains a bisphosphonate, including risedronate, a chelating agent and an enteric coating. Apotex submits that although Claim 11 lists other bisphosphonates, at the time, only risedronate and alendronate had been approved and were being used to treat osteoporosis.

[280] Apotex notes that Allergan acknowledged that BR 601 discloses formulations of the '188 Patent that are within BR 601. Apotex argues that this includes some formulations that would inherently provide pharmaceutically effective absorption and permit the formulation to be taken with or without food. Apotex argues that the fact that the '188 Patent also teaches formulations that are not covered in BR 601 is irrelevant to assessing anticipation.

[281] Apotex submits that BR 601 teaches that, by releasing the bisphosphonate and EDTA into the small intestine, the contents of the stomach are avoided and absorption can be improved without the need for the high amounts of EDTA previously thought to be required.

[282] Apotex submits that the same solution disclosed in the '188 Patent – of competitive chelation by lower doses of EDTA – is specifically disclosed as one of the two possible mechanisms involved in enhanced absorption in BR 601.

[283] Apotex further submits that BR 601 discloses that the composition is for use with or without food. Apotex submits that BR 601's reference to the prior art, which addressed the food effect, and to the need to avoid the "contents of the stomach" makes it clear that BR 601 was aimed at addressing the food effect. Apotex acknowledges that BR 601 does not use the word "fasted" or "fed", but submits that there is no restriction stated in BR 601. Apotex argues that the skilled person would expect any such limitations on its use to be spelled out.

[284] Apotex argues that if the formulations of the '188 Patent provide pharmaceutically effective absorption, then the formulations of BR 601 that fall within the claims of the '188 Patent would also inherently provide pharmaceutically effective absorption.

[285] Apotex points to Dr. Parr's evidence that it would be expected that absorption of the bisphosphonate from compositions containing EDTA and an enteric coating, as taught in BR 601, in the fed state would be within 50% of the absorption in the fasted state (i.e., pharmaceutically effective absorption).

[286] Apotex also points to Dr. Yates' opinion that the range of EDTA taught in BR 601 included amounts sufficient to chelate the calcium and magnesium cations, but low enough not to adversely increase permeability; in other words, that BR 601 taught how to achieve pharmaceutically effective absorption.

[287] Apotex also submits that BR 601 taught that adding up to 175 mg of EDTA in an enteric-coated tablet increases absorption by reducing the formation of insoluble complexes. BR

601 also taught to avoid the contents of the stomach. Apotex points to Dr. Yates' evidence about the "housekeeping wave", that the formulation would be retained in the stomach until food had exited, which would ensure that the formulation was delivered to the small intestine whether or not it was taken with food. As a result, the amount of the bisphosphonate absorbed would be similar – and pharmaceutically effective – if administered fed or fasted.

[288] In response to the Court's question about why EDTA and enteric coatings would be necessary to ensure release in the small intestine if the "housekeeping wave" would provide release only once the stomach is empty and only in the small intestine in any event, Apotex suggested that the issue is the amount of EDTA. Apotex added that because there would be low levels of calcium in an empty stomach, there would be no need for an excess amount of EDTA and no concern about increasing fasted absorption, but that the enteric coating was still needed to ensure against dissolution in the stomach.

[289] Apotex submits that although the impact of the food effect on bioavailability cannot be accurately predicted in advance, there would be an expectation that bioavailability would be similar. Only routine testing would be required to confirm the bioavailability.

[290] Apotex submits that BR 601 also enabled the subject matter of the claims of the '188 Patent. Apotex submits that it does not matter that there are many choices to make in BR 601. It is simply a matter of performing what the patent discloses.

[291] Apotex notes that BR 601 teaches that the composition can be in capsules or tablets, that the bisphosphonate and EDTA can be in a single core or multiple cores and that the enteric coating can be applied to the core or the cores. BR 601 also teaches how to make the compositions and sets out the amounts of the components. The example describes how to prepare a large quantity of an oral dosage form of alendronate, EDTA and an enteric coating.

[292] Apotex adds that the oral dosage forms claimed in the '188 Patent were not difficult to make and the skilled person, relying on their common general knowledge, could have easily made them based on the teachings in BR 601. If any experimentation were required it would have been routine.

B. *Allergan's Submissions*

[293] Allergan argues that BR 601 does not anticipate the '188 Patent. BR 601 does not disclose or enable the subject matter of the asserted claims. BR 601 does not provide "so clear a direction that a skilled person reading and following it would in every case and without possibility of error be led to the claimed invention" (*Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 26 [*Free World Trust*], citing *Beloit Canada Ltd v Valmet OY* (1986), 8 CPR (3d) 289, 1986 CarswellNat 588 (FCA) at para 29 [*Beloit*]).

[294] In addition, following BR 601 does not necessarily and inevitably bring you to the invention of the '188 Patent. A skilled person could practice the invention of BR 601 and not arrive at the '188 Patent's invention.

[295] Allergan submits that BR 601 provides for many combinations and permutations of bisphosphonates, chelating agents and enteric coatings and for delayed, prolonged and immediate release. BR 601 does not disclose a formulation with 35 mg risedronate, 100 mg EDTA, with an immediate release core that has an enteric coating that will not dissolve below pH 5.5. BR 601 does not include dosage forms which, if made, would inherently provide pharmaceutically effective absorption in the fed or fasted state.

[296] Allergan acknowledges that there is overlap between some of the formulations in BR 601 and the ‘188 Patent. However, the skilled person would be required – out of all the permutations and combinations in BR 601 – to choose all the essential components in the exact amounts; for example, 100 mg EDTA, and to choose an immediate release core. Allergan submits that there is no evidence that the skilled person would choose all the correct components and amounts or an immediate release core among the possibilities of BR 601. Allergan acknowledges that BR 601 discloses release in the small intestine, but once there, it must be immediate released. There is no guidance in BR 601 to choose an immediate release core. Only with hindsight would a skilled person know to do so.

[297] Allergan also acknowledges that if the skilled person made a formulation that matches identically with what is claimed in the ‘188 Patent, it would perform in the same way as the ‘188 Patent. However, this is unlikely as there are multiple choices to make and no obvious direction to go. Allergan adds that even then, a clinical trial would be needed. The skilled person would not know in advance – even if all the right choices were made – that the dosage would yield pharmaceutically effective absorption. Speculation is not sufficient. All experts agreed that

absorption is variable and unpredictable and it would be necessary to evaluate absorption in human clinical studies. This goes beyond routine experimentation.

[298] Allergan notes that if the skilled person adapted the sole example in BR 601 of the large batch of alendronate and used risedronate and equal amounts of EDTA as in the example, the formulation would fall outside the claims and teaching of the ‘188 Patent.

[299] Allergan disputes Apotex’s argument that BR 601 includes dosage forms that if made would be covered by the ‘188 Patent and inherently provide pharmaceutically effective absorption, and therefore anticipates the ‘188 Patent. Allergan submits that the inherent pharmacokinetics of BR 601 are unknown and unpredictable and were not disclosed in BR 601. BR 601 does not disclose that its formulations can be taken with or without food or that pharmaceutically effective absorption would result. As such there is no anticipation based on any possible inherent results. Inherent but undisclosed properties do not anticipate (*Novo Nordisk Canada Inc v Cobalt Pharmaceuticals Inc*, 2010 FC 746 at paras 170-175 [*Novo Nordisk*]).

[300] Allergan submits that BR 601 is not about solving the food effect problem. BR 601 does not disclose formulations that can be taken with or without food, does not discuss the food effect at all and does not address the concept of pharmaceutically effective absorption.

[301] BR 601 describes and addresses the problem of low oral bioavailability of bisphosphonates in the fasted state. BR 601 proposes using an enteric coating to prevent the chelating agent being “consumed” in the stomach, where calcium and magnesium ions are present even under fasted

conditions. BR 601 describes that once released in the small intestine, the chelating agent would do both: competitively chelate metals and increase the permeability of the intestinal mucosa. As noted in BR 601, this would require less bisphosphonate compared to "current treatments" while maintaining fasted administration. (i.e., avoids giving too much bisphosphonate).

[302] Allergan submits that even if BR 601 were about the food effect – which it is not – it does not teach that its formulations can be taken with or without food or beverage intake. Allergan argues that the skilled person would have concluded the opposite. The skilled person would understand that BR 601 is directed to increasing fasted bisphosphonate absorption, which the '188 Patent seeks to avoid.

[303] Allergan also disputes that the reference in BR 601 – that the formulations are enteric-coated to release after exiting the stomach and avoid consuming the chelating agent by chelation with the "contents of the stomach" – is a reference to the food effect. Allergan notes that both Drs. Yates and Parr ultimately agreed that the fasted stomach contains calcium that would consume the chelating agent.

[304] Allergan submits that because BR 601 does not address the food effect, it also does not disclose that its formulations would provide pharmaceutically effective absorption either with or without food. BR 601 does not mention anything about fed absorption being similar to fasted absorption for any of its formulations. Allergan adds that this would not be possible in any event because there was no testing in BR 601.

[305] Allergan further submits that BR 601 does not enable the asserted claims.

[306] Allergan notes that BR 601 refers to all bisphosphonates but focuses on alendronate, and provides a broad range of several different chelating agents and coatings and provides for immediate, delayed, and extended release cores.

[307] BR 601 does not provide any guidance to the skilled person about how to design formulations that can be taken with or without food or provide pharmaceutically effective absorption. Allergan notes that the inventors of the ‘188 Patent stated that finding the right amount of EDTA for 35 mg of risedronate was important and that 100 mg of EDTA (which they referred to as the “sweet spot” and which their safety experts advised was the highest amount for safety reasons) turned out to be the right amount. Allergan notes that BR 601 does not disclose the amount that is just the right amount, rather BR 601 provides for many options.

[308] Allergan adds that BR 601 does not include a claim for an immediate release core. BR 601’s formulations and claims include delayed, prolonged and immediate release. Delayed and prolonged release would not work.

[309] Allergan submits that the skilled person who followed the only example in BR 601 would not arrive at the subject matter of the asserted claims of the ‘188 Patent. The example in BR 601 of alendronate would have to be adapted to risedronate. The absorption of risedronate would not be predictable. If the skilled person then followed the example using 35 mg of risedronate and an equal amount of EDTA, as set out in BR 601, this would fall outside the scope of the asserted

claims (first claim set) of the ‘188 Patent, which claims 100 mg of EDTA with 35 mg risedronate. In addition, it would fall outside the EDTA to risedronate molar ratio of at least 2, as set out in Claim 1. Allergan adds that the skilled person would likely end up with a formulation that falls outside the scope of the ‘188 Patent.

[310] Far more than simple routine experiments would be required to arrive at the invention and to determine whether the oral formulation administered with or without food would result in pharmaceutically effective absorption.

C. *The Relevant Jurisprudence on Anticipation*

[311] As recently noted by Justice Zinn in *Bristol-Myers Squibb Canada Co v Pharmascience Inc*, 2021 FC 1 at paras 74-75 [*BMS 2021*]:

> [74] There are two inquiries to be made when assessing anticipation: disclosure and enablement: *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Sanofi*] at paras 25-27. In order to be found to be anticipatory, the single piece of prior art (the 303 Patent), must both (1) disclose the invention of the patent at issue (the 202 Patent), and (2) enable the skilled person to make the invention using that prior art and common knowledge, allowing for some trial and error experimentation to make it work.
>
> [75] The Supreme Court of Canada in *Free World Trust* at para 26 approved the test for anticipation described in *Beloit Canada Ltd. v. Valmet OY* (1986), 8 C.P.R. (3d) 289 (FCA) [*Beloit*], at p. 297, and noted that the test was difficult to meet:
>
> > One must, in effect, be able to look at a prior, single publication and find in it all the information which, for practical purposes, is needed to produce the claimed invention without the exercise of any inventive skill. The prior publication must contain so clear a direction that a skilled person reading and following it would in every case and without possibility of error be led to the claimed invention.

[312] In *Sanofi*, the Supreme Court of Canada reiterated that anticipation requires disclosure and enablement and explained both requirements. The Supreme Court, at parass 25-26, referred to a U.K. decision, *Synthon BV v SmithKline Beecham plc*, [2006] 1 All ER 685, [2005] UKHL 59 of Lord Hoffman:

> [25] He explains that the requirement of prior disclosure means that the prior patent must disclose subject matter which, if performed, would necessarily result in infringement of that patent, and states, at para. 22:
>
> > If I may summarize the effect of these two well-known statements [from *General Tire* and *Hills v. Evans*], the matter relied upon as prior art must disclose subject matter which, if performed, would necessarily result in an infringement of the patent. . . . It follows that, whether or not it would be apparent to anyone at the time, whenever subject matter described in the prior disclosure is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is satisfied.
> >
> > When considering the role of the person skilled in the art in respect of disclosure, the skilled person is "taken to be trying to understand what the author of the description [in the prior patent] meant" (para. 32). At this stage, there is no room for trial and error or experimentation by the skilled person. He is simply reading the prior patent for the purposes of understanding it.
>
> [26] If the disclosure requirement is satisfied, the second requirement to prove anticipation is "enablement" which means that the person skilled in the art would have been able to perform the invention (para. 26).

[313] The Supreme Court explained the requirements of enablement at para 27:

> [27] Once the subject matter of the invention is disclosed by the, prior patent, the person skilled in the art is assumed to be willing to make trial and error experiments to get it to work. While trial and error experimentation is permitted at the enablement stage, it is not at the disclosure stage. For purposes of enablement, the question is

> no longer what the skilled person would think the disclosure of the prior patent meant, but whether he or she would be able to work the invention.

[314] In *Sanofi*, at para 37, the Supreme Court set out a non-exhaustive list of factors to consider in making the determination of enablement, including that the skilled person may rely on the common general knowledge to supplement the information in the patent, and that routine trials are acceptable, but prolonged or arduous trial and error would not be considered routine.

[315] In *Abbott Laboratories v Canada (Minister of Health)*, 2008 FC 1359 at para 75 [*Abbott*], aff'd 2009 FCA 94, Justice Hughes considered the decision of the Supreme Court of Canada in *Sanofi*, noting that the requirement for an exact description of the invention had been found to be overstated in *Sanofi*. Justice Hughes set out the general principles that apply to anticipation. No subsequent jurisprudence suggests that these have changed (e.g., *Biogen* at para 116). Justice Hughes stated at para 75:

> [75] To summarise the legal requirements for anticipation as they apply to the circumstances of this case:
>
> 1. For there to be anticipation there must be both disclosure and enablement of the claimed invention.
>
> 2. The disclosure does not have to be an "exact description" of the claimed invention. The disclosure must be sufficient so that when read by a person skilled in the art willing to understand what is being said, it can be understood without trial and error.
>
> 3. If there is sufficient disclosure, what is disclosed must enable a person skilled in the art to carry out what is disclosed. A certain amount of trial and error experimentation of a kind normally expected may be carried out.

> 4. The disclosure when carried out may be done without a person necessarily recognizing what is present or what is happening.
>
> 5. If the claimed invention is directed to a use different from that previously disclosed and enabled then such claimed use is not anticipated. However if the claimed use is the same as the previously disclosed and enabled use, then there is anticipation.
>
> 6. The Court is required to make its determinations as to disclosure and enablement on the usual civil burden of balance and probabilities, and not to any more exacting standard such as quasi-criminal.
>
> 7. If a person carrying out the prior disclosure would infringe the claim then the claim is anticipated.

[316] In *Tearlab Corporation v I-MED Pharma Inc*, 2019 FCA 179 at paras 73 and 81 [*Tearlab*], the Court of Appeal noted the distinction between anticipation and obviousness, highlighting that anticipation must be found in a single document, not in a mosaic, as is permitted for the assessment of obviousness, and stated at para 73:

> As noted by Donald MacOdrum in *Fox on the Canadian Law of Patents*, 5th ed., looseleaf (Toronto, Ont.: Thomson Reuters Canada, 2019), at pp. 4-6 and 4-7 [MacOdrum]:
>
> > There is a crucial difference in assessing the effect of prior documents on the question of anticipation and obviousness. When approaching an enquiry as to the novelty of an alleged invention, anticipation must be found in a single document. In other words, it is not legitimate to read several documents together and thus, as the cases put it, to make a mosaic of extracts. In addition, that single document must disclose the precise invention claimed in the patent under attack. But, in considering invention versus obviousness, the prior art should be reviewed and its cumulative effect considered. [References omitted.]

D. *BR 601*

[317] The experts have commented on their understanding of the teaching of BR 601 and their views on this issue, and all other issues, differ. Before considering the experts' views, it is helpful to note what BR 601 disclosed in its own words.

[318] BR 601 is a Brazilian patent application, filed in December 2001 and published in September 2003 by the Brazilian patent office in its Official Gazette, in Portugese. The patent was never issued. An English translation is relied on for the purpose of this Action.

[319] The inventor is Alcebiades de Mendonga Athayde and the applicant is Libbs Pharmaceutical Company Ltda. (BR/SP).

[320] The title of BR 601 is "Pharmaceutical Composition Containing Bisphosphonate for the Treatment of Diseases Related to Calcium and/or Phosphate Metabolism, Its Uses in the Preparation of Medication to Treat Diseases Related to Calcium and/or Phosphate Metabolism, And Method for Treating Diseases Related to Calcium and/or Phosphate Metabolism". The abstract notes that "[t]his invention pertains to a pharmaceutical composition containing bisphosphonate and a chelating agent for the treatment of diseases related to calcium and/or phosphate metabolism, for example osteoporosis, Paget's disease, heterotopic ossification, and cancer related hypercalcemia. This invention also refers to the use of this composition in the preparation of a medication that is useful in the treatment of said diseases as well as the method for treating such diseases."

[321] BR 601 notes that bisphosphonates share the problem of low oral bioavailability, because of the low level of absorption in the GI tract. BR 601 states that this "necessitates the use of high doses of the drugs in relation to the quantity actually absorbed in the body, with the disadvantages of undesirable exposure of the body to the excess quantity of the drug, the cost involved in the overdose, and the size of the dosage unit" (i.e., the problem).

[322] BR 601 goes on to note that the importance of "this problem" is reflected in the number of patents and articles that address increasing the bioavailability of bisphosphonates. BR 601 notes, among others, WO 111 (bisphosphonates with absorption enhancers) and international patent application WO 9531203 (alendronate in liquid form). BR 601 also refers to Janner, noting that it demonstrated that the oral administration of EDTA in an aqueous solution improves the body's absorption of bisphosphonate, but concluded that this association is not clinically viable because of the high doses required for the chelating agent to be effective (i.e., more than 100 mg/kg of body weight).

[323] BR 601, referring to Janner, states "this confirms that even though we know the effect of chelating agents in improving absorption of bisphosphonates, making the use of this combination viable in treatment of diseases remains to be accomplished".

[324] BR 601 asserts that its invention solves the problem encountered in the prior art by making the chelating agent available only in the small intestine, the principal site of bisphosphonate absorption. It notes that targeting release in the small intestine eliminates interaction of these agents with the "contents of the stomach".

[325] BR 601 notes the "possible mechanisms" involved in increasing absorption by the use of chelating agents, which are: reducing the formation of insoluble complexes of bivalent ions with bisphosphonates; and, increasing the permeability of the intestinal mucosa. BR 601 explains that because the contents of the stomach contain calcium and magnesium ions the chelating agents are consumed before they reach the small intestine. BR 601 posits that the release of the chelating agents into the small intestine permits the dosage of the bisphosphonate to be reduced for the desired result, which is increased absorption.

[326] BR 601 again notes the restrictions on the quantities of the chelating agents that may be harmful to the body. It states "the solution offered by the invention is different and takes the opposite approach, since it provides effective use of bisphosphonates in the presence of chelating agents in quantities lower than the known quantities."

[327] BR 601 provides the following summary:

> In summary, the invention provides for the use of the compositions described with enhanced absorption, containing bisphosphonate and chelating agents in the treatment of diseases related to metabolism of calcium and/or phosphate since (a) there are no losses of chelating agent by conversion into undesirable compounds in the stomach, since they become available only in the small intestine because of the gastroresistant and enterosoluble coating used, (b) once it is in the intestine, the chelating agent captures the bivalent ions in preference to the bisphosphonate, permitting the bisphosphonate to remain free for absorption by the body, and (c) the chelating agent increases the permeability of the intestinal mucosa, thereby increasing the capacity to absorb the bisphosphonate. Stated otherwise, with this invention we obtain an effective treatment with a small quantity of bisphosphonate compared to the current treatment by its association with a chelating agent, and in lower quantities than those already studied in the state of the art.

[328] BR 601 describes that the composition includes at least one core containing bisphosphonates, one core or core coating containing a chelating agent, with the core or cores being coated individually or jointly by an enterosoluble layer. Three alternatives for the cores are described. BR 601 notes that oral administration of bisphosphonates is known to cause gastroesophageal intestinal irritation and, as a result, formulations are preferred where the bisphosphonate is coated with gastroresistant and enterosoluble layer. Several patents are noted as examples. BR 601 notes that an advantage of its invention over other formulations is that it avoids discomfort caused by the acid form of a bisphosphonate coming into contact with the mucosa in the esophagus.

[329] BR 601 describes its embodiments, noting among other things, that it is preferable for the daily intake of the chelating agent, in particular EDTA not to exceed 175 mg. It provides several examples of polymers that may be used to provide the gastroresistant insoluble coating, noting that these should be soluble in the predominant intestinal pH of about 5.5 or higher.

[330] BR 601 describes as one aspect of the invention, the method for treating diseases such as osteoporosis by the ingestion of an “effective quantity of the pharmaceutical composition described above (for example, between 1 and 150 mg of bisphosphonate for each ingestion, or about 0.01 to 2.15 mg per kg of body weight) at regular intervals (for example, daily or weekly) or irregular intervals, with immediate, delayed or prolonged release of the bisphosphonate, with the time interval, the effective quantity, and the rate of release depending on the pathology to be treated, as known to a person skilled in the art”.

[331] The only example set out in BR 601 is a formulation of a large quantity of alendronate, with EDTA individually coated by an intermediate water soluble layer and each of the cores is also coated, where dissolution occurred at pH level 6.8.

[332] There are 34 claims in BR 601. Claim 1 refers to bisphosphonates generally, a chelating agent and cores that are coated individually or together. Claim 11 states that the composition of a bisphosphonate chosen from one of 14 (including risedronate). Claim 15 provides that the coating is soluble in the pH range prevalent in the small intestine. Claim 16 provides that the coating is soluble at a pH above about 5.5.

[333] Claim 23 appears to be the first claim to set out a range for the amount of the bisphosphonate (i.e., any bisphosphonate listed). Claim 23 states that it is a composition according to Claim 1, characterized in that it contains between 1 and 150 mg of bisphosphonate.

E. *Overview of the Experts' Evidence on Anticipation*

(1) Dr. Yates

[334] Dr. Yates opined that BR 601 disclosed all the essential elements of the asserted claims of the '188 Patent and enabled the skilled person to prepare the subject matter of the asserted claims.

[335] Dr. Yates stated that BR 601 discloses a pharmaceutical composition containing a bisphosphonate, which "can be" risedronate, and a chelating agent for the treatment of diseases of calcium and/or phosphate metabolism, including osteoporosis. He stated that BR 601 solves the

problem of low bioavailability by having the release of the chelating agent and the bisphosphonate into the small intestine, and eliminating the interaction with the contents of the stomach. He opined that although BR 601 does not mention food or the food effect, the skilled person would understand that the intent of BR 601 is to overcome the food effect by avoiding the contents of the stomach that contain food and therefore releasing the drug only in the small intestine.

[336] He also opined that because there are no limitation set out in BR 601 about how its formulations are administered, the skilled person would understand that the formulations could be taken with or without food.

[337] Dr. Yates acknowledged that BR 601 does not refer to "pharmaceutically effective absorption" but opined that the skilled person would understand that formulations that can be used with or without food would have to have similar bioavailability in both the fed and fasted states.

[338] Generally, I am not persuaded by Dr. Yates' opinions about the teaching of BR 601 or that it disclosed or enabled the claims of the '188 Patent. As noted more fully below, Dr. Yates read in words and concepts and made assumptions about the teaching of BR 601, including that it was aimed at the food effect and could be administered in the fed and fasted states even though BR 601 did not mention this, described the problem of low bioavailability and the need for high amounts of bisphosphonates, and referred to the "current treatment" which was fasted administration.

[339] Although Dr. Yates was willing to read in words and concepts in BR 601, he was unwilling to accept the clear wording in other publications. For example, he would not agree that Janner

studied fasted rats because he did not find sufficient details in the methods section of Janner, although this is clearly described in Janner.

[340] Dr. Yates also suggested that BR 601 was about the food effect because of references to Janner and WO 111 that were about the food effect. However, Janner is not about the food effect and WO 111 is a very broad patent application not limited to oral formulations that only briefly mentions the food effect and does not provide a solution to it.

[341] Dr. Yates also suggested that BR 601 discloses EDTA as the preferred chelating agent because it is specifically mentioned, but would not agree that BR 601 discloses alendronate as the preferred bisphosphonate, although it is specifically mentioned and is the only bisphosphonate exemplified.

[342] Dr. Yates did not acknowledge that others in the field were good scientists or among the leaders in their field, merely competent or adequate. For example, he suggested that Dr. Mitchell was not up to Dr. Yates' standards when he worked at Merck and he doubted the conclusions in the Ezra publication, which was a review and summary of the bisphosphonate literature. He also suggested that the Patent Examiner was wrong in their assessment of BR 601 in the context of the application for the '188 Patent.

[343] Despite his scrutiny of the other prior art and other scientists, Dr. Yates did not apply the same scrutiny to anything in BR 601. Dr. Yates acknowledged that he had never seen BR 601

before it was provided to him in the context of litigation and that he knew nothing about the inventor or the pharmaceutical company.

[344] Although Apotex submits that it is irrelevant that little was known about the inventor of BR 601 or Libbs Pharmaceutical Company because BR 601 is nonetheless an anticipatory reference, I find that this is relevant to the assessment of the experts' evidence. In particular, Dr. Yates' willingness to make assumptions about what the inventor intended and to read in concepts that are not disclosed in the clear words of BR 601, despite his lack of knowledge of the inventor, and in contrast to his scrutiny of other better known scientists in the bisphosphonate field, coupled with other inconsistent statements, leads me to give less weight to Dr. Yates' evidence on this issue.

(2) Dr. Parr

[345] Dr. Parr explained that the solution taught by BR 601 is that, by releasing the bisphosphonate and EDTA into the small intestine, and avoiding the contents of the stomach, absorption can be improved without using the high amounts of EDTA taught in the art. Dr. Parr noted that BR 601 refers to two possible mechanisms for the increase in absorption: competitive chelation and altering intestinal permeability. Dr. Parr acknowledged that the reference in the '188 Patent to BR 601 refers only to increasing intestinal permeability.

[346] In Dr. Parr's view, all the essential elements of the claims of the '188 Patent are disclosed in BR 601. Dr. Parr acknowledged that BR 601 does not specifically refer to taking the oral dosage form with or without food or beverage intake. However, he opined that the reference in BR 601

that the dosage form avoids the contents of the stomach means that the oral dosage form can be administered with or without food or beverage intake.

[347] Dr. Parr also acknowledged that BR 601 does not specifically state that the invention will provide for pharmaceutically effective absorption of the bisphosphonate with or without food. However, Dr. Parr opined that the skilled person would understand that the compositions of BR 601 would do so based on his extrapolation of information in the ‘188 Patent compared to the pre-existing immediate release tablet.

[348] Dr. Parr also opined that BR 601 enables the skilled person to prepare the subject matter of the claims using their common general knowledge, noting that the preparation of formulations was routine.

[349] Dr. Parr’s evidence was grounded in his experience as a skilled formulator, however, his evidence did not persuade me that BR 601 addressed the food effect or pharmaceutically effective absorption, or that BR 601 set out all the information needed to prepare the formulations of the ‘188 Patent.

(3) Dr. Cremers

[350] Dr. Cremers stated that BR 601 does not disclose or enable the claims of the ‘188 Patent. Dr. Cremers noted, among other things, that BR 601 does not mention the food effect, and is not about solving the food effect. Dr. Cremers noted that the food effect was such a significant and well-known problem that if BR 601 set out to address it, it would have said so. Dr. Cremers

explained that the problem sought to be solved by BR 601 – as stated in BR 601 – was the need to use relatively high amounts of bisphosphonate in oral dosage forms, due to their low oral bioavailability. He noted that the solution in BR 601 was the opposite of what the ‘188 Patent seeks to do.

[351] Dr. Cremers explained that BR 601 provides for enteric-coated formulations for use without food, with a chelating agent to chelate ions and increase intestinal permeability in the “gut” (i.e., GI tract), which allows a lower amount of bisphosphonate to be used in the formulation. BR 601 provides only very broad disclosure of potential formulations.

[352] Dr. Cremers added that even if BR 601 could be interpreted as for use with food (which in his view it clearly cannot, noting, among other things, that at that time all oral bisphosphonates were taken fasted) it still does not disclose an oral dosage form of risedronate that can be administered with or without food and achieve similar absorption. He also noted that BR 601 discloses only one example of the bisphosphonate alendronate made in a large batch with no testing.

[353] Dr. Cremers added that experimentation on the scale required to make the oral dosage forms of the asserted claims, with regard only to BR 601 and common general knowledge, would be a significant and time-consuming formulation development and clinical research project.

[354] I prefer Dr. Cremers’ evidence on the issue of the teaching of BR 601. He did not reinterpret the clear words of BR 601 and he clearly explained the problem identified in BR 601 and how it

differed from the problem identified in the ‘188 Patent and why BR 601 does not disclose or enable the claims of the ‘188 Patent.

(4) Dr. Sinko

[355] Dr. Sinko explained that BR 601 discloses bisphosphonate formulations intended to increase absorption in the fasted state by including a chelating agent in an enteric-coated dosage form, so that the dosages of the bisphosphonates can be smaller. The formulations are not taught to be specific to any particular bisphosphonate, and BR 601 does not provide any results from tests on any formulation.

[356] Dr. Sinko added that BR 601 never mentions food, overcoming the food effect, or a dosage form that has similar absorption in the fasted and fed states.

[357] Dr. Sinko noted that BR 601 permits the combination of one of at least 14 different bisphosphonates in a range of 1 mg to 150 mg with “preferably” 175 mg of EDTA, and one of eight enteric coatings. Dr. Sinko stated that BR 601 is so broad that it does not disclose the essential elements of the claims of the ‘188 Patent and it could not enable a skilled person to practice the invention in the ‘188 Patent without significant trial and error experimentation, not knowing whether success was even attainable.

[358] Dr. Sinko acknowledged that there was overlap between the formulations of BR 601 and the ‘188 Patent. He explained that the “generic” ingredients overlapped but that arriving at the formulations of the ‘188 Patent would require many choices to be made and amounts selected from

a wide range. He also explained that no predictions could be made regarding absorption without testing.

[359] Dr. Sinko's evidence was balanced. He acknowledged that if all the correct choices were made from BR 601 there would be overlap with the '188 Patent. However, he supported his opinion that there were too many choices and little if any guidance in BR 601.

F. *BR 601 Does Not Disclose and Does Not Enable the Asserted Claims of the '188 Patent*

(1) BR 601 is an Anticipatory Reference

[360] As more fully described below with respect to obviousness, it would be very difficult for the skilled person to find BR 601 even if they conducted a diligent search.

[361] Regardless of the difficulty finding BR 601, it is not disputed that BR 601 is the anticipatory reference cited by Apotex. In addition, the '188 Patent refers to BR 601 for the statement that "others have attempted to increase the absorption of bisphosphonates by increasing the permeability of the intestinal mucosa through delivery of microparticles of chelating agents and bisphosphonates to the reported site of absorption" (at page 3). However, the '188 Patent also sets out a disclaimer that "the citation of any document is not to be construed as an admission that it is prior art with respect to the invention" (at page 35).

[362] The inventors acknowledged that they had a copy of BR 601, but could not elaborate on how or when it was provided. Dr. Burgio indicated that he did not review BR 601 as his work was well underway by the time this came to his attention.

(2) BR 601 Does Not Provide Sufficient Disclosure of the Claims of the ‘188 Patent

[363] As noted in *Free World Trust*, anticipation is a difficult test to meet. To anticipate the ‘188 Patent, BR 601 must provide a clear direction to the skilled person who follows the disclosure which leads the skilled person to necessarily infringe. It does not do so.

[364] While an anticipatory reference need not be an “exact” description, the disclosure must be sufficient so that when read by the skilled person willing to understand it, it can be understood without trial and error (*Abbott* at para 75; *Biogen* at para 116).

[365] As a starting point, BR 601 does not describe or address the same problem addressed in the ‘188 Patent and does not provide any direction to the skilled person to the invention of the ‘188 Patent. BR 601 is not about the food effect or achieving pharmaceutically effective absorption. The skilled person, reading the patent to try to understand it, would understand it to be addressing a different problem.

[366] BR 601 discloses a wide range of bisphosphonates, chelating agents, and coatings, without sufficient guidance to direct the skilled person to the formulations of the ‘188 Patent. Despite that the “ingredients” of the ‘188 Patent are buried in the very broad disclosure of BR 601, BR 601 neither “disclose the precise invention claimed” (*Tearlab* at para 73) nor does it contain “so clear

a direction that a skilled person reading and following it would in every case and without possibility of error be led to the claimed invention" (*Free World Trust* at para 26; *Tearlab* at para 72; *BMS 2021* at para 75).

[367] I disagree with Apotex that BR 601 inherently disclosed the attributes of the '188 Patent. As elaborated below, BR 601 was not about the food effect and did not disclose that pharmaceutically effective absorption would be achieved if its formulations were taken with or without food. Without such disclosure, even if the skilled person read BR 601 and chose exactly all the essential elements in the precise amounts disclosed in the '188 Patent (which would require significant trial and error) and arrived at some formulation of the '188 Patent, the lack of disclosure in BR 601 of the inherent properties dictates against finding that BR 601 anticipates the '188 Patent (*Novo Nordsik*). BR 601 makes no mention of administration in the fed or fasted state or pharmaceutically effective absorption.

(a) *The Problem Addressed by BR 601*

[368] The background, summary, description of the invention of BR 601 is set out above. BR 601 notes the low bioavailability of bisphosphonates and identifies the problem to be solved as the need to increase the bioavailability. BR 601 notes the concern about the use of high amounts of chelating agent required to increase absorption but that may be harmful to the body. BR 601 then notes that it takes the opposite approach and uses low amounts of chelating agents.

[369] All the experts agreed that BR 601 addressed the problem of the low bioavailability of bisphosphonates. However, they disagreed on how this was accomplished. They also disagreed whether BR 601 addressed the food effect and provided pharmaceutically effective absorption.

[370] Dr. Parr noted that the solution taught by BR 601 is that, by releasing the bisphosphonate and EDTA into the small intestine, and avoiding the contents of the stomach, absorption can be improved without using high amounts of EDTA. He noted that BR 601 refers to two possible mechanisms for the increase in absorption: competitive chelation and altering intestinal permeability. Dr. Parr added that the ‘188 refers to BR 601 only with respect to increasing intestinal permeability.

[371] Dr. Cremers noted, as did Dr. Parr, that BR 601 refers to the two possible mechanisms by which the chelating agent could increase bisphosphonate absorption: reducing complexes of bivalent ions with bisphosphonates and increasing permeability of the intestinal mucosa.

[372] Dr. Cremers explained that this differs from the ‘188 Patent. The ‘188 seeks to use enough chelating agent (EDTA) to complex the ions and minerals from food that make it into the small intestine (where the risedronate and EDTA are released), if the dosage form is taken with food. The ‘188 Patent is also about using a small enough amount of EDTA so that there will be no significant increase in the permeability of the intestinal mucosa if the dosage form is taken without food. Dr. Cremers stated that this is the opposite of what BR 601 provides; the intention in BR 601 is to use a chelating agent in order to increase permeability of the intestinal mucosa and increase absorption so as to permit a lower dose of the drug to be used.

[373] As Dr. Cremers' evidence supports, and the wording of BR 601 reflects, the skilled person would understand that BR 601 is directed at a different problem than the '188 and this knowledge would inform what the skilled person would draw from BR 601.

(b) *BR 601 Does Not Seek to Solve the Food Effect*

[374] Contrary to Apotex's submission, BR 601 does not address or solve the food effect.

[375] All the experts agreed that there is no mention of the food effect in BR 601 or how the formulations of BR 601 are administered. As noted by Dr. Cremers, the "current treatment" at the time of BR 601 was that bisphosphonates were administered fasted. The Apotex experts assumed that because BR 601 does not indicate how its formulations are administered, that both fed and fasted administration were options. This assumption is not logical or supported. A significant change in the administration of oral bisphosphonates would not go unmentioned. Moreover, as Dr. Cremers noted, if the inventor had solved the food effect, which was a well-known problem and of concern to those in the bisphosphonate field, it is "inconceivable" that they would have not said so in the disclosure of the invention.

[376] The inventor of BR 601, given the focus on a wide range of bisphosphonates and the references cited, would have been aware of the food effect. If the inventor had solved or even addressed the food effect, this would have been clearly stated.

[377] I give little weight to the evidence of Dr. Yates on this issue. BR 601 addresses a different problem than the '188. BR 601 does not mention food at all. As noted by Drs. Cremers and Sinko,

it refers to the “current treatment”. Drs. Cremers, Sinko and Parr all agreed that the “current treatment” in 2003 (date of publication of BR 601) was for the administration of bisphosphonates in the fasted state and that there are “contents of the stomach” even in the fasted state. Dr. Yates’ reliance on the reference to Janner, and to the “contents of the stomach” ignore that Janner was a fasted study and that the contents of the stomach, even if empty, include low levels of calcium and other ions. Moreover, Dr. Yates reads in words and concepts that are simply not stated and cannot be assumed.

[378] The silence of BR 601 regarding the food effect can be contrasted with the disclosure of the ‘188 Patent which clearly identifies the food effect, the concern with fasted administration and how to overcome this problem.

[379] Although Dr. Yates suggests that BR 601’s references to Janner and WO 111 are references to the food effect, this is an unsupported assumption. The reference to WO 111 in BR 601 is to the need to increase the bioavailability of bisphosphonates, without any reference to the food effect. Several other patents are cited also for this same problem. The reference to Janner is also about the use of chelating agents to increase absorption, and Janner concludes that the amount of EDTA required would be extremely high and not clinically viable.

[380] Dr. Yates stated:

> Even though the word "food" is not used in BR601, I think the skilled person would understand that the fasting stomach contains very little calcium. And so the intent of BR601 is to overcome the food effect by avoiding the contents of the stomach that contain food and therefore releasing the drug only in the small intestine where there is a separation as we discussed earlier between food

> and the drug because of the differential release of the tablet through the pylorus of the stomach.

[381] Although Dr. Yates agreed that at the time BR 601 was published, all administration of bisphosphonates required fasting – no food for 30 minutes after the dosage – and he acknowledged that BR 601 "doesn't mention food…", he relied on the fact that BR 601 does not say anything about a requirement for fasting and opined that BR 601 would be interpreted to mean that its formulations could be taken with or without food.

[382] With respect to the disclosure of BR 601, Dr. Yates would not accept that the only problem discussed in BR 601 was the problem with fasted absorption, despite that the references cited in BR 601 were about fasted absorption (e.g., Janner). Dr. Yates suggested that Janner did not clearly indicate that fasted rats were studied, but he ultimately and reluctantly agreed that Janner was studying the preferential binding by EDTA and whether it would increase fasted absorption.

[383] Dr. Yates ultimately acknowledged that the description of the low bioavailability of bisphosphonates referred to amounts that reflect fasted absorption. However, Dr. Yates maintained that the food effect is an issue in BR 601 and that the skilled person would know this even though it is not discussed in the application.

[384] As noted above, Dr. Yates was eager to interpret BR 601 beyond its clear disclosure.

[385] Dr. Parr opined that the reference to the contents of the stomach "is what was in the stomach under a fed condition or even a fasted condition" [my emphasis].

[386] Dr. Parr acknowledged that BR 601 does not specifically refer to taking the oral dosage form with or without food or beverage intake. However, in his view, the reference in BR 601 stating that the dosage form avoids the contents of the stomach means that the oral dosage form described in BR 601 can be administered with or without food or beverage intake. This statement differs from his acknowledgement that the fasted stomach contains "contents".

[387] Dr. Parr agreed that the reference in BR 601 to "current treatment" refers to the strict dosing requirements, including that the bisphosphonate be taken on an empty stomach at least 30 minutes before the first food of the day. Dr. Parr agreed that BR 601 does not teach that these strict dosing requirements (i.e., fasted) did not have to be followed.

[388] Despite these acknowledgements, Dr. Parr would not go so far as to agree that BR 601 was about fasted administration. He would only agree that it was not clear whether BR 601 refers to the fasted or fed state. However, Dr. Parr noted that BR 601 acknowledged the low-fasted absorption and BR 601 stated that this "necessitates the use of high doses of the drugs in relation to the quantity actually absorbed in the body, with the disadvantages of undesirable exposure of the body to the excess quantity of the drug".

[389] Dr. Parr's evidence does not support the view that BR 601 was about the food effect.

[390] I disagree with Dr. Yates and Dr. Parr that BR 601's reference to the "contents of the stomach" is a reference to the food effect or that the formulations of BR 601 could be taken with or without food. Given that BR 601 says nothing about changing the administration of

bisphosphonates, the state of the art at that time was that bisphosphonates were taken in the fasted state, and the inventor referred to "current" state, and said nothing about food or the food effect, this assumption cannot be made. Moreover, all the experts agreed that even a fasted stomach includes some contents.

[391] Dr. Cremers unequivocally stated that BR 601 does not discuss or address the food effect. He stated that BR 601 is about formulations that allow lower doses of bisphosphonates to be used, which for oral administration, the skilled person would understand needed to be taken at least 30 minutes before the first food of the day, i.e., in the fasted state.

[392] Dr. Cremers emphasized that BR 601 is not directed to solving the food effect problem, and is not about permitting bisphosphonates to be taken with food. BR 601 does not mention the food effect or the inconvenience of having to take bisphosphonates without food. BR 601 does not disclose "for use with or without food or beverage intake", which is essential to each of the asserted claims of the '188 Patent. Nor does BR 601 teach the skilled person how to make a formulation that can be given with or without food. BR 601 is about increasing bisphosphonate absorption when taken without food so that a lower dose could be used.

[393] Dr. Cremers stated that the reference in BR 601 to the "current treatment" is a reference to the need to take a bisphosphonate on a fasted stomach. Dr. Cremers stated that BR 601 does not suggest any change to these dosing instructions.

[394] Dr. Cremers explained that the skilled person would understand that the reference in BR 601 to "contents of the stomach" refers to gastric fluids present in the fasted stomach, such as calcium, that are known to interact with and effectively inactivate chelating agents, rendering them unable to increase absorption by the time they make it out of the stomach and into the small intestine. BR 601 promotes the use of an enteric coating so the formulation avoids release of the chelating agent in the stomach, and instead releases it after the dosage form has left the stomach. He stated that the skilled person would understand that the reason BR 601 uses an enteric coating is to prevent the chelating agent from being released in the stomach so it will not be deactivated.

[395] Dr. Cremers found it inconceivable that BR 601 would purport to solve the food effect without stating this or without even referring to the food effect problem. Dr. Cremers added that it was also inconceivable that BR 601 purported to solve the food effect for every bisphosphonate known at the time, and also permitted lower dosing. He emphasized that no skilled person would read BR 601 in this way.

[396] Dr. Cremers suggested that Dr. Yates had drawn several inferences to support his opinion which the skilled person would not do. First, the "contents of the stomach" does not mean "food." As noted, the skilled person would know that the stomach contains contents – for example, calcium – even without food that will interact with bisphosphonates and with a chelating agent. Dr. Parr had also noted this. Dr. Cremers explained that this is, in part, why the oral bioavailability of bisphosphonates is so low, even when taken without food. This is also the reason BR 601 teaches to avoid the stomach in terms of release, by using an enteric coating, so the chelating agent does not get "consumed" before reaching the small intestine (as BR 601 states). Second, Dr. Yates

assumed that BR 601 solved the inconvenience of the dosing restrictions. Dr. Cremers noted that BR 601 never mentions the inconvenience of having to take bisphosphonates without food.

[397] Dr. Sinko's evidence echoed that of Dr. Cremers. Dr. Sinko noted that BR 601 never mentions food, overcoming the food effect, or a dosage that has similar absorption in the fasted and fed state.

(c) *BR 601 and the Essential Elements of the '188 Patent; No Clear Direction*

[398] Dr. Yates and Dr. Parr were of the view that all the essential elements of the '188 Patent were disclosed in BR 601. Dr. Cremers took the view that BR 601 did not disclose the essential elements of the '188 Patent given the range of combinations and permutations presented and the lack of testing. Dr. Sinko acknowledged that the essential elements of the '188 Patent were generically disclosed in BR 601 but that too many choices were set out with no guidance.

[399] Dr. Parr stated that BR 601 disclosed all the essential elements of the claims of the '188 Patent; pharmaceutical compositions comprising bisphosphonates, including risedronate, EDTA in amounts up to 175 mg and enteric coatings. He noted that BR 601 includes only one example of alendronate being formulated with EDTA and the enteric coating, Methocel, which prevents the core from dissolving in the stomach and allows dissolution in the intestine.

[400] With respect to the amounts of the bisphosphonate, Dr. Parr noted that BR 601 discloses that between 1 and 150 mg of bisphosphonate can be used. Dr. Parr stated that based on the

risedronate products on the market at the time, the skilled person would first look at risedronate amounts of 5 mg for daily administration and 35 mg for weekly administration.

[401] Dr. Parr also noted that EDTA is an essential element of all the claims of the ‘188 Patent at issue. BR 601 discloses that the oral dosage forms can contain a chelating agent and EDTA is provided as a particular example.

[402] With respect to the amount of EDTA, BR 601 discloses that the ratio of chelating agent to bisphosphonate should be greater than 10% mol/mol and particularly greater than 50% mol/mol. BR 601 also teaches that the amount of EDTA should not exceed 175 mg. The molar ratios taught in BR 601 include a molar ratio of greater than 2.

[403] Dr. Parr noted that an enteric coating providing release in the small intestine is an essential element of all the claims of the ‘188 Patent. Dr. Parr stated that this was disclosed in BR 601, noting that BR 601 disclosed that the formulation becomes available in the intestine because of the gastroresistant and enterosoluble coating used, which are enteric coatings.

[404] Dr. Parr was asked about the disclosure in BR 601 and its references to Janner, and the statement in BR 601 that it takes the opposite approach by providing effective use of bisphosphonates with chelating agents in lower quantities. Dr. Parr agreed that BR 601 proposed to use lower quantities because they are delivered to the small intestine.

[405] Dr. Yates also opined that BR 601 disclosed all the essential elements of the ‘188 Patent.

[406] Dr. Yates agreed that BR 601 did not teach a specific bisphosphonate or a specific amount of the chelating agent or a preferred chelating agent. Dr. Yates suggested that EDTA is the preferred chelating agent because it is specifically mentioned, but he did not agree that alendronate is the preferred bisphosphonate, although it is specifically mentioned and is the only bisphosphonate exemplified.

[407] With respect to the range of EDTA in BR 601, Dr. Yates noted that the preferred upper daily limit is 175 mg and the lower daily limit would be 3 mg. Dr. Yates appeared to agree that testing would be needed to determine the "sweet spot" – i.e., the right amount of EDTA depending on the amount of bisphosphonate.

[408] Dr. Yates agreed that Claim 28 of BR 601 permits release of the drug from the enteric-coated dosage form as an immediate release, delayed or prolonged release, and that the '188 Patent claims only an immediate release dosage form. Dr. Yates acknowledged that only the immediate release would address the food effect – not a delayed or prolonged release. However, Dr. Yates suggested that BR 601 taught a single core in addition to microparticles, although the only example in BR 601 is for microparticles contained in a capsule or tablet.

[409] Dr. Yates agreed that BR 601 does not demonstrate that any dosage forms contained in it would work to improve the absorption of any bisphosphonate. The BR 601 contains no data – no formulation was tested. The only example was about alendronate.

[410] In Dr. Cremers' opinion, BR 601 does not disclose the essential elements of the '188 Patent and does not anticipate. Dr. Cremers noted that BR 601 contemplates every bisphosphonate, but does not provide any results of testing on any of them and sets out only one example. Dr. Cremers stated that the skilled person would understand that BR 601's preferred bisphosphonate is alendronate, noting that this is the only bisphosphonate claimed on its own in BR 601.

[411] With respect to the amount of chelating agent, Dr. Cremers noted that BR 601 does not impose an upper limit on the amount of chelating agent or EDTA, but states a preference for daily intake not to exceed 175 mg. BR 601 does not provide any narrower ranges or amounts, or teach what specific amount(s) to use with any particular bisphosphonate.

[412] Dr. Cremers noted that BR 601 provides only one example containing alendronate, EDTA microparticulate cores, a water-soluble intermediate coating, and an enteric coating. He added that the example does not specify the amount of alendronate or EDTA per dosage unit of the formulation, rather it provides amounts for a very large batch.

[413] Dr. Sinko explained that BR 601 permits the combination of one of at least 14 different bisphosphonates in a range of 1 mg to 150 mg with "preferably" 175 mg of EDTA, and one of eight enteric coatings.

[414] Dr. Sinko acknowledged that there was overlap between the formulations of BR 601 and the '188. He explained that the "generic" ingredients overlapped but noted that arriving at such formulations would require many choices to be made and amounts selected from a wide range,

without any guidance in BR 601. He noted that BR 601 did not disclose the immediate release core. Dr. Sinko had previously explained that there was a fundamental difference between an immediate release core – as claimed in the '188 and as essential for the invention – and BR 601, which permits prolonged, delayed and immediate release cores and does not claim one in particular. Dr. Sinko also noted that no predictions could be made regarding absorption without testing.

[415] There is no dispute that BR 601 does not disclose the precise invention; the combination of the "ingredients" of the formulation, or the required amounts – i.e., 35 mg risedronate, 100 mg EDTA and enteric coating and in an immediate release core as used in the '188 Patent. The issue is whether BR 601 discloses sufficient information to permit the skilled person to understand what is invented and to be able to perform the invention of the '188 Patent using the disclosure and their common general knowledge, without inventiveness and without more than routine experimentation.

[416] Allergan acknowledged that there is overlap between some of the formulations in BR 601 and the '188. However, I agree with Allergan that there is no direction in BR 601 that would guide the skilled person to choose all the essential elements or components of the '188 in the required amounts and to also choose an immediate release core, which is essential to the invention of the '188 to ensure immediate release once in the small intestine to solve the food effect.

[417] Allergan also acknowledged that if the skilled person did happen to make a formulation that matches identically with what is claimed in the '188, it would perform in the same way as the

‘188. In such case, however, it would still not be possible to predict whether pharmaceutically effective absorption would result. All the experts agreed that clinical human studies would be necessary.

[418] Despite that, hypothetically, a skilled person could – if all the right choices are made from a range of bisphosphonate, chelating agents, enteric coatings, along with an immediate release core – land on all the essential elements in all the exact amounts of the ‘188, and unbeknownst to them achieve pharmaceutically effective absorption, if the formulation were administered in the fed or fasted states, this result or attribute is not disclosed in BR 601. BR 601 never mentions this attribute and never mentions addressing the food effect – and simply does not do so. Therefore, it is not an inherent attribute and the result is not inherently disclosed (*Novo Nordisk*; see also *Sanofi* at para 32).

[419] In *Novo Nordisk*, at paras 170-175, the Court noted that simply claiming the compounds without disclosing their pharmacokinetic advantages does not mean that the properties or advantages are inherently included in the prior patent, and will not constitute anticipation.

[420] As noted by Allergan, the inherent pharmacokinetics of BR 601 are unknown and unpredictable. These were not disclosed in BR 601. BR 601 is not aimed at addressing the food effect and it is unknown whether the formulations of BR 601 could be taken with or without food and whether they would achieve pharmaceutically effective absorption, as elaborated on below.

[421] A skilled person who followed the disclosure of BR 601 would not be clearly directed to the claimed invention and would just as likely develop a formulation that did not come close to any of the formulations of the ‘188.

(d) *BR 601 Does Not Disclose Pharmaceutically Effective Absorption*

[422] As noted, BR 601 is not about the food effect, does not disclose that its formulations can be taken with or without food and refers to the current treatment, which is fasted administration. For these reasons and the fact that BR 601 says nothing about pharmaceutically effective absorption or any similar concept, BR 601 does not disclose that its formulations would provide pharmaceutically effective absorption if administered in the fed or fasted state. BR 601 does not mention this concept at all. In addition, all the experts agreed that the achievement of pharmaceutically effective absorption could not be predicted; human clinical studies would be required. No such studies – or any studies at all – are disclosed in BR 601.

[423] Dr. Yates acknowledged that BR 601 does not use the term “pharmaceutically effective absorption”, but opined that the skilled person would understand that BR 601 so provided. Dr. Yates relied on his assumption that BR 601 was about the food effect and also on his explanation of the “housekeeping wave”.

[424] Dr. Parr also acknowledged that BR 601 does not specifically state that its formulations will provide for pharmaceutically effective absorption of the bisphosphonate with or without food. Dr. Parr opined that the skilled person would understand that the compositions of BR 601 would meet this requirement based on his extrapolation of information about the absorption of the pre-

existing immediate release tablet (ACTONEL). He concluded that the composition containing EDTA taught in BR 601would have a less than 50% reduction in absorption because it would be released in the small intestine and would fall within the definition of "pharmaceutically effective absorption".

[425] However, Dr. Parr was reminded on cross examination that his assumption about the immediate release tablet was based on it being administered at least 30 minutes before the first food of the day rather than being administered with food.

[426] Dr. Cremers stated that BR 601 does not provide any basis for the skilled person to even think about the concept of pharmaceutically effective absorption, noting that this is not described in BR 601 at all.

[427] Dr. Cremers disagreed with Dr. Yates' opinion that the skilled person would predict that pharmaceutically effective absorption would likely be achieved for one or more formulations of BR 601, noting that this was based on Dr. Yates' assumption that BR 601 addressed the problem of the food effect with bisphosphonates, which it does not.

[428] Contrary to Apotex's view that Dr. Yates' evidence regarding the "housekeeping wave" was unchallenged, Dr. Cremers stated that the skilled person would not assume, as Dr. Yates did, that "the composition would be delivered into a virtually empty proximal small intestine whether or not it was taken with food". Dr. Cremers stated that there is no basis in BR 601 to make that assumption.

[429] Dr. Cremers also disagreed with Dr. Parr's opinion, noting that Dr. Parr relied on extraneous information, not on the disclosure of BR 601, relating to the immediate release tablet, and information regarding competitive chelation mechanisms and combined them with the molar ratios disclosed in BR 601 to infer that the compositions of BR 601 would fall within the definition of "pharmaceutically effective absorption." Dr. Cremers disagreed that the skilled person would combine the disclosure in BR 601 with any extraneous information in order to infer anything about fed versus fasted absorption or would reach this conclusion.

(3) BR 601 Does Not Enable the Claims of the '188 Patent

[430] The enablement branch of the test for anticipation assesses whether the skilled person could work the invention with the disclosure, the common general knowledge and some routine trials. Routine trials are not arduous or prolonged, involving repeated trial and error.

[431] Although BR 601 disclosed formulations that overlap with the '188, the disclosure provided no guidance to the skilled person. However, assuming that the disclosure was sufficient, the skilled person could not "work" the invention of the '188 without a great deal of trial and error and significant experimentation, including human clinical trials, to determine if pharmaceutically effective absorption was achieved whether the formulation was administered in the fed or fasted state.

[432] The skilled person could choose other bisphosphonates and other chelating agents in other amounts and/or a delayed or prolonged release core, rather than an immediate release core, with the result that the formulation would fall outside the '188 Patent.

[433] Dr. Yates opined that BR 601 met the enablement requirement of the anticipation test based on his view that BR 601 provides "extensive" details of what form the pharmaceutical compositions can take, such as: capsules and tablets; that the bisphosphonate and EDTA may be present in a single solid core or in multiple cores; other excipients that may be included in the pharmaceutical composition; that the enteric coating should be applied to the core or cores; and, the amounts of each of the main ingredients. Dr. Yates pointed to the example in BR 601 setting out how to prepare large amounts of the pharmaceutical composition of the invention. He noted that there is no limitation on the possible examples and that risedronate was also a widely marketed bisphosphonate at that time.

[434] Dr. Yates added that the types of oral dosage forms described and claimed in the '188 Patent, namely enteric-coated dosage forms containing the well-known bisphosphonate risedronate and the well-known chelating agent EDTA, were not particularly challenging from a technical perspective. In his view, any experimentation required would be simple and routine for the skilled person.

[435] Dr. Parr also stated that the dosage forms claimed in the '188 would not be difficult for the pharmaceutical formulator to prepare. Dr. Parr opined that it would have been routine for the pharmaceutical formulator to substitute the example of alendronate and EDTA with risedronate.

[436] Dr. Cremers did not agree. He stated that BR 601 does not enable the skilled person to perform and make oral dosage forms to meet the essential elements of the '188.

[437] Dr. Cremers noted that because BR 601 provides an extremely broad disclosure of potential formulations, this work would have required extensive trial and error experimentation involving formulation development and clinical work. The skilled person with regard only to BR 601 and the common general knowledge would need to make test formulations, with risedronate and a chelating agent and enteric coating parameters as variables in each formulation, and test each formulation in a pharmacokinetic study involving human volunteers. While the skilled person would be generally familiar with this kind of work, given the broad disclosure of BR 601, it would have taken significant resources to complete for any set of test formulations. If none of the tested formulations showed "pharmaceutically effective absorption," then additional test formulations would need to be developed and clinically tested.

[438] Dr. Sinko agreed, noting that although BR 601 "generically" disclosed the essential elements of some formulations, it is so broad that it could not enable the skilled person to practice the invention without significant trial and error experimentation and not knowing whether success (i.e., pharmaceutically effective absorption) would even be achieved.

[439] The evidence of Dr. Cremers and Dr. Sinko is more persuasive with respect to enablement. In the event that BR 601 had disclosed the invention of the '188, there was insufficient direction to permit the skilled person to perform the invention.

[440] Although Dr. Yates states that it would be simple and routine for an experienced formulator to make the formulations of the '188 with the disclosure of BR 601 and their common general knowledge, he also noted the "extensive details" in BR 601 about the many choices of

bisphosphonates, excipients, chelators, etc. These "extensive details" and the combinations and permutations set out in BR 601 with little direction suggest that it would be far more difficult to work the invention than Dr. Yates asserts.

[441] In addition, Dr. Yates and Dr. Parr both acknowledged that given the low bioavailability of bisphosphonates, their absorption cannot be predicted and human clinical studies would be required. I disagree with Dr. Yates that such a clinical study would be routine.

[442] The skilled person is not inventive – even if they are familiar with making formulations. As Dr. Cremers noted, experimentation on the scale required to make the oral dosage forms of the asserted claims would be a significant and time-consuming formulation development and clinical research project.

[443] As noted by Allergan, following the example of BR 601 and substituting risedronate for alendronate would not result in a formulation within the claims of the '188 Patent. Although Apotex points to Dr. Cremers' testimony that the example in BR 601 did not set out the amounts of the EDTA to be used, Dr. Cremers actually stated that the example did not provide amounts for per unit dosage, only for a large batch. The example provides for equal amounts of bisphosphonate and EDTA, which, as noted by Allergan, would not reflect the amounts set out in the '188 Patent.

G. *Conclusion on Anticipation*

[444] The evidence does not establish on a balance of probabilities that BR 601 disclosed or enabled the asserted claims of the '188 Patent. BR 601 does not provide all the information needed

to produce the claimed invention – i.e., the oral dosage form of risedronate that can be taken with or without food and will achieve pharmaceutically effective absorption either way. The skilled person reading BR 601 would not regard it as disclosing how to address the problem of the food effect. BR 601 discloses the generic elements of the claims of the '188 Patent but does not provide a clear direction to the skilled person. The skilled person would not understand that BR 601 was seeking to address the food effect (because it was not) and would regard BR 601 as addressing the issue of low fasted absorption. Even if the disclosure arm of the anticipation test were met, BR 601 does not enable the skilled person to perform the invention. The trial and error required to achieve a formulation of the '188 Patent that achieved pharmaceutically effective absorption would exceed that normally expected to be necessary.

X. Is the '188 Patent Obvious?

A. *Apotex's Submissions*

[445] Apotex submits that the "state of the art" is simply the prior art relied upon by Apotex.

[446] Apotex notes that the issue is whether the skilled person could bridge the difference between the state of the art and the subject-matter defined by a claim using their common general knowledge and any additional art that could be discovered by conducting a reasonably diligent search.

[447] Inventiveness requires going beyond where the skilled person would have been expected to go. The skilled person is assumed to be a person who is going to try to achieve success and not

one who is looking for difficulties or seeking failure (*Free World Trust* at para 44). Skilled work is not necessarily inventive work.

[448] Apotex notes that the skilled person is a "paragon of deduction and dexterity" (*Beloit*), is presumed to possess the common knowledge in the field, the literature that may be located in a diligent search, the ability to conduct routine experiments, and the ability to make logical deductions based upon their knowledge and the results of such experiments.

[449] Apotex submits that an invention is obvious-to-try if the skilled person would find it more or less self-evident to try to obtain the invention (i.e., conduct the experiment and observe the results). This test does not require a demonstration that it is "more or less self-evident that what is to be tried ought to work", although this is a factor to be considered (*Sanofi* at paras 66, 69).

[450] Apotex adds that there is no need for the skilled person to have certainty that the "try" will be successful – an amount of uncertainty is permitted. Apotex submits that while the actual course of conduct is a factor to consider in the obvious to try test, this does not change the fact that obviousness is an objective inquiry. The inquiry is about how the skilled person would have acted in light of the prior art (*Sanofi* at paras 70-71; *Aux Sable Liquid Products LP v JL Energy Transportation Inc*, 2019 FC 581 at para 42). Apotex cautions against relying on the actual course of conduct because the skilled person may have had more information than the inventors and avoided "wild goose chases".

[451] Apotex also submits that if it were obvious to arrive at the invention, and doing so would have resulted in the consequent discovery of an inherent beneficial property or advantage of the invention, then the discovery of this "golden bonus" does not add anything inventive to what had already been obtained. Moreover, the fact that there may be other obvious routes available to the skilled person does not make any particular route less self-evident or obvious.

[452] Apotex further submits that where other pharmaceutical companies solved the problem independently of each other, the claimed subject matter cannot be said to be inventive (*Mediatube Corp v Bell Canada*, 2017 FC 6 at para 154).

[453] Apotex disputes Allergan's criticisms of Dr. Yates. Apotex submits that Dr. Yates disagreed with propositions that were put to him because they were unsound propositions. He also disagreed with some statements in the art but explained why. Apotex responded that while Dr. Yates was not critical of statements in BR 601, "the propositions in BR 601 are what they are".

(1) The State of the Art

[454] Apotex submits that the state of the art is what Apotex cited and relied on. Apotex adds that Dr. Yates confirmed that all this art was well-known to the skilled person or would have been located in a reasonably diligent search.

[455] Apotex further submits that the '188 Patent sets out information that was part of the state of the art and the common general knowledge, including that: the primary site of bisphosphonate absorption is the small intestine (Mitchell 1998); attempts were made to increase absorption of

bisphosphonates (BR 601); bisphosphonates interact with cations, such as calcium, in foods, resulting in a reduction of their absorption (Mitchell 1999); and, the dosing instructions for oral bisphosphonates were "complex and inconvenient".

[456] Apotex also relies on BR 601 as prior art. Apotex submits that BR 601 disclosed enterically coated compositions containing a bisphosphonate, including risedronate, and a chelator, including EDTA, which avoid the contents of the stomach and are delivered to the small intestine where the chelator outcompetes the bisphosphonate, and improves absorption of the bisphosphonate.

[457] Apotex submits that because BR 601 is cited in the '188 Patent, Allergan cannot distance itself from it as prior art. In addition, based on *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 at paras 86-87 [*Hospira*], a document available to the public prior to the claim date can be considered part of the state of the art even if it would not be found in a reasonably diligent search.

[458] Apotex submits that bisphosphonates were well-known. The food effect problem was also well-known as were the rigid dosing instructions.

[459] Apotex adds that the use of enteric coatings was also known as such coatings were useful to bypass the stomach and dissolve in the small intestine. Several different enteric coatings were disclosed in prior art patents.

[460] Apotex submits that Mitchell 1996 is not a teach away or any obstacle to the use of EDTA. Apotex notes that Mitchell 1996 is not even cited in the ‘188 Patent and was not relevant by 2005.

[461] Apotex submits that EDTA was known as a very strong chelating agent that could preferentially outcompete bisphosphonates, leaving more of the bisphosphonates available to be absorbed. Apotex notes that higher amounts of EDTA were needed to increase intestinal permeability.

[462] Apotex points to the prior art, including Poiger that reported on the study of the effects of milk and the counteracting effects of EDTA on the absorption of tetracycline. Apotex submits that Poiger confirmed that EDTA overcomes the food effect by outcompeting tetracycline for the intestinal calcium and that EDTA in amounts up to 2.3 g were safe and would not have increased intestinal permeability or caused damage to the intestinal membrane.

[463] Apotex submits that by 2005 the art had evolved and the skilled person would know that the high levels of EDTA required in Poiger would not be required if an enteric coating was used.

[464] Apotex notes that Janner proposed that EDTA may enhance the absorption of bisphosphonates in two ways: by outcompeting the bisphosphonate and leaving more bisphosphonate for absorption and by opening of the tight junctions of the intestine and increasing permeability. Apotex acknowledges that Janner concluded that the amount of EDTA tested was too high for clinical use.

[465] Apotex points to Lin, which reported that lower amounts of EDTA increased absorption of bisphosphonates by competitive chelation, but higher amounts altered intestinal permeability.

[466] Apotex notes that there was no additional data set out in Ezra. Apotex adds that Ezra's conclusion in 2000 is not persuasive by 2005. Apotex notes the evidence of Dr. Yates and Dr. Parr disputing Ezra's conclusion that the use of EDTA was "impossible". Apotex adds that BR 601 did not accept this proposition.

[467] Apotex submits that WO 111 disclosed formulations of bisphosphonates and a chelator, including EDTA to provide enhanced absorption and stated that its formulations could be given under fed or fasted conditions.

[468] Apotex submits that EDTA was known to be safe for humans. Apotex notes that the daily allowable intake of EDTA had been set by the U.S. FDA and WHO at 2.5 mg/kg/day, noting that this amount included a large safety margin. Apotex also notes that Dr. Dillberger explained that, a dose of 810 mg of EDTA, which is less than the upper limit in the '188 Patent, would be considered safe.

[469] Apotex disputes that EDTA alone or with risedronate would damage the small intestinal mucosa. Apotex points to Dr. Dillberger's evidence on the studies done on EDTA in the small intestine.

[470] Apotex submits that Dr. Sinko's evidence that bisphosphonates alone could damage the small intestinal mucosa is unsupported. Apotex adds that the experts agreed that the intestinal mucosa has the ability to repair itself if damaged.

[471] Apotex also notes that the inventors used EDTA and made submissions to the U.S. FDA that 100 mg EDTA in its tablets was safe based on what was known about EDTA at the time.

(2) No Differences between the State of the Art and the Subject Matter of the Claims

[472] Apotex describes the subject matter of the claims of the '188 Patent as an enteric-coated dosage form for use with or without food and beverage intake that comprises risedronate and EDTA for release in the small intestine which provides similar absorption between fed and fasted states.

[473] Apotex submits that if BR 601 does not anticipate, then it clearly makes the '188 Patent obvious, based on BR 601's disclosure, the other prior art and the common general knowledge. Apotex argues that to the extent that there is any small difference between the state of the art and the claims of the '188 it is only that the art did not explicitly combine risedronate and EDTA in an enteric-coated oral dosage form for use with or without food intake, and explicitly teach that such a dosage form will provide similar absorption, meeting the definition of "pharmaceutically effective absorption". Apotex argues that bridging this small difference would have been simple and did not require any inventive ingenuity.

[474] Apotex submits that since the ‘188 Patent cites BR 601, Allergan can not dispute that BR 601 was publicly available and it is therefore part of the mosaic of prior art. Apotex also relies on Dr. Bonenfant’s evidence and suggests that he conducted a “reasonably diligent search” and located BR 601.

(3) Bridging Any Differences Did Not Require Inventive Ingenuity

[475] Apotex submits that the skilled person who set out to solve the food effect for oral bisphosphonates would have made the formulations taught in BR 601 and would have discovered that these formulations achieved pharmaceutically effective absorption. Apotex submits that any differences between the teachings in BR 601 and the subject matter of the asserted claims would have been easily bridged by the skilled person using their common general knowledge.

[476] Apotex again submits, as it did in its anticipation submissions, that BR 601 taught that its formulations can be taken with food or without food. Apotex further argues that pharmaceutically effective absorption would result from following the teaching of BR 601 and the skilled person would only need to do routine and non-inventive testing to confirm this. Apotex relies on Dr. Parr’s evidence where he extrapolated information based on the ACTONEL immediate release tablet to support his view that pharmaceutically effective absorption would result.

[477] Apotex also relies on Dr. Yates’ evidence regarding the “housekeeping wave” to submit that the use of EDTA and an enteric coating would ensure that release in the intestine would occur only once the stomach was empty and therefore, the formulation could be taken fed or fasted and would achieve pharmaceutically effective absorption.

[478] Apotex adds that it was routine work for the skilled person to adjust the formulation, including the level of enteric coating, to achieve pharmaceutically effective absorption.

(4) If BR 601 is Not Part of the Mosaic, the Claims of the ‘188 Patent are Still Obvious

[479] Apotex submits that the claims of the ‘188 Patent are obvious even if BR 601 is not considered as part of the mosaic of prior art. The skilled person who set out to solve the food effect would have known that the food effect was caused by the cations in food and would have looked to chelators to bind the cations. The skilled person would have separated the dosage form from the food and provided a chelator to competitively bind with cations. Enteric-coated risedronate formulations and bisphosphonate formulations with EDTA were already taught in the art. In addition, the skilled person would have known that adding sufficient EDTA to an enteric-coated risedronate dosage form would assist in chelating cations in the small intestine and would improve absorption.

[480] Apotex points to Dr. Dillberger’s evidence regarding the testing of EDTA administered to the intestine which revealed no safety concerns, but acknowledged that this testing was in dismembered rabbits, not humans.

[481] Apotex also points to the “blinded” evidence of Dr. Parr who arrived at this approach based only on the information for bisphosphonates in the 2004 edition of the Canadian Pharmaceutics and Speciality and without knowledge of the prior art or the ‘188 Patent. Dr. Parr also provided blinded evidence about achieving pharmaceutically effective absorption using the common general

knowledge and key pieces of prior art. Apotex acknowledges that blinded evidence is not a guarantee of reliability, but submits that it is compelling.

[482] Apotex notes the explanation of Dr. Yates about the "housekeeping wave" – that EDTA would outcompete the bisphosphonate and that enteric-coated dosage forms remain in the stomach until all the food is emptied and then deliver the contents of the formulation to an empty intestine. Apotex also points to the prior art regarding the use of enteric coatings.

[483] Apotex submits that adding a chelating agent such as EDTA in such dosage forms was obvious because the skilled person knew that the EDTA would chelate cations in the small intestine preferentially over risedronate, which would prevent risedronate from forming insoluble complexes.

[484] Apotex adds that the cations in the small intestine would be relatively low because the enteric-coated dosage form would leave the stomach only after any ingested food. Apotex submits that this "strongly suggests" that absorption would be similar whether the dosage form is taken in the fed or fasted state.

[485] Apotex further submits that it was routine work for the skilled person to adjust the formulation components, including the level of enteric coating, to achieve pharmaceutically effective absorption. The skilled person knew to avoid high amounts given that administration was to the small intestine, and to avoid increasing permeability in the fasted state. With respect to the other claim sets, Apotex submits that it was common general knowledge that 35 mg risedronate

administered weekly was useful to treat osteoporosis as this was the amount in the precursor ACTONEL. The skilled person would also know that a dosage form containing 35 mg risedronate, 100 mg EDTA and an enteric coating would not weigh more than 1 gram given the other excipients added would not bring it over this weight. In addition, most oral dosage forms on the market in April 2005 weighed less than 1 gram, to permit the tablet to be swallowed.

[486] Apotex adds that there is nothing inventive about providing bisphosphonates in a "kit", which includes dosing instructions, noting that ACTONEL and FOSAMAX® both contained similar instructions.

(5) The Invention was Obvious to Try

[487] Apotex emphasizes that the skilled person, although not inventive, applies deductive reasoning; reasoning that arrives at a logical conclusion from established premises. Apotex argues that the skilled person would have made deductions from the state of the art and the common general knowledge and would have easily arrived at the invention of the '188 Patent, without any inventiveness.

[488] Apotex submits that it would have been self-evident to try to obtain the invention of the '188. Apotex points to the "blinded" evidence of Dr. Parr, that the skilled person would have tried to obtain the invention and would have expected to succeed. Apotex notes that there need not be certainty of success.

[489] Apotex adds that it was obvious to try because it was self-evident to combine EDTA and a bisphosphonate in an enteric-coated form to overcome the food effect, which would also achieve similar absorption between the fed and fasted state.

[490] With respect to the other factors that inform the obvious to try test, Apotex submits that there were only a few identifiable and predictable solutions to the food effect; release in the small intestine by using enteric coatings; adding EDTA due to its strong chelating properties, and at safe amounts as established by the U.S. FDA and JECFA. Apotex also submits that there was motivation to solve the well-known food effect of bisphosphonates, including because of the inconvenient dosing requirements.

[491] Apotex also submits that the extent of the work and the effort required to achieve the invention was simply the routine work of a skilled person. Apotex suggests that the inventors' evidence does not indicate that they encountered any problems formulating the dosage forms. Apotex submits that P&G identified the use of enterically coated risedronate and EDTA tablets early in their project (the so-called gold medal approach) as they believed that the cations in food caused the food effect problem. Apotex submits that the skilled person would have taken this same approach.

[492] Apotex adds that the inventors' focus on the colonic delivery was a misstep and not what the skilled person would do. The inventors wasted time pursuing this. Apotex suggests that after the turning point in 2004 when the inventors focussed on the small intestine, their work went quickly and was routine. The inventors used 100 mg EDTA without testing other amounts and

without hesitation. The inventors' '132 Study confirmed what the skilled person would have expected – that a 10% enteric coating on tablets of risedronate and EDTA provided pharmaceutically effective absorption.

[493] Apotex argues that other indicia of obviousness should also be considered, including that other pharmaceutical companies landed at the same or similar solutions to the food effect. Apotex points again to BR 601; Elan's use of a penetration enhancer; and, Takeda's development of risedronate to address the food effect. With respect to Takeda, Apotex questions the lack of awareness by Drs. Dansereau and Burgio given that in the U.S. litigation a representative of P&G provided evidence about Takeda's invention. Apotex argues that the Court should draw an adverse inference against Allergan as it could have provided evidence to explain the allegations noted in the U.S. litigation that P&G intervened with Takeda resulting in the withdrawal of Takeda's patent application.

[494] Apotex submits that the evidence of the inventors on cross examination and the findings in the U.S. litigation call out the need for Allergan to make inquiries of P&G and to address this issue. Apotex disputes that they are suggesting fraud by P&G. However, Apotex submits that the Court should draw an adverse inference that there was a Takeda patent application and that it embraced the invention that is now the '188 Patent.

[495] Apotex also notes that the analogous product in the United States, ATELVIA, was found to be obvious.

B. *Allergan's Submissions*

[496] Allergan submits that the '188 Patent is inventive; not obvious. Nothing in the prior art taught the combinations of the components of the '188 Patent or provided any guidance about a formulation of risedronate that would provide pharmaceutically effective absorption when taken with or without food.

[497] First, Allergan submits that although some of the elements of the '188 Patent were known in the art, the combination of risedronate with the appropriate amount of EDTA and an enteric coating with an immediate release was not known. Second, Allergan submits that Apotex's theory of obviousness is flawed for several reasons: the only relevant prior art taught away from EDTA (Poiger); Dr. Yates "housekeeping wave" theory is inconsistent with the art and the reality; Dr. Parr's assumption that pharmaceutically effective absorption would result from formulations with EDTA and an enteric coating is based on a faulty premise; and, the need for an immediate release core, which is essential to the invention of the '188 Patent, was not taught in the art. Third, BR 601 would not have been found by the skilled person. Moreover, BR 601 does not make the '188 Patent obvious. It was not about the food effect, it disclosed countless possible components, it provided no guidance on what to choose, and it did not disclose any testing. Fourth, the differences between the state of the art and the subject matter of the claims required inventive ingenuity to bridge. The invention was not obvious to try for several reasons, including that: the skilled person would not have an expectation of success; human clinical testing, which was far from routine, would be required to determine if pharmaceutically effective absorption of any formulation had

been achieved; the work of the inventors was protracted and inventive; and, despite the motivation to address the food effect, no one else had done so.

[498] Allergan points to *Beloit* at para 21, where the Federal Court of Appeal noted :

> Every invention is obvious after it has been made, and to no one more so than an expert in the field. Where the expert has been hired for the purpose of testifying, his infallible hindsight is even more suspect. It is so easy, once the teaching of a patent is known, to say, "I could have done that"; before the assertion can be given any weight, one must have a satisfactory answer to the question, "Why didn't you?"

[499] Allergan generally submits that Apotex's obvious analysis is flawed because it is based on the assumption that every dosage form combining EDTA and an enteric coating would provide pharmaceutically effective absorption with or without food. Allergan submits that Dr. Yates' "housekeeping wave" theory that an enteric coating on its own results in the dosage form entering a virtually empty small intestine and causing it to provide similar absorption whether fed or fasted does not hold up.

[500] Allergan notes that there are other enteric-coated products that still suffer from the food effect problem (e.g., PREVACID®). In addition, there are other drugs that suffer from a food effect that have not been enterically coated (e.g., tetracycline, ciprofloxacin, estramustine), and have not been formulated with EDTA. Allergan submits that if an enteric coating ensured against absorption in the stomach then other pharmaceutical companies would have used enteric coatings to address the food effect of other drugs, and they did not.

[501] Allergan also notes that Mitchell 1996, the only art that reports on the use of enteric coatings for risedronate, taught away from the use of enterically coated bisphosphonates.

[502] Allergan submits that Dr. Parr's opinion – that formulations with EDTA and an enteric coating (including those in BR 601) would provide pharmaceutically effective absorption because the immediate-release risedronate tablets (ACTONEL) did so – is based on a faulty premise.

[503] Allergan notes that Dr. Parr based his opinion on information he extrapolated about the immediate-release tablets as providing pharmaceutically effective absorption because absorption was only reduced by 50% if taken with food. Allergan also notes that Dr. Parr's opinion about BR 601 was also based on this extrapolated information. However, Dr. Parr relied on data about administration 30 minutes before food, not with food (as is required for pharmaceutically effective absorption). Allergan submits that the evidence is that when a bisphosphonate is taken with food the absorption is reduced far more than 50%.

[504] Allergan adds that Dr. Parr admitted on cross examination that he did not know whether, if the bisphosphonate was taken at the same time as food, the reduction would be greater. Allergan adds that both Dr. Yates and Dr. Parr's theories also fail to account for the fact that the '188 Patent requires an immediate release in the small intestine in order to solve the food effect.

(1) BR 601 is Not Part of the Mosaic of Prior Art

[505] Allergan submits that BR 601 should not be considered as part of the mosaic of prior art for the obviousness analysis as it would not have been located by the ordinary skilled person in

April 2005. Allergan notes that Apotex's experts were provided with BR 601 and an English translation. None of the experts looked for BR 601 or found it. Allergan acknowledges that the inventors were provided with BR 601, but the source is not known.

[506] Allergan disputes Apotex's submission that because BR 601 is cited in the '188 Patent, it is deemed prior art or a binding admission on Allergan. Allergan notes that the '188 Patent specifically states that "[t]he citation of any document is not to be construed as an admission that it is prior art with respect to the present invention".

(2) BR 601 Does Not Render the '188 Patent Obvious

[507] Allergan submits that even if BR 601 is included in the mosaic, it does not render the invention of the '188 Patent obvious.

[508] Allergan acknowledges that BR 601 combines a chelating agent and enteric coatings in bisphosphonate formulations. Although some formulations of BR 601 would achieve pharmaceutically effective absorption, BR 601 does not teach what combinations (which bisphosphonate, which chelating agent, in what amounts, and with what type of core tablet) would do so. No testing is disclosed in BR 601. As noted above, the skilled person following the sole example of BR 601 and adapting it with risedronate would have made a formulation that falls outside the scope of the claims of the '188 Patent. In addition, there is no evidence about how the example in BR 601 would perform. There is also no prior art that teaches how to adapt the example in BR 601 to achieve pharmaceutically effective absorption.

[509] Allergan notes that the skilled person would have to select EDTA in an amount covered by the claims of the ‘188 Patent, which differs from the example of BR 601. There is no guidance in BR 601 or the other art.

[510] Allergan also notes that skilled persons would have to select an immediate-release core from among the possibilities in order to achieve pharmaceutically effective absorption. The prior art – including BR 601 – does not suggest that delivery of risedronate and EDTA in an immediate release is required to solve the food effect problem or that delayed or prolonged release will not work . The ‘188 teaches this.

[511] Allergan submits that Apotex has no evidence that it would have been obvious to choose the immediate release option or that the skilled person would select immediate release rather than prolonged or delayed release which are the other options in BR 601.

[512] Allergan notes that Dr. Yates and Dr. Parr both agreed that the skilled person would need to conduct human clinical studies to determine whether any of the many combinations and permutations in BR 601 would result in pharmaceutically effective absorption. Allergan submits that human clinical studies are far from “routine” for the ordinary skilled person.

(3) The State of the Art and “Teach Aways”

[513] Allergan submits Apotex’s position that EDTA posed no potential risk should be rejected as the prior art did not support its use for pharmaceutical compositions. Allergan submits that as of April 2005, there was no published literature disclosing any studies using EDTA to overcome

the known food effect for bisphosphonates. Allergan submits that the prior art taught away from using EDTA to enhance oral bisphosphonate absorption, with the exception of BR 601, if it is prior art at all.

[514] Allergan submits that there is nothing in the prior art that even suggests using EDTA in the amounts claimed in the ‘188 Patent to solve the food effect for risedronate without increasing fasted absorption.

[515] Allergan notes that the only prior art that reported on the use of EDTA to attempt to overcome the food effect was with respect to tetracycline. Poiger found that 2.3 grams of EDTA was required to overcome the food effect caused by the consumption of 200 ml of milk.

[516] Allergan submits that the skilled person would have no reason to think that this high amount of EDTA could be used to overcome the food effect for bisphosphonates, let alone without also increasing fasted absorption. In Allergan’s view, Poiger teaches away from using EDTA as a solution to the food effect problem for oral bisphosphonates.

[517] Allergan notes that WO 111 acknowledged the need for bisphosphonates that could be taken with food. However, WO 111 is not focussed on oral bisphosphonates, rather it contemplates several delivery routes and does not disclose any route that would allow the drug to be taken with food.

[518] Allergan submits that Janner and Lin taught that EDTA was not clinically feasible. Janner and Lin reported that EDTA can effect the absorption of alendronate and clodronate in the fasted state and only at much higher doses than would have been considered clinically feasible. Allergan notes that the ‘188 Patent seeks to avoid increased absorption in the fasted state. Allergan notes that Janner and Lin did not study whether EDTA could address the food effect.

[519] Allergan argues that if the skilled person considered the results in Lin, they would observe that even the lowest EDTA dose tested (1.2 mg/kg, which is equivalent to 84 mg in an average 70 kg human) increased fasted absorption in rats – which the ‘188 Patent teaches to avoid in humans.

[520] Allergan notes that Dr. Yates acknowledged that even the lowest amount of EDTA noted in Janner to provide any effect (10 mg/kg) would not be practicable for clinical use.

[521] Allergan also points to Ezra, a review of the bisphosphonate literature, including Janner and Lin. Ezra concluded that “the applicability of [EDTA] in human pharmacotherapy is impossible, considering its damaging effects on mucosal integrity.” Ezra noted that EDTA enhances the absorption of alendronate, but added that “the absorption still remains variable and occurs at EDTA concentrations that make this chelator unsuitable for clinical use.”

[522] Allergan notes that Dr. Yates disputed Ezra’s statement about the unsuitability of EDTA, despite that others did not and despite that this statement is supported by other prior art – e.g., Van Hoogdalem.

[523] Allergan further submits that the skilled person could not predict the amounts of the components that would improve absorption in the fed state while not increasing fasted absorption.

[524] Allergan also notes that both Drs. Cremers and Sinko explained that the skilled person would have had real concerns with the prospect of releasing a bisphosphonate and EDTA in the small intestine at relatively high localized amounts. Allergan submits that their opinions were unshaken on cross examination.

[525] Allergan acknowledges that by April 2005, the skilled person was aware of enteric coatings but submits that the prior art did not teach enteric-coated bisphosphonate formulations to address the food effect.

[526] Allergan submits that the only prior art that studied enteric-coated risedronate tablets is Mitchell 1996, which was an abstract. Mitchell 1996 reported that there was no significant difference between the tablets under fasted conditions, but under fed conditions the absorption from enteric-coated formulations was greatly reduced by 80-100%. The absorption in the immediate-release formulations was reduced by only 50%. Allergan submits that this taught away from pursuing enteric-coated dosage forms.

[527] Allergan notes that Dr. Parr acknowledged that the skilled person would have been aware of Mitchell 1996, but he was silent about it in his report. Allergan adds that the critique of Mitchell 1996, levelled by Dr. Parr on re-examination by counsel for Apotex, should be given no weight as it appears to be a late day attempt to second guess Mitchell 1996 and support Apotex’s position.

[528] Allergan also notes that Dr. Yates speculated that Mitchell 1996 may have reported on colonic delivery and that the enteric coating thickness, the meal used, and other factors may have been the reason for the low absorption of the enteric-coated tablets in the fed state. Allergan adds that Dr. Yates did not provide this opinion in his report, rather he speculated as a way to discount Mitchell 1996 because it does not align with Apotex's position. Allergan emphasizes that while the details of the study may not be fully known, Mitchell 1996 remains the only study of the absorption of enteric-coated risedronate.

[529] Allergan submits that Dr. Parr and Dr. Yates' reliance on Blümel and WO 907 does not contradict the teaching of Mitchell 1996.

[530] Allergan submits that the evidence shows that in 2005 no one used enteric coatings to solve the food effect problem for any drug.

[531] Allergan further submits that enteric coatings are not the solution for solving the food effect problem posited by Dr. Yates and his "housekeeping wave" theory. Allergan notes that Dr. Yates relied on his theory that enteric-coated oral dosage forms – on their own without EDTA – essentially solved the food effect problem because they remain in the stomach undissolved until the food moves out and the stomach returns to a fasted state, after which they enter a "virtually empty" small intestine. Allergan submits that Dr. Yates's theory is inconsistent with Blümel and Mitchell 1996, which showed that enteric-coated bisphosphonates administered around the same time as food (which is Dr. Yates's assumption about Blümel) exhibited very different absorption profiles.

(4) The Differences between the State of the Art and the Subject Matter of the Claims

[532] Allergan notes that by April 2005 the skilled person was aware of chelating agents like EDTA. However, the art did not teach combining EDTA with risedronate (or any bisphosphonate) in an oral dosage form to overcome the food effect problem, and not with an enteric coating.

[533] No prior art taught the "sweet spot"; the amount of EDTA sufficient to bind the metal ions and minerals in food, but not so much as to significantly alter fasted absorption.

[534] The prior art taught away from EDTA and enteric coatings, and provided no motivation to combine the two to address the food effect problem. Developing the invention of the asserted claims required inventive work. Allergan notes that by April 2005, other researchers had tried, but had not solved the food effect. Other strategies were pursued, including reduced frequency of administration, but this is not a solution.

(5) The Invention was Not Obvious to Try

[535] Even if BR 601 is considered (although Allergan submits that the skilled person would not have had BR 601), and even if it could be read as relating to food effect (which it cannot), bridging the gap between the state of the art and the asserted claims would have required inventive ingenuity.

[536] Allergan submits that inventiveness can lie in the combination of known elements. Allergan submits that while individual components of the '188 Patent were known, their combination to

solve the food effect and result in pharmaceutically effective absorption was not known. The combination was not obvious (*Bridgeview Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre)*, 2010 FCA 188 at para 51 [*Bridgeview*]).

[537] Allergan submits that it was not more or less self-evident that trying the invention would work. Allergan reiterates that the skilled person would not know in advance whether any formulation would provide similar absorption when taken with or without food. All the experts agreed that human clinical studies are required.

[538] Allergan notes that there was motivation to solve the food effect for bisphosphonates, which was a long standing problem, and other pharmaceutical companies were exploring ways to reduce the inconvenience of the dosing requirements. However, none had actually solved the food effect, until Dr. Dansereau and Dr. Burgio did so.

[539] Dr. Yates suggestion that Merck addressed the problem by developing a weekly dosage form to reduce the inconvenience of fasted dosing to one day per week is not a solution to the food effect.

[540] Allergan submits that the inventors' course of conduct further supports the inventiveness of the '188 Patent. Drs. Dansereau and Burgio's work over five years resulted in their invention of the first and only oral bisphosphonate dosage form that directly solved the food effect problem and provided similar absorption fed and fasted.

[541] Allergan submits that at the outset, the cause of the food effect was not known. Several approaches were considered. The first option explored – colonic delivery – was not successful. Their partner, Aventis, withdrew support after the failed dog study. The inventors carried on with the Enterion studies. In the second Enterion study, the inventors again found that colonic absorption was poor, but that absorption in the small intestine, whether fed or fasted was promising. This led the inventors to focus on release in the small intestine and the development and testing of the formulations in the '132 Study. The results led to the confirmation that 100 mg EDTA was the right amount for 35 mg risedronate to provide similar absorption fed or fasted. Allergan notes that due to this promising discovery, Aventis reinvested in the project.

[542] Allergan also disputes Apotex's submission that the inventors identified the use of EDTA early on. Allergan points to the P&G documents provided by Drs. Burgio and Dansereau that included memos and status reports on their project and which noted their query whether EDTA could be used, the safety of EDTA and the need to determine, among other things, possible safe amounts that could be considered. Allergan notes that [redacted] Allergan adds that P&G [redacted] and had to conduct phase III clinical studies and monitor safety.

[543] Allergan adds that Dr. Yates and Dr. Parr's critiques and opinions about what the inventors should have done, comes with hindsight knowing the results.

[544] Allergan also takes issue with Apotex's suggestion – on cross examination of the inventors – that P&G stole the invention from BR 601 or from an alleged patent application by Takeda. Allergan notes that the inventors clearly stated that they had no knowledge of any Takeda patent application and, at that time, their invention was well underway. Moreover, P&G is not a party to this proceeding in order to respond to these allegations. Allergan notes that the alleged Takeda patent application is not before this Court, nor is there any evidence about it. Apotex simply asserts that it overlaps with the '188 Patent. Allergan notes that there is no evidence of any details of a purported Elan solution; the only evidence is that Elan had no data to back up its claims, and it was ultimately rejected by Dr. Dansereau. Allergan adds that even if other pharmaceutical companies were exploring approaches to address the food effect, there is no evidence of what these approaches were or whether they would support the allegation of obviousness.

[545] Allergan submits that the invention – marketed as ACTONEL DR – was a "game changer" and remains the only oral bisphosphonate that directly addresses the food effect and treats osteoporosis.

[546] Allergan also observes that while Apotex and its experts suggest that anyone could have arrived at the invention, there is no evidence of why others did not do so.

C. *The Relevant Jurisprudence on Obviousness*

[547] The Supreme Court of Canada set out the law on obviousness in *Sanofi*. Subsequent jurisprudence has provided additional guidance on its interpretation and application.

[548] In *Janssen 2020* at paras 166-169, the Court set out the relevant principles and reiterated that the *Sanofi* test governs the determination of obviousness:

> [166] The four part obviousness framework was laid out by the Supreme Court of Canada in *Sanofi*, above, at paragraph 67:
>
> i. Identify the notional "person skilled in the art" and the relevant common general knowledge of that person;
>
> ii. Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> iii. 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;
>
> iv. 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?
>
> [167] In areas of invention where advances are often achieved by experimentation, such as the pharmaceutical industry, an "obvious to try" test might be appropriate (*Sanofi* at para 68). In such situations, the following non-exhaustive factors should be taken into account at the fourth step of the obviousness inquiry (*Sanofi* at paras 69-71):
>
> i. 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?
>
> ii. 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?

> iii. Is there a motive provided in the prior art to find the solution the patent addresses?
>
> iv. What was the actual course of conduct which culminated in the making of the invention?
>
> [168] This Court has considered the "actual course of conduct" factor as part of the "extent, nature and amount of effort required to achieve the invention" factor (*Teva Canada*, above, at para 85; *Tensar Technologies, Limited v Enviro-Pro Geosynthetics Ltd*, 2019 FC 277 at para 157). This approach is not inconsistent with the Supreme Court of Canada's guidance in *Sanofi* that obviousness is largely concerned with how a skilled worker would have acted in light of the prior art, but this is no reason to exclude evidence of the history of the invention (*Sanofi* at para 70). The Federal Court of Appeal has referred to the actual course of conduct factor as "an elaboration of the second factor" (Bristol-Myers Squibb Canada Co v Teva Canada Ltd, 2017 FCA 76 at para 44 [*Bristol-Myers Squibb*]).
>
> [169] The Court must be wary of hindsight bias from expert witnesses. It is not fair to a person claiming to have invented a combination invention to break the combination down into its parts and find that, because each part is well known, the combination is therefore obvious (*Bridgeview Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre)*, 2010 FCA 188 at para 51 [*Bridgeview*]). The question to ask is whether the POSITA, in light of the state of the art and their common general knowledge, would have come directly and without difficulty to the solution taught by the patent (*Beloit Canada Ltd v Valmet Oy*, (1986) 8 CPR (3d) 289 (FCA) at 294).

[549] In *Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8 at para 29 [*Pfizer*], the Court of Appeal clarified that "obvious" within the meaning of "obvious to try" means "very plain" and that possibility and speculation is not the test, nor is "worth a try"; rather, the invention must be "more or less self-evident", as noted in *Sanofi*.

[550] Unlike anticipation, the analysis required to determine that obviousness does not focus on a single piece of prior art. For obviousness, the question is whether the skilled person, relying on the cumulative relevant prior art and with the common general knowledge supplemented by information that could be discovered by a reasonably diligent search (at the relevant time), would reach the invention directly and without difficulty or whether inventive ingenuity would be required.

[551] In *Tearlab*, the Court of Appeal explained how prior art is used differently in assessing allegations of anticipation and obviousness, noting at para 73:

> [73] …There is nothing "contradictory" in finding that a prior art reference, when considered alone, does not anticipate, but that it can nonetheless render a claim obvious when combined with another reference.

[552] At para 81, the Court of Appeal explained that with respect to obviousness, "… it is the cumulative effect of the prior art that must be considered to determine whether the skilled but unimaginative technician would have come to the solution taught by the patent directly and without difficulty."

[553] In *Ciba Specialty Chemicals Water Treatments Limited's v SNF Inc*, 2017 FCA 225 at para 62 [*Ciba*], the Court of Appeal noted that, in bridging the differences between the invention and the prior art, "[t]he Skilled Person can have recourse to their common general knowledge supplemented by those pieces of prior art which could be discovered by a reasonably diligent search".

[554] In *Hospira*, the Court of Appeal clarified the distinction between the obvious to try test (step 4) and the factors that inform it, at para 90:

> [90] It should be noted that, whereas being "more or less self-evident to try to obtain the invention" (per *Sanofi* at para. 66) is a requirement for obviousness to try, being "more or less self-evident that what is being tried ought to work" (per *Sanofi* at para. 69) is not a requirement but merely a factor to be considered

[555] In *Hospira*, the Court of Appeal also considered the scope of the prior art that is relevant for the obviousness analysis, noting that at the obvious to try step, the fact that a prior art reference would not turn up in a reasonably diligent search or be part of a mosaic is relevant. The Court of Appeal noted at para 86:

> [86] In light of section 28.3 of the *Patent Act* and the applicable jurisprudence and commentaries, I conclude that it is an error to exclude from consideration prior art that was available to the public at the relevant date simply because it would not have been located in a reasonably diligent search. The likelihood that a prior art reference would not have been located by a PSA may be relevant to consideration of step 4 of the obviousness analysis (whether differences between the state of the art and the inventive concept constitute steps which would have been obvious to the PSA) in that the uninventive PSA might not have thought to combine that prior art reference with other prior art to make the claimed invention. However, excluding prior art simply because it is difficult to find is problematic because it would result in the possibility of a valid patent on an invention that had, but for some non-inventive tweak, already been disclosed to the public. In my view, that is not what Canada's patent regime is intended to permit.

[556] In *Bridgeview* at para 51, the Court of Appeal found that inventiveness can lie in the combination of known parts and the question is whether the combination is obvious. The Court of Appeal noted that "[i]t is not fair to a person claiming to have invented a combination invention to

break the combination down into its parts and find that, because each part is well known, the combination is necessarily obvious…".

[557] The Court of Appeal added at para 52, that "[t]he question the judge should have asked, but did not, is whether the common general knowledge that he identified would have led the skilled but uninventive person to come directly and without difficulty to the particular combination of elements of the invention disclosed in the 334 patent, as construed by the judge."

D. *Overview of the Experts' Evidence*

(1) Dr. Yates

[558] Dr. Yates opined that there were no differences between the state of the art and the subject matter of the asserted claims of the '188 Patent. Dr. Yates again stated that BR 601 disclosed all the essential elements of the '188 and that it addressed the food effect, even though there is no mention of this in BR 601.

[559] Dr. Yates stated that if there were any differences between BR 601 and the subject matter of the asserted claims, the skilled person would have bridged any gap using their common general knowledge and other prior art found in a diligent search. Dr. Yates stated that the skilled person would have readily combined several other prior art references even without knowledge of BR 601.

[560] With respect to the other prior art, Dr. Yates opined that EDTA was well known as was the use of enteric coatings, which on their own would prevent the oral dosage from being absorbed until it was released into the small intestine. In his view, the skilled person would combine the two, guided by the prior art and would obtain a dosage that yielded pharmaceutically effective absorption whether taken fed or fasted.

[561] Dr. Yates did not agree that the prior art taught away from using EDTA. In Dr. Yates' view, nothing in Janner, Lin or Ezra (which are relied on by Allergan as teaching away from the use of EDTA) would have deterred the skilled person from using EDTA to increase bioavailability of a bisphosphonate, particularly considering the use of an enteric coating to cause release only in the small intestine.

[562] Dr. Yates ultimately acknowledged that neither Janner nor Lin studied the food effect, rather the absorption of bisphosphonates in the fasted state.

[563] Dr. Yates stated that Ezra was simply a review article, which recapped the results in Janner and Lin. Dr. Yates stated that the skilled person would not agree with Ezra's conclusion that it was impossible to use EDTA due to its damaging effects on mucosal integrity.

[564] Dr. Yates cited other prior art as teaching that EDTA could be used with bisphosphonates to increase absorption, including with an enteric coating. For example, Dr. Yates relied on Poiger as teaching that EDTA could mediate the effect of calcium on tetracycline.

[565] Although Dr. Yates acknowledged that Mitchell 1996 reported that enteric-coated formulation of risedronate administered 30 minutes before food had a very low absorption, he did not regard Mitchell 1996 as teaching away from enteric coatings. Dr. Yates speculated that the results in Mitchell 1996 were due to other factors, such as the meal consumed. Dr. Yates referred to Blümel, who found that with higher amounts of alendronate, similar efficacy could be obtained with an enteric-coated formulation compared to the immediate release formulation. Dr. Yates agreed that Blümel did not study the food effect or measure absorption or bioavailability, but suggested it did so indirectly. Dr. Yates also referred to WO 907 which reported a two to four times increase in bioavailability of clodronate when enteric-coated. However, Dr. Yates agreed that WO 907 is not about the food effect.

[566] Dr. Yates also noted that the ‘559 Patent disclosed risedronate enteric-coated delayed release formulations, but agreed that this was a liquid formulation.

[567] Dr. Yates acknowledged that he had not been aware of many of the prior art documents he relied on for his opinion prior to being engaged in litigation in the United States or this litigation. For example, he had not been aware of BR 601, Poiger, WO 907 or WO 111 as of April 2005.

[568] Dr. Yates explained that if there were any differences between the state of the art and the subject matter of the claims, one could be combining risedronate and EDTA as an enteric-coated oral dosage form and the other could be providing sufficient EDTA to result in pharmaceutically effective absorption.

[569] Dr. Yates stated it was obvious that if a skilled person had a formulation of enteric-coated risedronate and required some enhancement of bioavailability, this could be achieved by adding EDTA as an excipient. He added that because of the separation from food by using enteric-coated tablets, the expectation would be that this would result in pharmaceutically effective absorption. Dr. Yates explained the "housekeeping wave" as the reason why an enteric-coated tablet will only enter the small intestine after the stomach is empty, and therefore the formulation can be taken fed or fasted.

[570] With respect to enteric coatings as addressing the food effect, Dr. Yates acknowledged that there are several medications that have a food effect that have not been enterically coated and there are several enterically coated medications that still have a food effect.

[571] Dr. Yates also acknowledged that as of April 2005 there was no data disclosing the results of any testing for an oral bisphosphonate with EDTA to determine if this would overcome the food effect. He also acknowledged that accurately predicting the impact of the food effect on bioavailability is impossible without conducting a fed bioavailability study and that determining the appropriate amounts, including of EDTA, requires a study.

[572] Dr. Yates opined that it was obvious to try to obtain the invention as it would have been self-evident to the skilled person that it would work. He noted that there were a finite number of identified predictable solutions known, the work described in the '188 Patent is the sort that is routinely and ordinarily done by the skilled person, and there was a clear motive – at least for the P&G inventors – to find the solution the patent addresses.

(2) Dr. Parr

[573] Dr. Parr first provided "blinded" evidence – i.e., without reviewing the prior art or the '188 Patent – based on his review of an excerpt of the 2004 edition of Canadian Pharmaceutics and Speciality.

[574] Dr. Parr stated that to address the reduced absorption of bisphosphonates in the presence of divalent ions from food, the pharmaceutical formulator would consider ways to remove the dosage form from the divalent ions and food and to block the divalent ions from interacting with the bisphosphonates. He added that the pharmaceutical formulator would be aware that enteric coatings can be used to protect dosage forms from the low pH in the stomach and from the high concentrations of food components and that chelators can reduce or block the interaction between ions, such as calcium, and bisphosphonates by sequestering the ions.

[575] Dr. Parr then reviewed a selection of the prior art and confirmed his opinion. Dr. Parr subsequently reviewed additional prior art and the '188 Patent. In Dr. Parr's opinion, the '188 is obvious based on both BR 601 and the prior art. Dr. Parr added that other prior art included disclosure of this combination (e.g., WO 111 and the '932 Patent).

[576] Dr. Parr did not agree that BR 601 did not address the food effect, stating that it was not clear. Dr. Parr stated that formulations of BR 601 would result in pharmaceutically effective absorption whether taken fed or fasted. He extrapolated information from the immediate release formulations and other information to calculate the absorption. On cross examination he was

directed to the fact that his calculations were based on the assumption that the immediate release formulation was taken 30 minutes before food rather than with food.

[577] Dr. Parr agreed that predictions about bioavailability could not be made and testing was required.

[578] Dr. Parr explained that formulations of EDTA and bisphosphonates had been described in the prior art and that EDTA was known to be safe at particular levels, including those exceeding the amounts set out in the ‘188. Dr. Parr pointed to Poiger, and the ‘932 Patent. Dr. Parr opined that the skilled person would not be deterred by the conclusions in Janner, Lin and Ezra.

[579] Dr. Parr disagreed with Dr. Sinko’s opinion regarding possible adverse impacts of EDTA on the intestine.

[580] Dr. Parr agreed with Dr. Yates’ overall opinion that there is no difference between the state of the art in April 2005 and the subject matter of the ‘188. He opined that the only possible difference would be that there was no specific example in the prior art of making an enteric-coated tablet containing risedronate and EDTA. Dr. Parr added that it would not have required inventive ingenuity to bridge this difference relying on the teaching of the prior art and the common general knowledge.

[581] Dr. Parr commented on the factors that inform the “obvious to try” test, noting among others, that it was self-evident to try to obtain the invention and self-evident that it would work.

Dr. Parr stated that the skilled person would have an expectation that an enteric-coated formulation of risedronate and EDTA taken in the fed state would result in absorption of the risedronate within about 50% of fasted absorption. Dr. Parr acknowledged that human clinical testing would be required to confirm this, but in his view, such testing was within the skills of the skilled person and routine.

[582] With respect to the work of the inventors, Dr. Parr stated that the skilled person would not have pursued delivery to the colon. Otherwise the inventors followed the steps that the skilled person would have taken and identified the approach of adding a chelator and enteric coating at the outset of the project. The inventors' choice of EDTA was based on the knowledge that it was a strong chelator of calcium [redacted]

(3) Dr. Dillberger

[583] Dr. Dillberger's evidence focussed on the safety of EDTA. He stated that there was extensive use of EDTA in food and pharmaceuticals as of April 15, 2005 and pointed to several reports and publications in support of his view. For example, JECFA 1974 determined the acceptable daily intake of EDTA for human was up to 2.5 mg/kg (or 150 mg of EDTA per day for a 60 kg adult). Dr. Dillberger noted that JECFA applied a safety factor of 100 to extrapolate the acceptable daily intake from animal studies to humans.

[584] Dr. Dillberger added that in 1993, the U.S. FDA confirmed that the acceptable daily intake of EDTA is 2.5 mg/kg.

[585] Dr. Dillberger disagreed with Allergan's expert, Dr. Sinko, that EDTA alone and in combination with a bisphosphonate has a toxic effect on the intestinal membrane that would be irreversible. He explained that enhancing small intestinal permeability is not harmful and, even if the small intestinal epithelium is damaged, it can regenerate. He maintained his opinion that EDTA at a reasonable level was safe enough to include in a drug product.

[586] Dr. Dillberger was of the view that neither Janner, Lin nor Ezra would discourage the use of EDTA. However, Dr. Dillberger agreed that the objective of the Janner and Lin studies was not on the potential damaging effects that EDTA may have on the small intestine.

[587] Dr. Dillberger disagreed that Janner and Lin did not present safety data on EDTA. In his view the fact that Janner and Lin could generate data on bisphosphonate absorption showed that the rats survived the experiment and tolerated EDTA for at least 24 hours (before they were euthanized).

[588] Dr. Dillberger disagreed with Dr. Sinko that combining EDTA and risedronate would be especially concerning if an enteric-coated dosage form were added. Dr. Dillberger stated that a skilled person would know that an enteric-coated dosage form containing bisphosphonate and EDTA would be safe and would not damage the small intestine. He referred to Yonezawa, which reported that EDTA did not damage the intestinal epithelium of the rabbits studied even when it was directly and continuously exposed for an hour to a high concentration of EDTA. Dr. Dillberger disagreed with counsel's suggestion that Yonezawa, which reported hemorrhaging and swelling

in the small intestine of the rabbits, actually demonstrated EDTA's damaging effects to the small intestine.

(4) Dr. Cremers

[589] Dr. Cremers first provided an overview of all the prior art cited and its' teaching. Dr. Cremers' opinion is that there were differences between the state of the art and the subject matter of the claims that would have required inventive ingenuity to bridge. The prior art and the common general knowledge did not guide the skilled person to combine the necessary amounts of risedronate and EDTA in an enteric coating with an immediate release in order to address the food effect.

[590] Dr. Cremers stated that as of April 15, 2005, the skilled person would have known that EDTA had been tested as an absorption enhancer with bisphosphonate formulations in animal studies, and the results taught away from the use of EDTA in bisphosphonate formulations for clinical use. Dr. Cremers also elaborated on the results of Janner, Lin and Ezra, among others. As previously noted, Dr. Cremers stated that BR 601 did not address the food effect at all, rather it sought to increase the absorption of a bisphosphonate in the fasted state.

[591] Dr. Cremers explained that in April 2005, chelating agents such as EDTA were known, but they were used to increase intestinal permeability, which is the opposite of what the '188 Patent teaches. Dr. Cremers pointed to the art that advised against using EDTA in bisphosphonate formulations (Janner, Lin, Ezra). Dr. Cremers stated that the skilled person would be hesitant to

combine a chelating agent in a delayed-release bisphosphonate formulation because of the potential for adverse effects from too much intestinal permeability.

[592] Dr. Cremers noted that enteric coatings were also known, but primarily for the purpose of minimizing gastroesophageal side effects. Moreover, an enteric-coated risedronate formulation had been found to provide lower absorption than the existing non-enteric-coated formulation (Mitchell 1996).

[593] Dr. Cremers disagreed with Dr. Yates on the teaching of some of the prior art, including the art regarding the safety of EDTA used in a delayed release oral dosage of a bisphosphonate and various patent applications.

[594] Dr. Cremers addressed the factors related to the obvious to try step of the obviousness analysis. Among other factors, he reviewed the work of the P&G inventors and noted that it was not routine and they did not arrive quickly or easily at the invention.

(5) Dr. Sinko

[595] As noted in Dr. Sinko's opinion on anticipation, Dr. Sinko acknowledged that there was overlap between the formulations of BR 601 and the claims of the '188 Patent, but did not agree that BR 601 anticipated the '188. Dr. Sinko noted that many choices would need to be made and that testing would be required to determine whether pharmaceutically effective absorption was achieved. He opined that BR 601 did not render the '188 obvious on its own or together with other prior art.

[596] In Dr. Sinko's view, there were differences between the state of the art and the claims of the '188 that would have required inventive ingenuity to bridge. Dr. Sinko opined that the skilled person would be dissuaded from combining EDTA and risedronate in an oral dosage form because they were both capable of harming the intestinal membrane. He noted that the prior art raised concerns about using EDTA in combination with bisphosphonates.

[597] Dr. Sinko also noted that the prior art also taught that enteric-coated risedronate tablets provided decreased absorption compared to non-coated tablets when both were given 30 minutes before food. In Dr. Sinko's view, this would teach a skilled person that an enteric coating would be expected to reduce absorption if it was given with food. It would not have been obvious that a combination of risedronate and EDTA in an enteric-coated dosage form would not only overcome the food effect, but provide similar risedronate absorption whether the dosage form was taken with or without food.

[598] In Dr. Sinko's view, the inventors' work in arriving at the '188 Patent was not routine. The documents reveal that it took many years and many experiments to arrive at the invention claimed in the '188 Patent, and the inventors persisted in their pursuit of the claimed invention despite several failures.

(6) Dr. Burgio

[599] Dr. Burgio described his work with Dr. Dansereau on what was first called the "Anytime Actonel" project, so named because the goal was to develop a bisphosphonate product without the complicated dosing instructions requiring fasting. Dr. Burgio's role was to design and oversee the

clinical studies to test the researchers' lead hypothesis that delivery of risedronate far away from the stomach to the ascending colon with a chelating agent might provide for similar absorption when taken in the fed state or the fasted state. Dr. Burgio noted that other team members pursued other hypothesis and approaches which did not work out.

[600] Dr. Burgio explained that he and Dr. Dansereau overcame several obstacles. Dr. Burgio described the lack of success with the dog study to test the delivery to the colon. Dr. Burgio noted that despite this failure, they persevered with a human trial using Enterion coated capsules to permit targeted delivery to the intestinal tract. Dr. Burgio explained why they chose to use particular amounts of risedronate and EDTA. [redacted]

[601] Dr. Burgio described the first Enterion study and its results, which then led to a second Enterion study with 79 human subjects. Dr. Burgio noted that the second Enterion study unexpectedly showed that absorption in the small intestine of risedronate with EDTA, both with and without food, was comparable to the absorption of the immediate release risedronate in the fasted state (i.e., the product that existed pre-2005). This result led to a new strategy to target release in the small intestine.

[602] Dr. Burgio noted that he and Dr. Dansereau were concerned about the need to avoid significantly increasing permeability of the intestinal membrane.

[603] Dr. Burgio explained that the goal was to chelate the cations in food so that the risedronate medication could be taken with food, but not have so much EDTA and risedronate that it would significantly increase absorption in the fasted state when there are no cations from food present to tie up the chelating agents. Dr. Burgio noted that although the second Enterion study showed that this balance was possible, it was necessary to test whether this could be achieved with a tablet. Dr. Burgio described the bioavailability study (referred to as the '132 Study) to test the prototype formulations, to determine which formulation would provide optimal results in delivering similar absorption in the fed and fasted states.

[604] Dr. Burgio explained that he did not recall how he became aware of BR 601, but noted that this occurred after he and Dr. Dansereau had made their invention. He opined that BR 601 was likely provided by someone in P&G's patent prosecution team.

(7) Dr. Dansereau

[605] Dr. Dansereau described the characterization of his project with Dr. Burgio in relation to the 2000 Olympics and P&G's identification of gold, silver and bronze medal approaches to solve the food effect. The gold medal approach would be a solution to provide "any time" and "fool proof" dosing – i.e., to yield similar risedronate absorption whether taken with food or without food.

[606] [redacted] He noted, as did

Dr. Burgio, that the original hypothesis was to try to separate the risedronate as far from food as possible before releasing it, to the region of the ascending colon where calcium levels would likely be much lower, and then also have a chelating agent co-released with the risedronate to preferentially bind to calcium ions that would be present. [redacted]

[607] Dr. Dansereau described the failed dog study followed by the two Enterion studies in the same way as Dr. Burgio. [redacted]

[608] Dr. Dansereau explained the results of the Enterion studies in the same manner as Dr. Burgio. Dr. Dansereau noted that [redacted]

[609] Dr. Dansereau described the pilot bioavailability study (the '132 Study) noting that the results showed that 100 mg EDTA in an enteric-coated 35 mg risedronate formulation delivered to the small intestine worked to overcome the food effect without significantly increasing absorption in the fasted state. [redacted]

E. *The '188 Patent is Not Obvious – Overview*

[610] As elaborated upon below, I find that the '188 Patent was not obvious.

[611] Overall, I find the evidence of Dr. Cremers and Dr. Sinko more persuasive on the issue of obviousness. Dr. Cremers clearly holds Dr. Yates in high regard, and agreed with Dr. Yates and Dr. Parr on several basic principles, yet he provided contrary views about the teaching of the art relied on by Dr. Yates and Dr. Parr and he explained his reasons in a clear, detailed and objective manner which aligned with the statements made in the art.

[612] Dr. Yates viewed the art differently leaving many questions why he would not accept certain propositions yet accept others. In addition, much of the art that Dr. Yates relied on for his opinion was not known to him at the relevant time, rather it was provided to him for the purpose of litigation. Dr. Yates' interpretation of the prior art – including art that did not address the food effect, the safety of EDTA or the oral administration of bisphosphonates – was in some instances

based on presumptions and in some instances appeared to be contrived to support his view that the ‘188 was obvious.

[613] Dr. Parr’s blinded evidence does not warrant it being given more weight. Dr. Parr’s evidence was scrutinized in the same manner as the evidence of others (*Janssen 2019* at paras 58-59).

[614] The state of the art in 2005 did not teach the combination of the essential elements of the ‘188 Patent in the necessary amounts to achieve pharmaceutically effective absorption in the fed and fasted states.

[615] As a starting point, the skilled person would not look to BR 601 as the guiding light to solve the food effect for bisphosphonates for several reasons. BR 601 does not even mention or allude to the food effect or pharmaceutically effective absorption (as noted above with respect to anticipation), rather it focusses on increasing fasted absorption, it does not provide the results of any testing and it includes only one example of a large batch of alendronate.

[616] Although BR 601 disclosed the “generic” essential elements of the ‘188 Patent, it did not provide any guidance to the skilled person about what to choose and in what amounts. As acknowledged by Allergan, some formulations of BR 601 would overlap with the ‘188 Patent, but arriving at these formulations would require a great deal of trial and error and experimentation. BR 601 did not provide any guidance to the skilled person to lead them to the necessary combinations.

[617] If the skilled person were given BR 601, they would likely consider that this was only an application that never resulted in a patent. The skilled person would also be unaware of the inventor and pharmaceutical company, given that none of the experts had ever heard of either. The skilled person would scrutinize the "teaching" of BR 601 with this in mind. As noted, the focus on increasing fasted absorption, the lack of testing and the single example, would not teach the skilled person that formulations of BR 601 solved the food effect and achieved pharmaceutically effective absorption. Even if the skilled person considered BR 601 together with the other prior art – as part of the mosaic – the skilled person would not be led to the invention of the '188 Patent. Much more work would be necessary to fill the gaps.

[618] The differences between the state of the art and the subject matter of the claims required inventive ingenuity to bridge.

[619] While Apotex argues that any small differences would be easily bridged by the skilled person, the evidence supports the contrary view; more than simple routine work was necessary. It was not obvious to try to obtain the invention for several reasons. First, it was not self-evident that it would work. All the experts noted, among other things, that human clinical testing would be required. Second, there was motivation to solve the food effect but the solutions were not predictable and other approaches had only mitigated the inconvenience of fasted dosing but had not solved the food effect. Third, the work involved was more than routine testing for an ordinary skilled person. Dr. Yates opined that it was a simple matter for the skilled person to conduct clinical testing. However, Dr. Cremers described a much more involved process that would require more than routine tests which went beyond the work of the ordinary skilled person. Fourth, the inventors

described their work over five years as extensive and challenging. Apotex's critique of the inventors' approach and missteps is considerably easier in hindsight, but the documentary evidence corroborates and chronicles the inventors' account that several approaches were considered, tested, re-thought, re-tested and ultimately they found the solution, after some missteps.

[620] My conclusions are based on the application of the four part *Sanofi* test and the other governing jurisprudence.

F. *The Skilled Person*

[621] The skilled person is described above at paragraphs 162-166. As noted, it is the ordinary skilled person that is the benchmark.

[622] To the extent that Dr. Yates may have elevated the ability of the skilled person based on the team he led at Merck, for example, with respect to the skilled person's ability to conduct clinical studies as a routine matter, I have considered the ability of the ordinary skilled person.

G. *The Common General Knowledge*

[623] The common general knowledge is not in great dispute and is set out above at paragraph 273.

[624] In a nutshell, bisphosphonates were known as was their low bioavailability, the food effect was known, the inconvenience of fasted administration of bisphosphonates was known, the use of

enteric coatings for purposes such as reducing gastric irritation and to prevent dissolution in the stomach was known, EDTA was known to be a strong chelating agent, and it was known how to develop dosage forms, including those with enteric coatings.

H. *The Subject Matter of the Claims*

[625] The subject matter of the asserted claim sets is set out at paragraphs 229-231.

[626] In brief, the first claim set focuses on an oral dosage for use with or without food or beverage intake of 35 mg risedronate and 100 mg EDTA in an enteric coating that provides targeted and immediate release in the small intestine. The oral dosage provides pharmaceutically effective absorption whether taken with or without food.

[627] In addition, there are use claims, directed to the weekly use of the claimed oral dosage forms (claim 77) for the treatment or prevention of osteoporosis (claim 72) and kit claims which provide some means of facilitating patient compliance (claim 79), including packaging.

I. *The State of the Art*

[628] As noted in *Tearlab*, for the obviousness analysis, it is the cumulative effect of the prior art that must be considered. The question is whether the skilled person, being unimaginative, would have arrived at the invention directly and without difficulty based on the cumulative prior art, information that could be discovered by a reasonably diligent search, and the common general knowledge.

(1) BR 601 is Part of the Mosaic of Prior Art

[629] As noted above, I do not find that BR 601 anticipated the claims of the ‘188 Patent. However, a prior art reference that does not anticipate may be considered as part of the mosaic in the obvious analysis (*Tearlab*).

[630] A preliminary issue is whether BR 601 should be considered as part of the cumulative art or “mosaic of prior art”.

[631] Dr. Bonenfant explained how he found BR 601 using specialized databases available to him, but he acknowledged that the search terms were provided to him. Moreover, Dr. Bonenfant would not meet the definition of “skilled person”, rather he has special expertise in both inputting patent information into specialised databases and retrieving such information.

[632] Dr. Schmidt and Ms. Mittelbach both described the process to find a patent in Brazil. Both indicated that in-person attendance at the Brazilian patent office was required. Without knowing exactly what you are looking for, it would be difficult – even for the person who attends in person – to find BR 601. Dr. Schmidt acknowledged that he was provided with the application number by counsel for Apotex. He explained that he found BR 601 in the database by inputting the application number, which led him to Official Gazette No. 1705. He also acknowledged that he had never searched for BR 601 prior to being engaged by Apotex to do so in 2020. Dr. Schmidt and Ms. Mittelbach both explained that once the Official Gazette publication is available, which includes on average more than 300 patent applications each week, a person would need to peruse

hundreds of pages to find the abstract, which might then lead them to request a copy of a patent application.

[633] There is no evidence that any of the experts looked for or found BR 601 or were even aware of it until it was provided to them. Dr. Yates acknowledged that he was not aware of BR 601 until it was provided to him for the purpose of similar litigation in the U.S. Dr. Yates added that he knew nothing about the inventor or Libbs Pharmaceutical Company. Dr. Parr also noted that he was previously not aware of BR 601. Dr. Cremers indicated that he was unaware of BR 601 until this litigation.

[634] In my view, BR 601 would not have turned up in a "reasonably diligent search". Very special search skills and search terms with some prior knowledge of what was being searched for would have been required. Regardless, BR 601 will be considered part of the mosaic of prior art.

[635] In accordance with *Hospira* at para 86, it would be an error for the Court to exclude BR 601 from the mosaic of prior art because it would not be found by the skilled person in a reasonably diligent search.

[636] As guided by *Hospira*, the likelihood that BR 601 would not turn up (and, based on the evidence, it would not turn up) is relevant to the obvious to try test; i.e., would the skilled person have thought to combine BR 601 with the other prior art to bridge the differences between the state of the art and the invention?

[637] This is a tricky distinction when applied to the facts. If BR 601 is part of the prior art, then the differences between the state of the art and the invention would need to account for whatever can be distilled from BR 601 as part of the "state of the art". However, if the skilled person would not have found BR 601, how can the skilled person consider it in the context of combining it with other prior art at the obvious to try stage of the analysis of obviousness? This is only possible in circumstances where the unknown prior art is handed to the skilled person. To avoid this dilemma and running afoul of *Hospira*, I have considered BR 601 as if it were prior art, but as noted, the "teaching" of BR 601 requires careful scrutiny.

(2) The Prior Art

[638] The prior art is described at Part VII above at paragraphs 232-263 based on the statements in that art, and not based on how the experts interpreted it.

[639] Apotex relies on the teaching of the prior art to support its view that the essential elements of the claims of the '188 Patent were disclosed in the prior art, in particular BR 601, and that the art did not teach away from the use of EDTA or enteric coatings for bisphosphonates. Apotex also submits that the art as of 2005 must be considered rather than focussing on out of date references, such as Mitchell 1996.

[640] Allergan submits that nothing in the prior art taught the use of risedronate and EDTA in an enteric coating with an immediate release resulting in pharmaceutically effective absorption. Rather, the prior art taught away from the use of enteric coatings and EDTA, that EDTA was not

safe for use in humans at high levels, and more generally, that some of the prior art cannot be interpreted in the manner described by the Apotex experts.

[641] The art relied on and the experts' opinions on the teaching of the art are described below.

(a) *BR 601*

[642] Dr. Yates and Dr. Parr both stated that BR 601 disclosed all the essential elements of the '188 Patent and that the small differences – the combination of risedronate and EDTA as an enteric-coated dosage form or the provision of sufficient EDTA to provide pharmaceutically effective absorption, would have been easily bridged by the skilled person.

[643] Dr. Yates agreed that the description in BR 601 of the low bioavailability of bisphosphonates referred to amounts that reflect fasted absorption. Although Dr. Yates agreed that at the time of BR 601 all bisphosphonates required fasting – no food for 30 minutes after the dosage – he focussed on the fact that BR 601 is silent about a requirement for fasting. Dr. Yates maintained that the skilled person would know that BR 601 was also about the food effect, even though it is not discussed.

[644] Dr. Yates also agreed that BR 601 does not demonstrate that any dosage forms contained in it would work to improve the absorption of any bisphosphonate. He acknowledged that BR 601 contains no data, no formulation was tested and the only example was of alendronate.

[645] Dr. Yates also agreed that BR 601 did not teach a specific bisphosphonate, or a specific amount of the chelating agent or a preferred chelating agent. Dr. Yates suggested that EDTA is preferred because it is mentioned, but did not agree that alendronate is preferred even though it is also specifically mentioned and is the only bisphosphonate exemplified.

[646] With respect to the range of EDTA disclosed in BR 601 (3 to 175 mg), Dr. Yates appeared to agree that testing would be needed to determine the "sweet spot" – i.e., the right amount of EDTA depending on the amount of bisphosphonate.

[647] Dr. Yates also agreed that Claim 28 of BR 601 provides for the release of the drug from the enteric-coated dosage form as an immediate release, delayed or prolonged release. Dr. Yates acknowledged that only the immediate release would address the food effect and delayed or prolonged release would not.

[648] Despite Dr. Yates' strongly held view that BR 601 disclosed everything needed to arrive at the invention of the '188 Patent, he acknowledged that testing would be necessary to determine the right amount of EDTA, that the immediate release dosage form was necessary and that there was no other known use of EDTA with a bisphosphonate. He stubbornly maintained his view that the BR 601 was about the food effect although there is nothing in BR 601 to suggest it is and the problem it addressed differs. This is in contrast to the detailed description in the '188 Patent regarding the food effect and the need to address it.

[649] Dr. Parr also stated that all the essential elements of the claims of the ‘188 Patent are disclosed in BR 601.

[650] On cross examination, Dr. Parr agreed that BR 601 noted the problem of the low fasted absorption of bisphosphonates. With respect to his opinion that BR 601 addressed the food effect, Dr. Parr acknowledged that BR 601 does not define “contents of the stomach” and that the fasted stomach contains calcium and other divalent ions that would interfere with absorption of bisphosphonates.

[651] Dr. Parr also agreed that BR 601’s reference to the “current treatment” is a reference to the strict dosing requirements, including that the bisphosphonate be taken on an empty stomach at least 30 minutes before the first food of the day and that BR 601 does not teach that the strict dosing requirements of the treatment at that time (fasted) did not have to be followed. However, Dr. Parr would only go so far as saying that it was not clear whether BR 601 refers to the fasted or fed state.

[652] Dr. Parr was asked about his opinion that BR 601 provided for pharmaceutically effective absorption, which he based on the information about the immediate release ACTONEL. When challenged about his assumptions, Dr. Parr did not agree that if the immediate release ACTONEL were taken with food – rather than 30 minutes before the first food of the day – the absorption would be decreased further than 50%. Dr. Parr noted he had not seen such data and could not comment. He noted that the data indicates only that if taken 30 minutes before food there is a 50% reduction in absorption.

[653] Dr. Parr was asked, whether as a formulator and knowing the formulation, he could predict absorption whether fed or fasted. He responded that it would depend on the data available; if there was sufficient data, the skilled person could predict generally whether it would go up or down.

[654] Dr. Cremers did not agree that BR 601 disclosed the invention. Dr. Cremers stated that BR 601 provided only very broad disclosure. Dr. Cremers reiterated that BR 601 does not address the food effect, nor does it teach the use of, or what amounts of EDTA to bind the metal ions and minerals in food while at the same time not significantly altering absorption in the fasted state by enhancing intestinal permeability. Dr. Cremers stated that BR 601 does not teach, or motivate the skilled person to pursue a solution to the food effect problem.

[655] Dr. Cremers noted that BR 601 includes only one example, but no testing. He stated that there is no way you can predict that this formulation could be taken with food and that it would result in pharmaceutically effective absorption.

[656] Dr. Cremers was asked if the skilled person applied the example of BR 601 and used 35 mg risedronate and 100 mg of EDTA with an enteric coating and this was taken with food, would it exhibit pharmaceutically effective absorption. Dr. Cremers responded that he did not know because BR 601 focused on increasing the bioavailability of the drug in the fasted state. He acknowledged that if the formulation were given with food, then there could be pharmaceutically effective absorption but additional testing would be needed. He added that he would need to see bioequivalence studies and dissolution profiles.

[657] Dr. Sinko acknowledged that there was overlap with the formulations in BR 601 and the claims of the ‘188 but did not agree that BR 601 made the ‘188 obvious.

[658] As I found above with respect to anticipation, BR 601 was not about the food effect. Again, the extent to which a skilled person would look to BR 601 at all is questionable. Moreover, BR 601 presents many choices without providing any direction about the necessary choices and does not provide the results of any testing. While some of the formulations of BR 601 would provide pharmaceutically effective absorption, this result would require the skilled person to make all the exact choices in the exact amounts as in the ‘188 Patent. All the experts agreed that no predictions could be made whether any of the formulations of BR 601 would provide pharmaceutically effective absorption.

[659] While some of the formulations of BR 601 would provide pharmaceutically effective absorption, this result would require the skilled person to make all the exact choices in the exact amounts as in the ‘188 Patent.

(b) *The Use of EDTA*

[660] Dr. Yates cited Poiger, which studied the use of EDTA in humans with tetracycline, as “proving” that EDTA could overcome the calcium-mediated inhibition of absorption of a drug.

[661] Dr. Yates acknowledged that he was not aware of Poiger in 2005 or before the U.S. litigation. He acknowledged that he did not do any independent literature search for the state of the art as of April 2005.

[662] Dr. Yates acknowledged that Poiger's use of 2.3 grams of EDTA to overcome the calcium in 200 mL of milk, was 23 times higher than the amounts disclosed in the '188. Dr. Yates agreed that the effect of 2.3 grams of EDTA on the absorption of tetracycline administered in the fasted state would not be known. Dr. Yates also agreed that Poiger indicated that the large amount of EDTA used would not be practical. Dr. Yates acknowledged Poiger's conclusion that the combined administration of tetracycline and EDTA "might be worthy for further consideration".

[663] With respect to animal studies on the effects of EDTA on bisphosphonates, Dr. Yates did not agree that the conclusions of Janner, Lin and Ezra would dissuade the skilled person from the use of EDTA because, in his view, the addition of an enteric coating would cause release only in the small intestine.

[664] Dr. Yates agreed that Janner did not directly address the food effect, rather reported that oral bisphosphonates even when fasted are poorly absorbed. He also agreed that Janner was studying the preferential binding of EDTA and whether it would increase fasted absorption. However, on cross examination, Dr. Yates suggested that it was not clear that Janner studied only fasted rats.

[665] Dr. Yates agreed that Janner does not mention enteric coatings. He also agreed that the food effect was known at that time and the Poiger study had been published over 10 years earlier, yet Janner did not study whether EDTA would solve the food effect.

[666] Dr. Yates noted that there were many differences between rats and humans. Experiments would be needed to determine the effect on bioavailability in humans. Dr. Yates added that, if the formulation were enteric-coated, studies would be needed to confirm the amount of EDTA needed to give the desired effect.

[667] Dr. Yates also relied on WO 111 in support of his opinion that the '188 Patent is obvious noting that WO 111 combined bisphosphonates and absorption enhancers. However, Dr. Yates agreed that WO 111 leaves the skilled person with a "research project" to determine which enhancer-bisphosphonate combination would provide the results presented. Dr. Yates agreed that WO 111 states that the preferred bisphosphonate is alendronate and the patent sets out a huge range of absorption enhancing agents that could be used with it. He acknowledged that all the examples in WO 111 are of alendronate, several are oral solutions or liquid solutions – not tablets – and none of the examples used EDTA as the absorption enhancer. Dr. Yates also agreed that testing would be required to determine the exact amount and effect of any additive, including EDTA.

[668] Dr. Yates agreed that WO 111 contemplates several routes of administration, not simply oral administration, and including colonic absorption.

[669] More generally, Dr. Yates agreed that as of April 2005, there was no data disclosing the results of any testing for an oral bisphosphonate and EDTA to determine if this would overcome the food effect. Dr. Yates pointed to the BR 601 but agreed that there was no data in that application.

[670] With respect to other medicines that contain EDTA, Dr. Yates could not recall the amount of EDTA used, but stated it was lower than 100 mg. He agreed that the relevant documents put to him showed the highest amount of EDTA in previous formulations was 4 mg.

[671] Dr. Parr noted that the skilled person would have known that the easiest way to prevent divalent ions in food from interacting with risedronate would be to sequester the ions so that they are not available to interact with the risedronate and would have looked to chelating agents, including EDTA, to achieve this.

[672] Dr. Parr pointed to Poiger and stated that the skilled person would have understood that the issues with tetracycline were the same as the issues with risedronate. Dr. Parr stated that the skilled person would know that EDTA is safe. The skilled person would also be aware that formulations of EDTA and bisphosphonates had been described in BR 601, WO 111 and the ‘932 Patent. Dr. Parr stated that the ‘932 Patent for an oral liquid dosage of alendronate showed that EDTA could be used to help maintain bioavailability of the bisphosphonate.

[673] Dr. Parr also stated that the skilled person would not have been concerned about increasing intestinal permeability using up to 175 mg of EDTA, as in the claims of the ‘188 Patent, because much larger doses would be required to do so.

[674] Dr. Parr opined that the skilled person would not have been deterred in using EDTA by Janner, Lin or Ezra because EDTA was not being used as an absorption enhancer, but to chelate metal ions.

[675] On cross examination, Dr. Parr agreed that neither Janner nor Lin investigated whether EDTA had any damaging effects on mucosal integrity.

[676] As noted above, Dr. Dillberger's overall opinion was that there was "extensive use" of EDTA in food and pharmaceuticals as of April 15, 2005 and that it was completely safe. He disagreed that Janner, Lin and Ezra taught away from the use of EDTA.

[677] Dr. Cremers noted that the skilled person would have known that EDTA had been tested as an absorption enhancer with bisphosphonate formulations in animal studies, and the results taught away from the use of EDTA in bisphosphonate formulations for clinical use.

[678] Dr. Cremers stated that the skilled person would understand that neither Janner nor Lin provides any teaching about a dosage form that can provide similar absorption when taken with, or without food. The skilled person would understand that both Janner and Lin signal against the clinical use of EDTA with bisphosphonates in humans.

[679] Dr. Cremers noted that Lin investigated the absorption of alendronate from the GI tract also using fasted rats. The results showed that EDTA enhanced the absorption of alendronate, but cautioned against its use.

[680] Dr. Cremers emphasized that Lin did not assess the impact of EDTA on alendronate absorption with food or delivered directly into the small intestine. Contrary to Dr. Yates' opinion,

he stated that the skilled person would not apply the results of Lin to the context of an enteric-coated formulation delivering EDTA and a bisphosphonate directly into the small intestine.

[681] Dr. Cremers disagreed with Dr. Parr that either the '932 Patent, BR 601 or WO 111 disclosed the use of EDTA in bisphosphonate formulations to overcome the food effect, or to achieve similar absorption with or without food.

[682] Dr. Cremers described the '932 Patent as about liquid formulations of alendronate to increase compliance in patients who had difficulty swallowing and is not related to absorption of solid oral bisphosphonate dosage forms. While the patent notes EDTA as an example of a complexing agent, the skilled person would understand that the formulation tables included in the '932 Patent refer to the use of citric acid and sodium citrate.

[683] Dr. Cremers noted that WO 111 broadly contemplates virtually any bisphosphonate, in any amount, combined with essentially any compound (or compounds) that can potentially enhance absorption, also in any amount. Dr. Cremers noted that WO 111 mentions EDTA as a potential additive, but the only formulations described in WO 111 are in the examples and none are formulations that contain EDTA (or any chelating agent), and none have an enteric coating.

[684] Dr. Cremers also noted that only one paragraph in WO 111 states that "[i]n a preferred form, the pharmaceutical formulation according to the invention is adapted for oral administration and may be given during fasted or fed conditions."

[685] In Dr. Cremers' view, the skilled person would find no guidance in WO 111 about which bisphosphonates should be combined with which of the many possible "additives," and in what amounts, in order to adapt the invention for oral administration. WO 111 does not teach how any such adapted formulation performs in terms of bisphosphonate absorption in fasted or fed conditions, and the skilled person would not know whether any such adapted formulation would achieve "pharmaceutically effective absorption". WO 111 does not disclose a dosage form that provides similar absorption, when taken with or without food, or teach that this is even possible. Also, WO 111 does not teach the skilled person to make an oral formulation that provides release of a bisphosphonate and additive together in the small intestine, bypassing the stomach, as in the case of an enteric-coated dosage form, or what absorption would be with or without food.

[686] Dr. Cremers did not agree with Dr. Yates and Dr. Parr that Poiger taught the use of EDTA to address the food effect. Dr. Cremers noted that tetracycline is not a bisphosphonate and that its results cannot be transferred to any formulation that releases EDTA directly into the small intestine. Poiger does not suggest that the formulation could be administered in the fasted state. Dr. Cremers did not agree that Poiger established that 2.3 grams of EDTA is safe, although this amount was used with milk. Dr. Cremers noted that taking 2.3 grams of EDTA in a fasted state would significantly affect intestinal permeability and be very dangerous.

[687] Dr. Cremers described Poiger as a small proof of concept study of five human volunteers that investigated the co-administration of tetracycline with EDTA, with milk, and with both, where it would be mixed in the stomach. Dr. Cremers noted that it did not use enteric coatings that bypass

the stomach in terms of release, which makes the technique studied fundamentally different from the formulations of the ‘188 Patent.

[688] Dr. Cremers disagreed with Dr. Yates’ opinion on the teaching of Poiger; i.e., that parallels could be drawn between tetracycline and bisphosphonates. Dr. Cremers explained that while bisphosphonates and tetracycline both suffer from a food effect, tetracycline has high bioavailability unlike bisphosphonates. Dr. Cremers stated that the skilled person would not assume that the results would apply to bisphosphonates or to any other class of drug or apply when both are being released in the intestine, as is the case with an enteric-coated dosage form. The skilled person would also note that Poiger concluded that “the combined administration of [tetracycline] and EDTA might be worthy for further consideration.” Dr. Cremers added that he was not aware of any formulation containing tetracycline and EDTA that had been developed and marketed as of April 15, 2005, or ever.

[689] Dr. Cremers took issue with Dr. Yates’ opinion that EDTA was known to be “extremely safe in humans”. Dr. Cremers noted that none of the articles relied on by Dr. Yates to support his view about the safety of EDTA in humans are related to the use of EDTA together with any bisphosphonate or with delivery of EDTA for release in the small intestine as in the case of enteric-coated formulations.

[690] Dr. Cremers also disagreed with Dr. Parr’s opinion that there were no safety concerns regarding the use of EDTA. Dr. Cremers reiterated that the skilled person would have safety concerns with including EDTA in an enteric-coated delayed-release risedronate oral dosage form.

[691] Dr. Cremers acknowledged that while EDTA is generally safe, the amount used must be carefully considered, and if it is used together with a formulation that releases quickly into the small intestine, which gives “a very big concentration” of the bisphosphonate and EDTA, both are potentially toxic.

[692] Dr. Cremers stated that the skilled person would not be able to predict whether EDTA in the 100 or 200 mg range, delivered to the small intestine over a short period of time, would appreciably increase permeability or result in tissue injury. Human clinical studies would be required. In addition, the skilled person would not be able to predict from the art whether that amount of EDTA would significantly bind metal ions and minerals in food while not significantly altering risedronate absorption as compared to absorption in the fasted state.

(i) Conclusions on EDTA

[693] Considering the opinions of the experts on their interpretation of the art with respect to EDTA and the descriptions in that art, the evidence supports the conclusion that the art taught away from its use and did not teach that it was safe, particularly with bisphosphonates.

[694] Janner, Lin and Ezra discouraged the use of EDTA, did not study its safety and focussed on fasted absorption only. Although there is general agreement that EDTA can be safe for humans at some levels, the art did not teach what level would be safe with a bisphosphonate for delivery to the intestine.

[695] Poiger is not the guiding light given that it was a very small study, focussed only on a different type of drug and with high levels of EDTA to combat the food effect of a small amount of milk. Nor does WO 111 provide any guidance to combine particular bisphosphonate and chelators or how to adapt any formulation for an oral dosage.

[696] Dr. Yates agreed that the highest amount of EDTA that had been used in an approved medicine at the relevant time was 4 mg.

[697] Dr. Dillberger's evidence about the safety of EDTA in food and other products does not inform the skilled person about the safe level of EDTA in an oral bisphosphonate. Dr. Dillberger's assumption that Janner and Lin indirectly studied the safety of EDTA because the tested rats did not die before they were euthanized the next day is an incorrect assumption, and is far from an endorsement of the safety of EDTA for rats, let alone humans. Nor does Dr. Dillberger's reference to the Yonezawa study of dismembered rabbits support the safety of EDTA.

[698] As noted, although BR 601 disclosed the use of EDTA with bisphosphonates, it was not about the food effect and did not disclose any testing.

(c) *The Use of Enteric Coatings*

[699] Dr. Yates stated it was obvious that a formulation of enteric-coated risedronate could have some enhancement of bioavailability by adding EDTA as an excipient. He noted that due to the separation from food by using enteric-coated tablets, the expectation would be that pharmaceutically effective absorption would result.

[700] Dr. Yates stated that it does not matter if a person is fed or fasted when taking an enteric-coated tablet because an enteric-coated tablet will only enter the small intestine when there is "virtually no food contents in the upper part of the small intestine" (i.e., when stomach is empty).

[701] Dr. Yates acknowledged that Mitchell 1996 reported that an enteric-coated formulation of risedronate, when given 30 minutes before food showed a significant reduction (by 80-100%) in absorption. However, Dr. Yates did not agree with this conclusion. Dr. Yates suggested that the details of the Mitchell study were not known and that perhaps Mitchell was doing colonic delivery.

[702] Dr. Yates referred to Blümel as supporting the use of enteric coatings with higher amounts of bisphosphonates (alendronate) to achieve similar pharmacological efficacy compared to an immediate release formulation.

[703] Dr. Yates opined that Blümel measured absorption and bioavailability indirectly. Dr. Yates also agreed that Blümel was not designed to measure the food effect. However, Dr. Yates stated that he presumed that patients were not asked to fast for more than 30 minutes, so in his view this addressed the food effect because some tablets would not have exited the stomach 30 minutes after dosing.

[704] On cross examination, Dr. Yates agreed that Blümel did not directly measure absorption so no comparisons could be done between the absorption with an enteric-coated tablet given with food and after a four hour fast. Dr. Yates stated that "all we can say is that the enteric-coated tablet

behaved in terms of suppression of bone turnover in a very similar way to either daily or weekly immediate release alendronate, and so that is the takeaway from Blümel."

[705] Dr. Yates again referred to the "housekeeping wave", noting that an enteric-coated tablet will be retained in the stomach until after food has left the stomach. Dr. Yates stated, "it is as plain as day that that means that the interaction between the food and the solid object such as an enteric-coated tablet will – there will be a separation. That is all you need to know." He added that it is obvious that this would address the food effect.

[706] Counsel for Allergan probed Dr. Yates about his theory that the effect of an enteric coating on a dosage form is that there would be no food effect. Dr. Yates then qualified his statement, noting that "it depends on the specifics of the formulation as to whether or not there will be adequate separation between the food and the tablet. It depends on the specifics of the coating, the pH at which it dissolves. But certainly one would anticipate that a coating that dissolves relatively quickly after leaving the stomach would overcome the food effect." Dr. Yates responded that this was the likely explanation for the efficacy of the absorption of alendronate found by Blümel.

[707] Dr. Yates also pointed to WO 907 as teaching that there was a two to four fold increase in bioavailability of clodronate when administered as an enteric-coated formulation. Dr. Yates acknowledged that he could not recall whether he was aware of WO 907 before being engaged in this litigation. Dr. Yates also agreed that WO 907 does not mention the food effect.

[708] Dr. Yates opined that there were several possible reasons for the inconsistent findings in Blümel and WO 907 compared to Mitchell 1996, including the type of meal given in the Mitchell study. He noted that this suggested that there would need to be an adjustment to the formulation of enteric-coated risedronate to improve bioavailability.

[709] Dr. Yates agreed that no one had studied the use of an enteric-coated tablet dosed 30 minutes before food, except for the McClung study (which is not prior art) and which studied risedronate.

[710] On cross examination, Dr. Yates agreed that there are many enteric-coated drugs that still suffer from the food effect. In addition, there were medications with a food effect that had not been formulated with an enteric coating. Dr. Yates noted that about half of all oral drugs have some food effect.

[711] Dr. Yates also acknowledged that he was not aware of any approved medicine other than ACTONEL DR and ATELVIA (in the U.S.) that contains both an enteric coating and EDTA.

[712] Dr. Parr agreed that Mitchell 1996 studied enteric-coated dosage forms of risedronate compared to the immediate release risedronate after a four hour fast and 30 minutes before food with the result that the immediate release dosage administered 30 minutes before food had a 50% decrease in absorption and the enteric-coated dosage form had a 80-100% decrease in absorption. Dr. Parr agreed that this showed a severe food effect, but added that the skilled person would have

questions about the details of this study. He also suggested that the formulation was faulty if it resulted in 100% reduction in absorption.

[713] Based on Dr. Parr's assumption from the immediate release dosage and his calculations, he opined that the skilled person would expect that an enteric-coated formulation of risedronate and EDTA taken in the fed state would result in absorption of the risedronate within about 50% of fasted absorption. He later acknowledged that testing would be required to determine if there was pharmaceutically effective absorption.

[714] Dr. Cremers agreed that it was known that enteric coatings for bisphosphonates were disclosed to reduce upper GI irritation. Dr. Cremers also noted that enteric coatings can be formulated to release a drug in the intestine or in the stomach.

[715] Dr. Cremers cited Mitchell 1996, stating that the skilled person would not believe an enteric coating was the answer if considering how to overcome the food effect for risedronate.

[716] Dr. Cremers disagreed with some of Dr. Yates' opinions on Mitchell 1996 and the differences between Mitchell 1996 and Blümel, noting that they were based on speculation.

[717] Dr. Cremers noted that the Blümel study was of alendronate, sometimes with an enteric coating, to compare side effects, particularly digestive disturbances. Blümel did not directly assess alendronate absorption and was not about addressing the food effect, or investigating whether the dosage forms studies could be taken with or without food.

[718] Dr. Cremers described WO 907, also cited by Dr. Yates, as a six person study of enteric-coated clodronate that is not about the food effect problem associated with bisphosphonates, nor about designing dosage forms that can be taken with or without food.

[719] Dr. Cremers noted that there were patents that disclosed the use of enteric coatings in oral bisphosphonates, for example the ‘479 and ‘559 Patents, but none taught that enteric coatings would address the food effect or achieve similar absorption in the fed and fasted states.

(i) Conclusions on Enteric Coatings

[720] Overall, the evidence with respect to the prior art on enteric coatings does not teach the skilled person that an enteric coating will address the food effect of risedronate either on its own or with EDTA. Mitchell 1996 is not contradicted by Blümel or WO 907 as neither addressed the food effect. Dr. Yates’ view that Blümel indirectly addressed the food effect is based on an assumption and is not persuasive. Mitchell 1996 remains a teach away for the use of an enteric-coated risedronate formulation if the goal is to address bioavailability and the food effect.

[721] Dr. Yates’ explanation of the “housekeeping wave” does not persuade me that enteric coatings on their own were the answer to the food effect and that the skilled person would rely on this theory. If this theory were widely accepted, it would seem logical that enteric coatings would have been used routinely and earlier to address the food effect.

J. *Differences between the State of the Art and the Subject Matter of the Claims*

[722] To summarise, as of April 2005, the art did not disclose studies using EDTA to overcome the food effect for bisphosphonates. As found, BR 601 was not about the food effect and moreover, it did not disclose any testing. The prior art – in particular, Janner and Lin – taught away from using EDTA to enhance oral bisphosphonate absorption. EDTA was generally safe, but nothing showed it was safe for use at the levels adopted in the '188 Patent and/or that such levels would not also increase fasted absorption, which the '188 Patent sought to avoid.

[723] As acknowledged by Apotex's expert, Dr. Yates, the highest amount of EDTA ever used as an excipient in an approved medicine was 4 mg, and EDTA had never been used to solve the food effect problem in an approved medicine.

[724] Poiger does not "prove" – as Dr. Yates suggested – that EDTA will overcome the food effect. Poiger studied tetracycline, which, as Dr. Cremers explained, does not have the same properties as bisphosphonates. Poiger was a small study that concluded that further study was warranted and it appears that such further study was not conducted. Given the large amount of EDTA needed (2.3 grams) to deal with less than a cup of milk when administered with tetracycline, Poiger did not teach, let alone prove, that EDTA is a solution to the food effect problem for oral bisphosphonates.

[725] Janner and Lin remain the "teach aways" from the use of EDTA as of April 2005.

[726] Although EDTA was known to be generally safe at certain levels, Dr. Dillberger acknowledged on cross examination that neither Janner nor Lin studied or provided any safety

information about EDTA. Dr. Parr also agreed that neither Janner nor Lin were designed to investigate whether EDTA had any damaging effects on mucosal integrity.

[727] With respect to enteric coatings, Mitchell 1996 remains a teach away from their use with risedronate. Dr. Parr and Dr. Yates' reliance on other art does not support a different view. Blümel does not measure or report on the absorption of the bisphosphonate (alendronate). Blümel does not disclose anything about the timing of food intake relative to dosing. Dr. Yates' speculation is just that – speculation. WO 907 is about enteric-coated clodronate, and makes no mention of food or the food effect. The '559 and '932 Patents relate to enteric-coated capsules containing liquids or semi-solids and osmotic pumps and do not mention the food effect.

[728] The evidence overall supports the view that the art as of April 2005 did not disclose the use of enteric coatings to solve the food effect problem for any drug. As previously found, BR 601 is not about the food effect. As Dr. Yates acknowledged, there are other enterically coated drugs that still suffer from a food effect and there are other drugs with a food effect that are not formulated with an enteric coating. If an enteric coating were the solution, it seems that there would be more widespread use of enteric coatings for this purpose.

[729] Dr. Yates' housekeeping wave explanation – that enteric-coated oral dosage forms, on their own without EDTA, solved the food effect problem because the dosage form remains in the stomach until all the food moves out and the stomach returns to a fasted state, and is then released into a "virtually empty" small intestine – is not persuasive with respect to bisphosphonates. If it were as Dr. Yates described, the food effect would not be the problem that it is.

[730] Although the Apotex experts found no differences between the state of the art and the subject matter of the claims, based on their interpretation of the prior art, they acknowledged possible differences, which in their view were small and easily bridged.

[731] Allergan submits that the differences were not so small and lay in the combination of all the elements at all the right amounts, along with an immediate release delivery.

[732] First, in my view, the differences noted by Drs. Yates and Parr are not small differences and are not the only differences. These differences are what sets the ‘188 Patent apart from the art, some of which addressed the components of the ‘188 Patent but did not address their combination or the amounts, which together provide for pharmaceutically effective absorption in the fed and fasted states.

[733] Second, although BR 601 disclosed the use of bisphosphonates with a chelating agent and an enteric coating, BR 601 does not bridge the differences for the reasons noted above, including that BR 601 did not address the food effect, and does not provide sufficient direction with respect to what to choose, and in what amounts or the necessity for an immediate release core. Nor does BR 601 taken together with the other prior art bridge the difference. Too many choices must be made without any direction or ability to predict what will work.

K. *Bridging the Differences Required Inventive Ingenuity; it was Not Obvious to Try to Obtain the Invention*

[734] As noted in *Janssen 2020* at para 169, citing *Bridgeview*:

> [169] The Court must be wary of hindsight bias from expert witnesses. It is not fair to a person claiming to have invented a combination invention to break the combination down into its parts and find that, because each part is well known, the combination is therefore obvious (*Bridgeview Manufacturing Inc v 931409 Alberta Ltd (Central Alberta Hay Centre)*, 2010 FCA 188 at para 51 [*Bridgeview*]). The question to ask is whether the POSITA, in light of the state of the art and their common general knowledge, would have come directly and without difficulty to the solution taught by the patent (*Beloit Canada Ltd v Valmet Oy*, (1986) 8 CPR (3d) 289 (FCA) at 294).

[735] While I am not attributing hindsight bias to any expert, the caution in *Bridgeview* is noted. *Bridgeview* is particularly apt in the present circumstances because the key issue is whether all the teaching and "teach aways" of the prior art would inform the skilled person, who is unimaginative, to use their deductive powers and arrive at the necessary combinations of the essential components to achieve the subject matter of the claims at issue. Based on the review of all the evidence, I have concluded that the skilled person, using their common general knowledge and the prior art, would not have been led directly and without difficulty to combine the elements of the asserted claims of the '188 Patent.

[736] This conclusion is supported by all the factors that guide the determination of whether the '188 Patent was obvious.

(1) Not Self-Evident to Try to Obtain the Invention and Not Self-Evident that it would Work

[737] It was not self-evident to try to obtain the invention – the combination of risedronate with EDTA in an enteric coating with an immediate release to achieve pharmaceutically effective absorption – as there was no such guidance in the prior art. Nor was it self-evident that this

combination would work to achieve pharmaceutically effective absorption whether administered with or without food. As noted in the jurisprudence, "worth a try" is not the test (*Pfizer* at para 29).

[738] Although Dr. Yates opined that it was obvious to try to obtain the invention and there would be an expectation that it would achieve pharmaceutically effective absorption when administered fed or fasted, he agreed that as of April 2005, there was no data disclosing the results of any testing for an oral bisphosphonate and EDTA to determine if this would overcome the food effect.

[739] Dr. Yates acknowledged that for oral drugs that have lower bioavailability, like bisphosphonates, it is necessary to conduct a study to evaluate the food effect. Dr. Yates agreed that accurately predicting the impact of the food effect on bioavailability is impossible without conducting fed bioavailability studies.

[740] Dr. Yates also agreed that if a drug company were seeking to develop a formulation to be taken with food, using the same approach as the '188 Patent, they would have to run a clinical study to determine its effectiveness. The results could not be based on speculation.

[741] Dr. Parr also stated that it was more or less self-evident for the skilled person to try to obtain the invention. He added that it was more or less self-evident that combining risedronate with EDTA in an enterically coated dosage form would allow risedronate to be administered in the fed state and achieve pharmaceutically effective absorption. Based on Dr. Parr's assumption from the immediate release dosage and his calculations, he opined that the skilled person would

expect that an enteric-coated formulation of risedronate and EDTA taken in the fed state would result in absorption of the risedronate within about 50% of fasted absorption. However, he later acknowledged that testing would be required to determine if there was pharmaceutically effective absorption.

[742] Dr. Cremers took the opposite view – that it would not have been obvious for the skilled person to try to overcome the differences and obtain the invention. Dr. Cremers noted that while the art provided strong motivation to solve the food effect, it contained no direct solution to that problem, and pointed in other directions to try to alleviate patient inconvenience, such as reducing dosing frequency. The art did not provide motivation to solve the food effect problem in the way that the '188 Patent disclosed.

[743] Dr. Cremers noted that as of April 2005, the skilled person knew about the restrictive dosing requirements for oral bisphosphonates and that pharmaceutical companies and other researchers were investigating how to reduce this inconvenience, but had not been able to achieve a bisphosphonate oral dosage form that directly overcame the food effect.

[744] Dr. Cremers' opinion is that it required inventiveness to pursue and develop the use of EDTA in an amount that could bind the metal ions and minerals, but not significantly alter bisphosphonate absorption by enhancing intestinal permeability, noting that the art did not provide any guidance about the amount. In addition, it required inventiveness to combine risedronate and EDTA together in an enteric-coated oral dosage form, in order to release the risedronate and EDTA in the small intestine, and with an amount of EDTA that would effectively bind the metal ions and

minerals in food, but not significantly alter absorption by enhancing intestinal permeability when fasted. It also required inventive ingenuity to develop and arrive at the types, amounts, and characteristics set out in the respective claims in order to provide "pharmaceutically effective absorption" and achieve a bisphosphonate oral dosage form to address the food effect.

[745] Dr. Cremers stated that it would not have been self-evident that what was being tried ought to work because the art did not teach a direct solution to the food effect problem and there were no predictable solutions or approaches.

[746] All the experts agreed that predictions could not be made and that human clinical testing would be required. Dr. Yates qualified this view focussing on "accurate" predictions. Dr. Parr noted that if details of the formulations were known he could make general predictions regarding increases or decreases. However, such details would not be known without trial and error and such predictions are not enough for it to be self-evident that the invention would work.

[747] The jurisprudence has established that a fair expectation of success – which appears to be as far as Dr. Yates and Dr. Parr's evidence would go – is not enough (*Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FCA 286 at para 4).

(2) Motive

[748] The evidence of the Apotex experts is inconsistent with respect to motivation. In Dr. Yates' view, the food effect and the restrictive fasted dosing requirements for bisphosphonates were only small inconveniences to patients because they could opt to have a weekly dosage.

[749] Dr. Yates suggested that P&G was motivated to solve the food effect only because it was looking for market differentiation, including from Merck, which had a weekly dosage form. However, in his written report, Dr. Yates stated that there was "clear" motivation to solve the food effect. He nuanced his view, stating that his written opinion "relates to the motivation of a company like P&G that is looking to have some differentiation of their product relative to the market leader, which was Fosamax… But P&G was motivated because they had a problem in differentiating from once daily and once weekly Fosamax, and they saw this as a means of providing some differentiation." Dr. Yates explained that only P&G or others who already had a bisphosphonate on the market who were seeking product differentiation would have been highly motivated to solve the food effect.

[750] Dr. Yates' comments about motivation are curious given that he was keen to suggest that BR 601 sought to solve the food effect, because it was a big and well known problem, even though BR 601 said nothing about the food effect. Dr. Yates also interpreted other art as addressing the food effect, when that art did not do so. Dr. Yates' view is also in contrast to the other experts, including Dr. Parr, who noted that the food effect was a problem along with the rigid dosing requirements which adversely affected patient compliance and treatment and that there was motivation to solve the problem. The inventors explained that overcoming this problem became their personal challenge.

[751] Dr. Yates' view is that of an outlier, particularly given Apotex's innuendo that P&G may have taken the idea of the invention from BR 601 or Takeda. If there was no motivation to solve the food effect, as Dr. Yates suggests, why would others be interested in addressing it?

[752] Dr. Cremers explained that there was strong motivation to address the food effect and the rigid dosing requirements, yet no one had done so directly. However, the art did not point to the solution of the problem. Pharmaceutical companies and researchers were exploring other approaches to mitigate the problem, but these approaches did not solve the food effect.

(3) The Nature, Extent and Effort Required to Achieve the Invention

[753] The Apotex experts were generally of the view that the P&G scientists wasted time pursuing the dead end of colonic delivery, but otherwise, once on the right track, they did what any skilled person would do guided by the art and the common general knowledge to achieve the invention. However, on cross examination, Dr. Parr acknowledged that colonic delivery was not unheard of and that other patents, including WO 111, disclosed colonic delivery.

[754] Dr. Yates stated that the work described in the ‘188 Patent would be routine for the skilled person. Dr. Yates noted that all the examples incorporated known amounts of risedronate, EDTA and include known excipients typically used in enteric-coated forms. He added that none of the formulations set out in the examples were “out of the ordinary”.

[755] Dr. Parr also stated that it would have been within the skill set and routine for the skilled person to arrive at the invention of the ‘188 Patent.

[756] Dr. Cremers took a different view, stating that given the lack of direction in the art, the skilled person would have had to engage in a drug development project to solve the food effect.

[757] Dr. Cremers noted that the skilled person would have needed to develop a large number of test formulations, with different types and amounts of the bisphosphonate and chelating agent and enteric coating parameters as variables in each formulation, and test each formulation in a pharmacokinetic study involving human volunteers to identify which, if any, would achieve similar absorption between the fed and fasted states. The skilled person would not have been able to predict that combining those elements together would work to overcome the food effect.

[758] Dr. Cremers noted that while this work would be generally familiar to the skilled person, it would have required considerable research, innovative thinking and creativity (which the skilled person is not supposed to possess), and extensive experimentation – with no guarantee of success. It would likely have taken even a highly skilled drug development team years to complete.

[759] Dr. Cremers' evidence on the nature of the work required to arrive at the invention is more realistic and persuasive. Dr. Yates and Dr. Parr appear to rely on the fact that the disclosure of the '188 Patent would permit the skilled formulator to arrive with ease at the invention. This is not the approach to determining what would be required to arrive at the invention without such disclosure.

(4) The Inventors' Course of Conduct

[760] The nature and extent of the work required and the invention story or course of conduct are closely related factors (*Bristol-Myers Squibb Canada Co v Teva Canada Ltd*, 2017 FCA 76 at para 44). In this case, both factors point to the same conclusion – that this was not simple, routine or quick work.

[761] Dr. Yates opined that the amount of work conducted by the inventors was easily within the capabilities of even a mid-sized pharmaceutical company. The studies done by the inventors, including the '132 Study, were relatively small and of the type a skilled person would conduct routinely. Dr. Yates stated that the skilled person would have been surprised at the inventors' focus on delivery to the colon. In his view, the inventors wasted about three years exploring this. Dr. Yates noted that the inventors [redacted]. They also used 35 mg risedronate in all formulations.

[762] Dr. Parr stated that, apart from pursuing delivery to the colon, which no skilled person would have pursued, the inventors and their team at P&G followed the steps that the skilled person would have taken. Dr. Parr stated that the inventors arrived at the idea of adding EDTA at the outset of the project [redacted].

[763] On cross examination, Dr. Parr acknowledged that he was not aware of the prior art references that contemplated colonic delivery of bisphosphonates. Dr. Parr was also not aware of other drugs that provide colonic absorption. Dr. Parr agreed that there were no prior art studies on whether a bisphosphonate could be provided for colonic absorption. He stated that the question still remains whether colonic absorption is possible with a bisphosphonate.

[764] Dr. Burgio and Dr. Dansereau provided oral, written and documentary evidence that described their work in detail and chronicled its development, including the various approaches considered, the questions they had, the set backs encountered and their efforts overall over the

course of five years. Dr. Burgio and Dr. Dansereau described the lack of success with the dog study to test the delivery to the colon, yet despite this failure, they persevered with a human trial using Enterion capsules to permit targeted delivery to the GI tract. They explained why they chose to use particular amounts of risedronate and EDTA. [redacted] They also explained their choice of enteric coating and the need for immediate release in the intestine.

[765] In Dr. Cremers' view, the efforts of the P&G scientists would not be regarded as routine for the skilled person.

[766] Dr. Cremers reviewed the P&G documents that chronicled the inventors' work. Dr. Cremers disagreed with Dr. Yates and Dr. Parr's opinion that the work of the inventors was routine and non-inventive. Dr. Cremers described various documents that set out the problem and the proposed approaches to be explored, following the bronze, silver and gold medal analogy.

[767] In Dr. Cremers' opinion, it was evident that the P&G scientists considered many different options and approaches which indicated that they were uncertain that any one particular solution would be successful.

[768] Dr. Cremers noted that the researchers first explored risedronate absorption in the colon. Although Drs. Parr and Yates suggest that this would have been known to be a dead end, Dr. Cremers expressed a different view and also noted that time and effort spent exploring this approach shows that they did not know what the solution would be.

[769] Dr. Cremers also noted that Aventis, a research partner with P&G in this project, withdrew their support after the failed dog study regarding colonic delivery. Dr. Cremers characterized the withdrawal of Aventis as a signal that they did not think that P&G would find a solution to the food effect.

[770] Dr. Cremers also described the two Enterion studies conducted by P&G which tested whether risedronate and EDTA released in the ascending colon could increase absorption compared to dosing without EDTA under fasted conditions. [redacted]. In 2004, a second Enterion study, designed to simulate the presence of food was conducted. The study found that when 35 mg risedronate with 100 mg EDTA was delivered to the small intestine no food effect was observed.

[771] In addition to the differing views of the experts – on the one hand, that this was simple work for the skilled person and on the other, that research, commitment, trial and error, and human clinical experiments were required – we have first hand evidence of the two inventors who led the team at P&G. Nothing suggests that the inventors were less skilled than the skilled person.

[772] In my view, the details provided by the inventors show that their project in seeking a solution to the food effect required commitment, time, and trial and error. The inventors' description of their work supports the conclusion that they did not arrive at the solution to the food effect for bisphosphonates quickly or easily. A whole team explored several options, several of which were non-starters. They encountered several set backs, yet persevered. Their early exploration of colonic delivery was not successful, but it cannot be said that they "wasted" effort because colonic delivery was not as unheard of as Dr. Parr and Dr. Yates suggested.

[773] Apotex now seeks to downplay the actual course of conduct as merely one of several factors that guide the determination of whether the invention was obvious to try. I have considered all the factors and they all support the conclusion that it was not obvious to try to obtain the invention.

[774] The evidence does not establish on a balance of probabilities that it was more or less self-evident to try to obtain the invention. The off chance that a formulation of BR 601 would align with the '188 Patent does not make the invention obvious (*Bridgeview* at paras 51-52).

[775] With respect to Apotex's submission that the skilled person would have made deductions – which are not inventive – and would have easily arrived at the invention of the '188 Patent based on several basic premises, I do not accept all the basic premises that Apotex rely on, which include reliance on Poiger as teaching the use of EDTA to address the food effect (which it did not teach for bisphosphonates), BR 601 as teaching lower amounts of EDTA and enteric coatings – also to address the food effect (which it did not), the housekeeping wave and the use of enteric coatings to address the food effect (which it does not do on its own) and routine tests to arrive at the necessary combinations and amounts.

[776] I reject Apotex's suggestion that an adverse inference should be drawn about Allergan's failure to explain the Takeda patent application, which Apotex suggests disclosed elements of the '188 Patent. There is no evidence before the Court about what the Takeda patent application was about or whether it actually came to fruition, only innuendos based on excerpts of transcripts of the similar challenge to ATELVIA in the U.S. Drs. Burgio and Dansereau stated that they were not aware of the contents of the Takeda application. I accept that evidence.

[777] I am also not influenced by the findings in the U.S. Court regarding the obviousness of ATELVIA. The law in Canada is not identical and the evidence I have heard is not identical. In addition, it appears that in the U.S. litigation the issues were narrowed by agreement. I have assessed all the evidence in this case regarding ACTONEL DR – no more and no less – and have reached my own conclusions.

XI. Is the ‘188 Patent Invalid Due to Lack of Utility, Insufficient Disclosure and/or Overbreadth?

A. *Apotex’s Submissions*

[778] Apotex submits that the claims of the ‘188 Patent include subject matter that does not deliver what the invention purports to invent, i.e., formulations that achieve pharmaceutically effective absorption. Apotex submits that the higher coating formulations in the ‘132 Study, which are included as examples in the ‘188 Patent, do not work.

[779] Apotex notes that as part of the patent bargain the patentee must fully describe the invention and how to put it into practice in clear and precise terms. Apotex submits that the ‘188 Patent omits relevant details and is misleading. Apotex submits that the ‘188 Patent discloses that the high coating formulations will work, which is not so, and does not disclose that the high and low coatings will perform differently.

[780] Apotex argues that the skilled person relying on the disclosure would discover that some formulations did not achieve pharmaceutically effective absorption and would have to undertake research, formulation development and bioavailability studies to adjust the formulation. In other words, the disclosure would not lead them to perform the invention reading the disclosure, which contravenes the patent bargain.

[781] Apotex submits that only one of the four formulations in the ‘132 Study – the formulation with a 10% enteric coating – was found to provide pharmaceutically effective absorption. An

identical formulation and two others, all of which had a 30% enteric coating, did not do so. Apotex suggests that the evidence of Drs. Burgio and Dansereau – [redacted] – is a new theory.

[782] Apotex submits the fact that it has relied on the disclosure to develop its own product, which also achieves pharmaceutically effective absorption, is not relevant to the determination of the sufficiency of the disclosure or the utility of the '188 Patent.

[783] Apotex also submits that the '188 Patent claims more than what it disclosed and, as a result, it is also invalid for overbreadth.

B. *Allergan's Submissions*

[784] Allergan notes that the threshold to establish utility is low and that not every potential use needs to be realized; a scintilla of utility is sufficient. A single use related to the nature of the subject-matter is sufficient (*AstraZeneca Canada Inc v Apotex Inc*, 2017 SCC 36 at para 55 [*AstraZeneca*]).

[785] Allergan submits that the utility of the claims of the '188 Patent was demonstrated. Allergan notes that utility need not be demonstrated in the patent itself. Allergan points to the work of the inventors before the filing date, including the '132 Study.

[786] Allergan disputes Apotex's allegation that the '188 Patent claims embodiments that did not work. Allergan submits that the results of the '132 Study showed that a delayed release tablet of 35 mg risedronate and 100 mg EDTA targeting release in the small intestine with immediate release would provide pharmaceutically effective absorption. Allergan points to the evidence of Drs. Burgio and Dansereau.

[787] Allergan notes that in *Astrazeneca Canada Inc v Mylan Pharmaceuticals ULC*, 2011 FC 1023 at para 168, aff'd 2012 FCA 109, the Court stated that "[f]or the purposes of demonstrating utility, it is sufficient that the test results are 'strongly suggestive' of utility, and that no other logical explanation for the test results is likely." Allergan submits that the '132 Study strongly suggests that the formulations claimed in the '188 Patent will achieve pharmaceutically effective absorption and that there is no other explanation for the results of the '132 Study.

[788] Allergan notes that the inventors explained that in the '132 Study, [redacted]. Drs. Burgio and Dansereau also explained that the '132 Study [redacted] included other formulations [redacted].

[789] Allergan adds that the '132 Study test results for the [redacted].

[790] Allergan disputes that the '188 Patent claims more than what it disclosed; it is not overbroad.

[791] Allergan notes that the Patent does not obscure its invention by failing to disclose that the 10% coating thickness works, while a 30% coating thickness would not work. Allergan reiterates that both will work. Allergan notes that Examples I and III of the ‘188 Patent teach formulations that will provide pharmaceutically effective absorption whether taken with or without food or beverage.

[792] Allergan submits that the ‘188 Patent discloses all the elements necessary for the skilled person to practice the invention.

C. *The Relevant Jurisprudence on Utility, Sufficiency and Overbreadth*

[793] The Supreme Court of Canada clarified the test for utility in *AstraZeneca* and the distinction between the *Patent Act* requirements in section 2 (regarding usefulness) and subsection 27(3) (regarding disclosure) at paras 42-43:

> [42] Section 27(3) of the *Act* provides that in the specification, a “patentee must describe the invention ‘with sufficiently complete and accurate details as will enable a workman, skilled in the art to which the invention relates, to construct or use that invention when the period of the monopoly has expired’” (*Whirlpool*, at para. 42, quoting *Consolboard*, at p. 517).
>
> [43] There is a difference between the requirement in s. 2 that an invention be “useful” and the requirement to disclose an invention’s “operation or use” as per s. 27(3). As explained by Dickson J. (as he then was) in *Consolboard*, the former is a “condition precedent to an invention” and the latter a “disclosure requirement, independent of the first”:
>
> > … the Federal Court of Appeal erred also in holding that s. 36(1) [now s. 27(3) and (4)] requires distinct indication of the real utility of the invention in question. There is a helpful discussion in *Halsbury’s Laws of England* (3rd ed.), vol. 29, at p. 59, on the meaning of “not useful” in patent law.

> It means "that the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do". There is no suggestion here that the invention will not give the result promised. . . .
>
> . . . the Federal Court of Appeal has confused the requirement of s. 2 of the *Patent Act* defining an invention as new and "useful", with the requirement of s. 36(1) [now s. 27(3)] of the *Patent Act* that the specification disclose the "use" to which the inventor conceived the invention could be put. The first is a condition precedent to an invention, and the second is a disclosure requirement, independent of the first. [Emphasis added]

(*Consolboard*, at pp. 525 and 527)

While the above passage uses the word "promise", it does not refer to, nor does it embody, the Promise Doctrine.

[794] In *AstraZeneca* at paras 54-55, the Court also set out the test for utility:

> [54] To determine whether a patent discloses an invention with sufficient utility under s. 2, courts should undertake the following an analysis. First, courts must identify the subject-matter of the invention as claimed in the patent. Second, courts must ask whether that subject-matter is useful — is it capable of a practical purpose (i.e. an actual result)?
>
> [55] The Act does not prescribe the degree or quantum of usefulness required, or that every potential use be realized — a scintilla of utility will do. A single use related to the nature of the subject-matter is sufficient, and the utility must be established by either demonstration or sound prediction as of the filing date (*AZT*, at para. 56).

[795] Recently in *Apotex Inc v Janssen Inc*, 2021 FCA 45 [*Apotex 2021*], the Court of Appeal addressed the law on utility, confirming at para 49:

> [49] Moreover, it is not necessary that tests conclusively prove the requisite utility: Donald H. MacOdrum, *Fox on the Canadian Law of Patents*, 5th ed., s. 6:13(a); *Pfizer Canada Inc. v. Novopharm Limited*, 2009 FC 638, 76 C.P.R. (4th) 83 at para. 87, aff'd 2010 FCA 242, 88 C.P.R. (4th) 405, rev'd on other grounds 2012 SCC 60, [2012] 3 S.C.R. 625. It is sufficient that the test results are strongly suggestive of utility, and that there is no other logical explanation for the test results is likely: *AstraZeneca Canada Inc. v. Mylan Pharmaceuticals ULC*, 2011 FC 1023, 96 C.P.R. (4th) 159 at para. 168, aff'd 2012 FCA 109, 101 C.P.R. (4th) 275. By this measure, PSA levels appear to be sufficient.

[796] The Court of Appeal also agreed that test results should be interpreted in the context of all the test results, noting at para 41:

> [41] The Federal Court noted the shortcomings of each of the 001 and 004 Studies, but observed that the results thereof have to be interpreted in the context of all of the test results, unless one test conclusively proves that the compound had no utility: Reasons, para. 214; *Teva Canada Ltd. v. Novartis AG*, 2013 FC 141, 428 F.T.R. 1 at paras. 215-216 (*Teva*). I agree with the statement in *Teva* at paragraph 215 that testing should be considered cumulatively when assessing demonstrated utility.

[797] In *Valeant*, at para 112, the Court explained, with respect to sufficiency of disclosure:

> [112] Pursuant to s 27(3) of the *Patent Act*, the specification of a patent must correctly and fully describe the invention. The questions the Court must address to determine sufficiency are: (a) what is the invention? (b) how does it work? and (c) having only the specification, can a PSA successfully produce the invention using only the instructions contained in the disclosure? The possible need for non-inventive trial and error to enable the PSA to use the invention does not render the disclosure of a patent insufficient (*Apotex Inc v Shire LLC*, 2018 FC 637 at para 151; *Teva Canada Limited v Leo Pharma Inc*, 2017 FCA 50 at paras 55-56, 60; *Teva Canada Ltd v Pfizer Canada Inc*, 2012 SCC 60 at paras 50-51).

D. *The Claims are Not Invalid due to Lack of Utility, Insufficiency of Disclosure or Overbreadth*

[798] Apotex has not established that the claims of the ‘188 Patent are invalid due to lack of utility or insufficiency of disclosure, nor are they overbroad.

[799] There is no conclusive evidence that the higher coating formulations in the ‘132 Study would not achieve pharmaceutically effective absorption. The evidence is that of the inventors – that in a larger study the formulations would do so. As noted in *AstraZeneca*, a strong suggestion of utility can be sufficient.

[800] Dr. Burgio explained that in the ‘132 Study, the results for the low coating prototype demonstrated that the 100 mg amount of EDTA with 35 mg risedronate facilitated absorption in the fed state, while not significantly altering absorption (i.e., increasing intestinal permeability) in the fasted state. He explained [redacted].

[801] Dr. Burgio acknowledged that the results for the three other prototype formulations did not demonstrate similar absorption in the fed and the fasted states. He explained [redacted].

[802] Dr. Burgio also explained [redacted] their views regarding the possible outcome of a larger study [redacted]

[redacted]

[803] [redacted]

[804] Dr. Sinko also explained that due to the [redacted], no conclusions could be made that it would not provide pharmaceutically effective absorption. He explained that this formulation may have done so, and would do so in a larger study.

[805] The subject matter of the claims – an oral formulation that can be taken with or without food or beverage intake of 35 mg risedronate with 100 mg EDTA in an enteric coating for release in the small intestine in an immediate release – does serve a practical purpose. The evidence supports that the formulation, even with the higher coating, given the high variability in absorption, would likely also achieve pharmaceutically effective absorption whether taken in the fed or fasted state. Moreover, even if the absorption is not within the strict definition of "pharmaceutically effective absorption" there will be absorption and a positive effect on treatment of osteoporosis. There would be more than a scintilla of utility.

[806] As confirmed in *Apotex 2021*, test results should be considered in the context of all the tests. A test or formulation that might not provide pharmaceutically effective absorption would not be fatal to the utility requirement.

[807] There is no doubt that the 35 mg risedronate with 100 mg EDTA with a 10% enteric coat worked and would meet the low threshold of a "scintilla of utility." In addition, there is a strong suggestion that the formulations with 30% coating would also provide pharmaceutically effective absorption and there is no conclusive or even persuasive evidence that the 30% coating formulations would not be useful.

[808] Apotex has not provided evidence to contradict that of Drs. Dansereau or Burgio regarding their view about a larger study [redacted]. Moreover, even Apotex's own experts noted that despite the variability of absorption from dose to dose, there is a positive impact on treatment as long as the formulation is taken regularly; in other words, the formulations would be useful.

[809] Dr. Yates, in opining on whether the invention was obvious to try and self-evident that it would work, commented that the formulations of the '188 Patent were within the capabilities of the skilled person and would be simple and routine for the skilled person to prepare. Contrary to Apotex's submission, this further supports the conclusion that the disclosure was sufficient for the skilled person and that the skilled person could conduct non-inventive trial and error to adjust the coating if necessary (*Valeant* at para 112).

[810] The disclosure of the ‘188 Patent provides sufficient details to permit the skilled person to make the claims of the ‘188 Patent. Some non-inventive work that may be required does not mean that the disclosure is not sufficient.

[811] In conclusion, Apotex has not rebutted the presumption that the ‘188 Patent is valid. Apotex has not established on a balance of probabilities that the ‘188 is anticipated by BR 601 or obvious. Nor has Apotex established on a balance of probabilities that the ‘188 is invalid due to lack of utility, insufficient disclosure or overbreadth.

XII. Does Apotex Infringe the Asserted Claims of the ‘188 Patent?

A. *Allergan’s Submissions*

[812] Allergan submits that Apotex will infringe the first asserted claim set by making and selling APO-RISEDRONATE DR and will also induce the infringement of the second set (the use claims) because APO-RISEDRONATE DR is intended to be used to treat osteoporosis.

[813] Allergan disputes Apotex’s position that the first asserted claim set is a “product for use” claim and that it would only be infringed if the product is indicated in the proposed product monograph for the exact same use. Allergan submits that the asserted claim set is simply a product claim; the oral dosage form.

[814] Allergan submits that the first set of claims are for a novel dosage form of risedronate; the invention is the dosage form (i.e., a thing) which is for use with or without food or beverage. The

Patent does not claim a new use for an old product. Nor does it claim a use for treatment of a different condition or disease. Allergan submits that the jurisprudence relied on by Apotex does not apply, because the asserted claims are simply product claims.

[815] As noted in the analysis of the construction of the claims, Allergan relies on *Fox*, and the principle that the word "for" in a product claim is construed to mean that the product is "suitable for use". Allergan submits that the oral dosage form claimed is suitable for use with or without food or beverage because it will achieve pharmaceutically effective absorption either way.

[816] Allergan notes that Apotex concedes that APO-RISEDRONATE DR will comprise all of the claimed elements of the asserted claim set and that its product will achieve pharmaceutically effective absorption whether taken with or without food. Therefore, APO-RISEDRONATE DR is suitable for use with or without food and, as a result, it will infringe the claims of the '188 Patent.

[817] Allergan adds that whether the product is used is not relevant to infringement of the first asserted claim set. The manufacture and sale of the product by Apotex are both infringing acts; it does not have to be used to infringe.

[818] Allergan submits that where what is claimed is new and inventive, as in the first asserted claim set, the claims are pure product claims and the manufacture and sale of that product by a generic manufacturer can infringe. If the product is old and the use is new, then manufacture and sale do not infringe, unless there is some evidence of intention to do so, for example, in the product monograph.

[819] Allergan notes that the second set of claims, regarding use for the treatment of osteoporosis, would not be directly infringed by Apotex by the manufacture and sale of its product. However, the use of the Apotex product would infringe.

[820] Allergan submits that the jurisprudence relied on by Apotex (for example, *AB Hassle* and *BMS 2017*) is not on point and does not apply because the claims at issue in the cases relied on claimed a new use for an old or existing product.

[821] Allergan submits that *Bayer AG v Apotex Inc*, [1995] OJ No 141, 60 CPR (3d) 58 (Gen Div) [*Bayer (Nifedipine)*], aff'd [1998] OJ No 3849, 82 CPR (3d) 526 (CA), is analogous and applicable to the present case. Allergan notes that in *Bayer (Nifedipine)* the patent claimed a new instant oral release capsule of an old drug, Nifedipine, for use to treat angina (the existing use). The oral release capsule was described in the patent as having a shell containing the pharmaceutical composition that could be released by biting and breaking the shell, rather than swallowing it whole. The Court noted that it was a product claim and did not address how the oral capsule was to be used, but found that it had the capability to be released by biting the shell, which the generic product also possessed. The Court found that the intention to infringe was not relevant to infringement in fact.

[822] Allergan submits that because the first asserted claim set are product claims, in accordance with *Bayer (Nifedipine*), it does not matter how the product is to be used, rather what the product is in fact. Allergan submits that in fact, the Apotex product is an oral dosage form that is suitable

for use with or without food or beverage and will achieve pharmaceutically effective absorption in either state.

[823] Allergan notes that in *Bayer (Nifedipine)*, the Court found that Apotex infringed the claim even though its product monograph stated that the capsule be swallowed whole. The Court rejected Apotex's argument that it did not infringe because its generic product was to be swallowed whole, not bitten. Allergan submits that the same approach applies to the present case; it does not matter that the Apotex product is stated to be for use with food and not without food because it is suitable for and capable of use in both states.

[824] Allergan further submits that *Janssen 2020*, also relied on by Apotex, does not apply as the claims at issue were for a new dosing regimen for an existing product for use treating the same condition. Allergan submits that even if *Janssen 2020* were applicable, it does not support Apotex's position. Allergan notes that the Court found that even though the generic's product monograph fell short of instructing to infringe, read in its entirety, it included information that taught that the product could be administered according to the new claimed dosing regimen.

[825] Allergan submits that despite the proposed APO-RISEDRONATE DR product monograph, which replicates the ACTONEL DR product monograph, and states that the product "should be taken with food" and warns "Do not take APO-RISEDRONATE DR before food or on an empty stomach as it may cause abdominal pain", read as a whole, the proposed product monograph teaches that APO-RISEDRONATE DR can be used with food or without food and that similar absorption will result. In other words, it is not restricted to only use with food.

[826] Allergan submits that the Apotex product will infringe the asserted claims because APO-RISEDRONATE DR is "suitable for" use with or without food or beverage intake because it will provide pharmaceutically effective absorption regardless. Allergan further submits that it is irrelevant whether the product is used at all, or how it is intended to be used because the result will be pharmaceutically effective absorption and treatment of the osteoporosis.

[827] Allergan points to the reference in the product monograph to the crossover study which compares the bioavailability of the product when taken with breakfast and when taken four hours before (i.e., fasted) and which shows absorption within 30%. Allergan submits that this information, as explained by Dr. Adachi, would inform the physician and others that the product can be taken either with or without food and will achieve pharmaceutically effective absorption.

[828] Allergan also notes that the warning regarding upper abdominal pain is also in the ACTONEL DR monograph. Allergan notes that Dr. Adachi explained that the upper abdominal effects reported were mild to moderate and did not result in patients discontinuing treatment. Allergan adds that upper abdominal pain could also occur if taken with food. Allergan submits that Modi, A et al, "Gastrointestinal symptoms and association with medication use patterns, adherence, treatment satisfaction, quality of life, and resource use in osteoporosis: baseline results of the MUSIC-OS study" (2016) Osteoporos Int 27:1227-38 [the MUSIC-OS study], which reported on a range of side effects for bisphosphonates in general, does not suggest that upper abdominal pain was a reason for patients to discontinue treatment with risedronate, noting that only a minority of all bisphosphonate users in the study did so.

[829] With respect to the use claims (for treatment) and the kit claims, Allergan notes that APO-RISEDRONATE DR is indicated for the treatment of osteoporosis in post-menopausal women, on a weekly regimen. As a result, Apotex will induce the infringement of the use claim set. Similarly, the kit claims will be infringed, because APO-RISEDRONATE DR includes blister packaging, which constitutes a means for facilitating compliance.

B. *Apotex's Submissions*

[830] Apotex submits that Allergan has not met its burden to establish that APO-RISEDRONATE DR will infringe the asserted claims. Apotex submits that a claim to a pharmaceutical composition or dosage form that is "for use" in some respect will be infringed only if it is indicated to be for that use as set out in the product monograph for the composition or dosage form.

[831] Apotex points to its proposed product monograph which clearly instructs that APO-RISEDRONATE DR is only to be taken with food. The patient does not have the choice to take the oral dosage form either with or without food, unlike the claimed invention of the '188 Patent. Apotex submits that its product does not embody the invention of the '188 Patent, and does not embody the essential element of "for use with or without food or beverage intake". As a result, it does not infringe.

[832] Apotex submits that Allergan's argument that the asserted claims are product claims and that the intention for use does not matter, ignores the clear words of the claims.

[833] As noted above with respect to the construction of the claims, Apotex characterises the first asserted claim set as "product for use" claims given that the oral dosage form is "for use with or without food…", which is an integral part of the claim and the invention.

[834] Apotex submits that *Bayer (Nifedipine*), relied on by Allergan, does not apply. In that case, the claim was simply to the product without any reference to how it is to be used.

[835] Apotex submits that *AB Hassle* applies to the present case. The claim at issue was for omeprazole for use in the treatment of a bacterial infection (campylobacter). The Court concluded that its use for other than campylobacter infections would not infringe. Apotex submits that this is analogous as the use of APO-RISEDRONATE DR is not "for use with or without food or beverage…" and following *AB Hassle*, Apotex would not infringe.

[836] Apotex also points to *BMS 2017,* where the claim at issue was for a pharmaceutical composition of aripiprazole (an existing drug) for the treatment of bipolar disorder, and not for schizophrenia as originally claimed. The Court referred to the product monograph and found that the generic product was not manufactured for the claimed use and, as a result, it did not infringe. Apotex acknowledged that if its product were used for bipolar disorder, it would work, but it was not intended for such use.

[837] Apotex submits that in the present case, APO-RISEDRONATE DR is for use only with food, not for the claimed use of "with or without food…". However, if APO-RISEDRONATE DR were used without food it would still work. In accordance with *BMS 2017*, the fact that it could be

so used is not the issue, because it is clearly not intended or indicated for such use, rather it is only for use with food.

[838] Apotex submits that *Janssen 2020* does not support Allergan's position. Unlike *Janssen 2020*, there is nothing in the proposed product monograph for APO-RISEDRONATE DR that states that its product is for the claimed dosing regimen, i.e., for use with or without food. Apotex submits that a "stray sentence" about the pharmacokinetics does not suggest that it can be used with or without food. The key part of the product monograph is the "Dosage and Administration" section.

[839] Apotex submits that the most relevant parts of the product monograph are in the "Dosage and Administration" section, which clearly state that it "should be taken in the morning, with breakfast". Apotex adds that this is reinforced in the "Patient Medication Information" section and in the patient leaflet provided to patients by pharmacists and to physicians as part of the Apotex product monograph.

[840] Apotex further submits that Dr. Adachi attempted to downplay the impact of the upper abdominal pain associated with fasted dosing, noting this did not occur in the majority of patients and was only mild or moderate, despite the evidence to the contrary. Apotex notes, among other things, that the Osteoporosis Canada website confirms the caution regarding fasted administration of ACTONEL DR and clearly directs patients to take it only with food.

[841] Apotex also notes that it obtained [redacted] from Health Canada, [redacted] due to the same risks of upper abdominal pain, as well as other considerations, including that it would label its product for use only with food. Apotex also points to Dr. Jamali's evidence that [redacted].

[842] Apotex further submits that it will not induce infringement, noting the three-pronged test is stringent (*Corlac Inc v Weatherford Canada Inc*, 2011 FCA 228 at para 162 [*Corlac*]). Apotex again points to its proposed product monograph. Apotex submits that any infringing acts by a physician, who prescribes "off label" use would not be influenced by Apotex.

C. *The Relevant Jurisprudence on Infringement*

[843] As noted in *Janssen* 2020 at paras 225-226:

> [225] ...Infringement is any act that deprives the patentee and their legal representative of the exclusive right, privilege, and liberty of making, constructing and using the invention and selling it to others (*Patent Act*, s 42). Janssen [the brand] bears the burden of proving infringement (*Monsanto Canada Inc v Schmeiser*, 2004 SCC 34 at para 29 [*Monsanto*]).
>
> [226] To determine whether a patent claim is infringed, having purposively construed the claims and identified essential claim elements, the Court must determine whether the allegedly infringing product falls within the scope of the claims (*Free World Trust* at paras 48-49). There is no infringement if an essential element is different or omitted, but there may still be infringement if a non-essential element is substituted or omitted (*Free World Trust* at para 31).

[844] The test for inducement of infringement was established in *Corlac* at para 162:

> i. The act of infringement must have been completed by the direct infringer;

> ii. The completion of the acts of infringement must be influenced by the acts of the alleged inducer to the point that, without the influence, direct infringement would not take place;
>
> iii. The influence must knowingly be exercised by the inducer, that is, the inducer knows that this influence will result in the completion of the act of infringement.

[845] In *Corlac,* the Court of Appeal noted that the test is difficult to meet.

[846] As noted in *Janssen 2019*, at para 234, the generic must induce infringement of all the essential elements of the asserted claims. The Court noted, at para 235, that reasonable inferences can be drawn from the product monograph:

> [235] The Court can make reasonable inferences from the product monograph, evidence relating to the dosage form of APO-ABIRATERONE, or its labelling and marketing to determine infringement by inducement: Ramipril at para 11. Merely referring to the patented use when explaining contraindications or as part of a list of scientific references is not sufficient to establish inducement.

[847] In *Janssen 2020,* at para 273, the Court noted that the second part of the *Corlac* test is the key aspect of the inducement analysis. At para 276, the Court noted that the product monograph is a key document:

> 276 The jurisprudence is consistent that the PM is a key document in the inducement analysis, and the entire PM is to be considered (*Aventis Pharma,* above, at paras 51-52). With respect to the recommended dosing regimen, the "Dosage and Administration" section of the Teva PM is pertinent.

[848] The relevant principles to be applied in the present case are:

- The brand (in this case Allergan) has the onus to establish infringement by Apotex.

- An infringing act is one that deprives the patentee (Allergan) of their rights in making, constructing and using the invention and selling it to others (*Patent Act*, s 42).

- The claims as construed and their essential elements are the starting point.

- The Court must determine whether the allegedly infringing product (in this case, APO-RISEDRONATE DR) falls within the scope of the asserted claims. There is no infringement if an essential element is different.

- The three-part test in *Corlac* determines whether the generic (in this case, Apotex) has induced infringement of all the essential elements of the asserted claims.

    - The second part of the *Corlac* test – that the infringement must be influenced by the acts of the alleged inducer to the point that, without the influence, direct infringement would not take place (the "but for" test) – is key to the analysis of inducement.

    - The product monograph (in this case, the proposed product monograph for APO-RISEDRONATE DR) is a key document in the inducement analysis; the whole product monograph should be considered.

D. *Overview of the Experts' Evidence on Infringement*

[849] Dr. Cremers stated that the Apotex product included all the essential elements of the '188 Patent.

[850] Dr. Cremers emphasized that the oral dosage as described in the claim will work regardless of whether it is taken with or without food. In Dr. Cremers' opinion, a physician would advise the patient according to the product monograph to normally take the oral dosage with breakfast but would also point out that if the patient took it fasted, it was not a "big deal". It would still be effective.

[851] Dr. Cremers acknowledged the dosing instructions in the product monographs for ACTONEL, ACTONEL DR and the Apotex product. Dr. Cremers noted that he would need more information to determine whether a dosing instruction that clearly stated "do not take this drug with food", could permit the drug to be taken with or without food. He agreed that if he concluded that the drug could only be taken with food, it would not fall within a claim that provides that the drug can be taken with or without food.

[852] In Dr. Adachi's opinion, the Apotex product will infringe all the asserted claim sets.

[853] Dr. Adachi acknowledged that the dosing instructions in the product monograph for ACTONEL DR direct that it be taken with food. However, Dr. Adachi stated that physicians treating osteoporosis would know that ACTONEL DR can be taken with or without food. Dr. Adachi explained that physicians would read the product monograph as a whole. Dr. Adachi pointed to the results of the crossover study on bioavailability, reported in the product monograph, which in his view, support the use of the oral dosage form without food or with food.

[854] Dr. Adachi noted that the proposed APO-RISEDRONATE DR product monograph includes the same instructions and information and would be read the same way.

[855] Dr. Adachi explained that the direction to take the oral dosage form with food was due to the potential risk of mild to moderate abdominal pain. Dr. Adachi acknowledged the results in the MUSIC-OS study which were for bisphosphonates in general, but noted that in his experience over 90% of patients did not experience abdominal pain. In Dr. Adachi's view, ensuring that the patient take the oral dosage form is the most important thing in order to get a treatment effect.

[856] Although Dr. Adachi's opinion is that the oral dosage form can be taken with or without food and it will work, he explained that he prescribes ACTONEL DR to be taken "around breakfast", either shortly before, during or shortly after breakfast.

[857] Dr. Adachi is the only expert who is a skilled physician, with years of experience treating patients with osteoporosis. His opinion, regarding how ACTONEL DR (and APO-RISEDRONATE DR) would be prescribed and how it would be used, while valuable, evolved from his initial written opinion. Dr. Adachi conveyed that, while the oral dosage would be effective whether taken with food or without, the dosing instructions in the product monograph are generally followed. In his own practice, he explained that he advises patients to take it "around breakfast". Although for some patients, without a history of abdominal pain, or those who for other reasons did not eat breakfast, administration without food was an option. For the majority, Dr. Adachi appears to agree that the oral dosage form is to be taken with food (breakfast) and not on an empty stomach.

[858] In Dr. Yates' opinion, the Apotex product will not infringe the claims of the '188 Patent either directly or indirectly.

[859] Dr. Yates concluded, based on the clear wording of the Apotex proposed product monograph, that the APO-RISEDRONATE DR product does not fall within the scope of the asserted claims as it is not a product that can be taken with or without food or beverage.

[860] Dr. Yates stated that the reference in Apotex's proposed product monograph to the crossover pharmacokinetic study is irrelevant to the issue of infringement for two reasons. First, the crossover study compares patients who took the oral dosage after an overnight fast and remained fasted for four hours (which Dr. Yates suggests is an unlikely scenario) with those who took the oral dosage with breakfast. Second, Dr. Yates stated that the only part of the draft product monograph a physician and patient would look at to inform them how to take the drug is the "Dosage and Administration" section and not references to other studies.

[861] Although Dr. Yates has not treated patients with osteoporosis, except in experimental settings, he is a medical doctor and his opinion with respect to dosing instructions in product monographs cannot be discounted for this reason.

E. *The Apotex Product Does Not Infringe the Asserted Claims of the '188 Patent*

[862] I find that Apotex will not infringe the asserted claims of the '188 Patent by making, constructing, using or selling its APO-RISEDRONATE DR product. Nor will Apotex induce infringement of the asserted use claims of the '188 Patent. This conclusion is based on: the

construction of the claims and their essential elements; the application of the principles from the jurisprudence; the clear wording of the product monographs of both ACTONEL DR and APO-RISEDRONATE DR, which are almost identical; and, the experts' evidence.

[863] This is not a situation where the generic manufacturer has carved out a use that differs from that of the brand in order to not infringe. While Apotex directs that its product be used only with food, which differs from the claims of the '188 Patent – which include as an essential element that the oral dosage form can be used either with or without food – the brand, ACTONEL DR, also directs that its product be used only with food. ACTONEL DR does not appear to live up to the claimed invention and its goal of "Anytime Actonel" or of giving the patient the choice and convenience of taking the oral dosage form with or without food. This restriction on the invention is due to the risk of abdominal pain. However, as found above, the Patent is valid and it is not disputed that the product would be effective in treating osteoporosis whether taken with or without food.

[864] Allergan has contributed to this outcome itself by highlighting in its ACTONEL DR product monograph that it should only be taken with food and including clear warnings that it should not be taken without food. In other words, ACTONEL DR, as described in its own product monograph and patient leaflet, does not reflect the invention described in the '188 Patent. Although Allergan now emphasizes that the upper abdominal pain that may result from fasted administration is moderate or mild and does not affect the majority of patients, the risk of upper abdominal pain is still very much highlighted in the product monograph. Notably, upper abdominal pain is identified as an adverse effect even when taken as indicated (i.e., with food). A higher incidence

of upper abdominal pain is noted if taken without food. If this were not a real concern for patients in general, why would it be emphasized to the extent that it is inconsistent with the claimed invention?

[865] The ACTONEL DR product monograph does not highlight that, despite the risk of abdominal pain, the product can be taken without food. Nor does it suggest that there is only a low risk of mild to moderate pain. Allergan could have contextualized the risks of abdominal pain, if it is indeed a low risk of only mild pain, and on the effectiveness of the product when taken with or without food – if there was scientific evidence to support this – but did not do so. Moreover, the reference to the crossover bioavailability study is hardly an indication that the dosing instructions can be ignored.

(1) The Claims and the Essential Elements

[866] The starting point to assess infringement is the construction of the asserted claims and the identification of the essential elements.

[867] The first set of claims is construed as claims for an oral dosage form that can be used (i.e., can be consumed, administered or taken) at the choice of the user/patient either with or without food or beverage intake. This oral dosage form contains about 35 mg of risedronate sodium (Claim 6) and about 100 mg of disodium EDTA (Claim 36) in a core coated with a methacrylic acid copolymer enteric coating (Claim 60) that begins to dissolve at about pH 5.5 (Claim 54). This oral dosage form also weighs less than 1 gram (Claim 63). Claim 1 requires that this oral dosage form provides targeted release of EDTA and risedronate in the small intestine in an immediate release

fashion. Claim 1 also requires that this oral dosage form provides pharmaceutically effective absorption whether it is used (i.e., consumed, administered, taken) with or without food or beverage intake.

[868] An essential element of the claims is that the oral dosage form can be taken with or without food or beverage intake. The goal of the invention is that it addresses the food effect and permits the patient to choose when and how to take the oral dosage of risedronate.

[869] Dr. Cremers identified eight essential elements of Claim 1 of the ‘188 (of which the first asserted claim set is based) noting that the first essential element is “an oral dosage from of a bisphosphonate for use with or without food or beverage, comprising… ” and the last essential element is “to provide pharmaceutically effective absorption of the bisphosphonate with or without food or beverage intake”.

[870] Dr. Yates stated that a dosage form that could be taken only without food, i.e., in the fasting state, would not fall within the scope of the claims. Dr. Yates noted that the choice of taking the product either with or without food at their preference is an integral part of the invention.

(2) The Jurisprudence Relied on by the Parties

[871] The jurisprudence relied on by the parties to support their respective positions is not on all fours with the claims at issue. The claims at issue cannot be labelled to fit within a particular line of cases or interpretive principles. The jurisprudence guides the Court to focus on the wording of the claims, as construed, and to determine whether the Apotex product falls within the asserted

claims. All the relevant evidence, in particular the proposed product monograph, must be considered in making this determination.

[872] The first asserted claim set is not a "product for use" claim in the sense that it claims a use to treat a particular condition. The use claims for the treatment of osteoporosis are a separate claim set. The first set of asserted claims address how the product is to be used. The manner of use is integral to the invention. The oral dosage form achieves pharmaceutically effective absorption whether taken fasted or fed. But the "claim to fame" is that it can be taken in either state at the preference of the patient. If it cannot be, then it does not fall within the claims.

[873] Apotex relies on the jurisprudence which dealt with claims that were for the use of an existing product to treat a new condition or disease, previously unclaimed. None of those cases, or any cases that the parties have referred to or the Court has found, use the term "product for use" to characterize the claims.

[874] In my view, the jurisprudence either relied on or distinguished by the parties is not analogous to the asserted claims at issue. The claims at issue are different. However, certain general principles can be drawn from the jurisprudence which can be applied.

[875] In *AB Hassle* the claim at issue was for a new use of an old drug, omeprazole, to treat a bacterial infection (campylobacter). The Court concluded that its use for other than campylobacter infections would not infringe the claim. The Court focussed on the claimed invention, which was

the new use. The Court found that it was not infringed by the generic's use of the old drug for its old use as indicated on the product label.

[876] Apotex submits that this is analogous as the use of APO-RISEDRONATE DR is not "for use with or without food or beverage…" and following *AB Hassle*, Apotex would not infringe. Allergan submits that *AB Hassle* is distinguishable because in the present case, the claim is for a novel product, not a "product for use".

[877] In *AB Hassle*, the Court noted at para 32, that the patent did not include any claims for the compound itself, only for its new use. The Court concluded at para 36:

> 36 For the applicants to successfully show that Apotex infringes claim 3, it is necessary for the applicants to demonstrate on the evidence that Apotex proposes to make and sell such a pharmaceutical preparation for use in the treatment of *Campylobacter* infections. In my view, the applicants have not shown on the evidence that Apotex intends to make, use or sell the pharmaceutical preparation for use in the treatment of *Campylobacter* infections.

[878] In my view, the claims in *AB Hassle* are not similar to the claims at issue. As noted by the Court, there were no claims for the compound, unlike the present case. The claim at issue in *AB Hassle* was only the use to treat a condition previously not claimed as a use. *AB Hassle* dealt with the more typical scenario of a claim for the new use of an existing compound or product.

[879] In *BMS 2017*, the claims at issue were also for a new use for an old product (aripiprazole), previously claimed for use to treat schizophrenia. The new use was to treat bipolar disorder. The generic alleged that it was not making aripiprazole for the treatment of bipolar disorder, but for its

original use for schizophrenia. The generic's proposed product monograph reflected that the use was restricted to schizophrenia. The Court found no evidence, other than speculation, that the generic would use the product for the new use and as a result, found no infringement by the generic. The Court noted at para 27, "[s]imply put, if Apotex [the generic] does not manufacture Apo-Aripiprazole for the claimed uses, but rather, manufactures Apo-Aripiprazole solely for the unclaimed use, there can be no direct infringement of claim 16."

[880] The claims at issue in *BMS 2017* were claims for the new use related to the treatment or condition, and not how the product was to be used.

[881] In *Novopharm Limited v Sanofi-Aventis Canada Inc*, 2007 FCA 167 [*Novopharm*], the Court of Appeal addressed whether the generic product infringed the claims for a new use for an existing product (ramipril). Ramipril had previously been approved for use in the treatment of hypertension. At the relevant time, there was no patent for ramipril itself, or for ramipril in the treatment of hypertension. Other uses had subsequently been claimed and approved. The generic, Novopharm, sought a Notice of Compliance for its generic version of ramipril only for its original use – to treat hypertension – and not for any of the new uses.

[882] The Court of Appeal found that the allegation of non-infringement was justified because the generic drug manufacturer was only seeking a Notice of Compliance for a use that was not within the new use claimed. The Court of Appeal also found that the generic would not induce others to infringe by prescribing or using the generic product for the new use.

[883] In *AB Hassle, BMS 2017* and *Novopharm*, although the claims at issue were for new uses (i.e., uses for the treatment of conditions not previously claimed) and were not the same type of claims at issue in the present case, the Court considered what the generic's product would be used for, with reference to the product monograph and other evidence, and whether that use fell within the claims. In my view, this is the common thread in the jurisprudence.

[884] Allergan argues that *Bayer (Nifedipine)* provides guidance for the analysis of the infringement of a product claim. Allergan submits that the instant oral release capsule at issue in *Bayer* (*Nifedipine*) was treated as a product claim as should the claims of the '188 Patent at issue.

[885] In *Bayer* (*Nifedipine*), the invention was an instant oral-release capsule of Nifedipine. The patent defined the instant oral-release capsule as "a capsule, having a shell, generally of gelatine, containing a fluid pharmaceutical composition which can be released from the shell by biting and breaking the latter." However, the claims only refer to the instant oral release capsule and the process to make it.

[886] Apotex, the generic in that case, asserted that the sales of its capsule, Apo-Nifed, were not made pursuant to its licence with Bayer because its capsules were intended only to be swallowed whole and not for instant oral-release by biting.

[887] The Court addressed, among other issues, whether the claims of Bayer's patent were infringed by Apotex. The Court characterized the claims at issue as product claims and found that

Apotex directly infringed the claims by making and selling Apo-Nifed. The Court noted at para 25:

> [25] Apart from the admission, there is ample additional evidence for this court to conclude that Apotex's drug does in fact fall within the claims of '582. Apotex argued that the product and process claims of '582 were restricted to use by biting for the treatment of angina pectoris whereas Apotex's drug is intended to be swallowed. Claims 1 and 14 of '582 are product claims. They describe a physical product. The product claims do not address how the capsule is to be used. They provide only that the capsule contain a composition which "can be released from the shell by biting and breaking the latter". What matters is not how Apotex's capsules are intended to be used but what Apotex's capsules are in fact. They are formulated such that they are in fact suitable for perlingual administration. Whether they are intended to be or are ultimately used in that manner is beside the point.

[888] The Court also noted that Apo-Nifed was lemon flavoured and there would be no reason to flavour the solution within the shell except to mask its taste when the capsule was bitten. The Court added, at para 45, that "[t]he intention to infringe or not to infringe is irrelevant in considering the question of infringement."

[889] I do not agree with Allergan that the claims in *Bayer (Nifedipine)* are analogous to the claims at issue. The patent at issue in *Bayer (Nifedipine)* had 28 claims. Claims 1-18 all refer to an instant oral release "capsule compris[ing] a shell of gelatin which contains a solution of…" or "an instant oral release capsule as defined in… [a previous claim]", with variations on the solution. Contrary to what the Court stated at para 25, none of the claims say anything about a capsule that contains "a composition which can be released from the shell by biting and breaking the latter". That may be in the disclosure of the patent, and the Court's construction may have referred to the

use by biting, but it is clearly not mentioned in any of the claims of that patent. Claims 1-18 are claims for the product which is the instant oral release capsule. Claims 19-28 are process claims.

[890] The Court in *Bayer (Nifedipine)* treated the claims as product claims because they were product claims. The claims did not restrict the use of the oral release capsule to biting. The Court's finding – that Apo-Nifed was suitable for the same use as claimed and that Apotex's intention about how its product be used was not relevant to infringement – is based on the wording of the claims – as products – and on the evidence which the Court relied on to find that Apo-Nifed fell within the claims.

[891] Allergan argues that approach of the Court in *Bayer* (*Nifedipine*) reflects the interpretive principle set out in *Fox*, that a product that is described as "for use" means "suitable for use", and Apo-Nifed was suitable for use, and as a result, how it was intended to be used was not relevant to the issue of its infringement. However, in *Bayer* (*Nifedipine*), the claims were simply for the instant oral release capsule. The claims did not even claim a use for treatment.

[892] In my view, *Bayer (Nifidepine*) is not analogous. The Court found on the facts of that case that the evidence established that Apo-Nifed was formulated to be "suitable for perlingual administration", but I do not agree that it established a general principle that any product that is suitable for the same manner of use (even where use is not part of the claim) would infringe. As noted above, Apotex does not dispute that its product will provide pharmaceutically effective absorption if taken either with food or without food. This acknowledgement does not mean that the essential elements of the claims can be ignored.

[893] Allergan also argues that the Court should consider what the claims are in fact, and that in the present case, the claims are product claims. However, the analysis of infringement begins with determining if the generic product includes all the essential elements of the claims. The wording of the claims must be considered. In the present case, "for use with or without food or beverage intake" appears twice in the key claim, the experts agree that this is an essential element of the claims, and the Court's construction reflects that this is an essential element.

[894] Although *Bayer (Nifedepine)* is not on point, it does reflect the general principles that the wording of the claims is the starting point for the analysis of infringement – to determine what is claimed in fact – and that all the relevant evidence must be considered to determine whether the generic's product falls within the claims.

[895] In *Janssen 2020,* the claim at issue was for a new dosing regimen, which was an injection into muscle tissue. The Court found direct infringement because the generic manufacturer's product monograph identified intramuscular injection as a possible route of administration in the "indications" section. The Court noted that even though the product monograph fell short of instructing to infringe, read in its entirety, it included information that taught that the generic product could be administered according to the new claimed dosing regimen.

[896] In *Janssen 2020,* the Court identified the essential elements of Claim 1 which included the dosing regimen. The Court concluded that the Teva product would incorporate all the essential elements of Claim 1. The Court agreed that the "capable, approved and intended use for the Teva

Product as specified in the Teva Product Monograph incorporates all dosing and administration elements".

[897] The Court stated, at paras 253- 254:

> [253] The Teva PM teaches that the prefilled syringes to be sold by Teva can be administered in combination according to the claimed dosing regimen. While this information may not rise to the level of "instructions to infringe" sufficient to induce practitioners to prescribe and use the syringes according to the claimed dosing regimen, it is sufficient to establish direct infringement of the product claims.
>
> [254] The Teva PM also teaches that its prefilled syringes can be administered according to other, non-infringing dosing regimens. However, Teva need not direct that the claimed dosing regimen is the only regimen, or even the recommended regimen, by which its syringes should be administered. Sale of prefilled syringes adapted for administration in accordance with the claimed dosing regimen, as taught in the Teva PM, will deprive Janssen of the full enjoyment of the 335 Patent monopoly (Monsanto, above, at para 34). Actual use of the syringes in accordance with the claimed dosing regimen is not required.

[898] While the claims in *Janssen 2020* are not the same as the claims at issue, there are more similarities than in the jurisprudence regarding infringement of claims for new uses for old products. In *Janssen 2020,* the Court noted that the claimed invention was a dosing regimen, "not simply a dosage form" (at para 147). The asserted claim set at issue in the present case is for an oral dosage form that is for use with or without food or beverage. However, in my view, whether the claims are labelled as a dosage form (a product) or a dosing regimen (which the Court in *Janssen 2020* found similar to a combination claim) or a "product for use", the issue remains whether the Apotex product falls within the essential elements of the asserted claims. In all the

cases cited, the Court has considered the product monograph and any other relevant evidence to determine if the generic product will be used for the same uses or in the same manner as the claims.

[899] In the present case, applying the approach in *Janssen 2020*, the question is whether Apotex's proposed product monograph for APO-RISEDRONATE DR indicates that it is a product that falls within the claims of the '188 Patent. The product monograph need not set out clear directions to infringe, but there must be some indication in the product monograph that the generic product can be used the same way as the claims of the '188 Patent. As noted below, there is no such indication in the proposed APO-RISEDRONATE DR product monograph.

(3) "Suitable For" Use

[900] The guidance from *Fox*, regarding the "normal" construction of "for" in a claim, does not assist Allergan in the present case.

[901] *Fox* states:

> "For" in a patent product claim is normally construed as meaning "suitable for". The effect of this interpretation of a product claim is that the claim extends to any product which is suitable for the stated purpose, whether or not it is in fact used or intended for use for such purpose.

[902] As noted, the asserted claims are not simply product claims. As construed, an essential element is that the oral dosage can be taken with or without food. Even if the term "for use with or without food…" is construed as "suitable for use with or without food…", the Apotex product is not suitable for that use, as clearly indicated in its proposed product monograph which replicates

that of ACTONEL DR. While it may result in pharmaceutically effective absorption if taken with or without food, and it is "suitable for use" to treat osteoporosis, it is clearly indicated as not suitable for use without food, due to the warnings about abdominal pain.

[903] I also note that the "normal" construction noted in *Fox* is subject to exceptions. In particular, *Fox* notes that "while 'for' in a patent product claim is normally read as 'suitable for' one has to be very cautious of any principle of construction which is said to codify the meaning of particular words."

[904] I understand this to reflect the need to first look at the claims and construe them in accordance with the principles of claim construction.

(4) The Product Monograph

[905] I have reviewed the ACTONEL and ACTONEL DR product monograph (a combination product monograph) and the APO-RISEDRONATE DR product monograph in their entirety. With respect to ACTONEL DR and APO-RISEDRONATE DR, the product monographs are almost identical.

[906] Under the heading "Warnings and Precautions", it is noted that "ACTONEL DR delayed release tablets are formulated to release in the small intestine to provide effective absorption of risedronate when taken as directed with breakfast". Under the heading "Drug-Food Interactions", the product monograph states "ACTONEL DR should be taken with food. When compared with ACTONEL 5 mg, treatment with ACTONEL resulted in a higher incidence of upper abdominal

pain when administered before breakfast under fasting conditions. For dosing information see DOSAGE AND ADMINISTRATION."

[907] Under the heading "DOSAGE AND ADMINISTRATION", the product monograph includes a list of six instructions. It notes that "ACTONEL DR should be taken in the morning, with breakfast, (this may include high fat foods…). A higher incidence of upper abdominal pain was seen when ACTONEL DR was taken in a fasted state before breakfast (see WARNINGS AND PRECAUTIONS…)". In addition, the section directs that the tablet be swallowed whole with sufficient plain water while the patient is upright, that the patient not lie down for at least 30 minutes, and that the tablet should not be chewed, cut or crushed, but should remain intact. Under the "Recommended Dose and Dosage Adjustment" section, it is noted that for all indications and doses, "the patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to the instructions."

[908] The Patient Medication Information (patient leaflet), under the heading "How to take ACTONEL DR", directs patients to take ACTONEL DR on the same day each week "in the morning with breakfast…" And "Do not take ACTONEL DR before food or on an empty stomach as it may cause abdominal pain". It adds that the tablet should be swallowed whole, with water, in an upright position and that the patient not lie down for 30 minutes.

[909] The product monograph repeatedly directs the patient to take the product with food, in particular breakfast, and to not take it on an empty stomach.

[910] Although Dr. Adachi opined that the product monograph supports the use of the oral dosage form for use both with and without food, he acknowledged that the dosing instructions focus on administration with food.

[911] Dr. Adachi acknowledged that he prescribes ACTONEL DR to be taken "around" breakfast. He adheres to the guidance of the product monograph except where a patient cannot take it with breakfast or where that patient had not experienced upper abdominal pain. This suggests that in most cases, he follows the guidance of the product monograph. The Osteoporosis Canada website, which reflects the product monograph, provides the same dosing instructions. Although an experienced physician may deviate from this guidance for particular patients, the main message is that ACTONEL DR (and APO-RISEDRONATE DR) should only be taken with food – i.e., with breakfast.

(5) The Product Monograph Does Not Indicate Use With Or Without Food

[912] The single sentence in the pharmacokinetics section of the product monograph, which is over one page in length, and which Dr. Adachi relies on to support this opinion, states, "[i]n a crossover pharmacokinetic study that evaluated the food effect, the bioavailability of ACTONEL DR 35 mg delayed-release tablets decreased by ~30 % when administered immediately after a high fat breakfast compared to administration 4 hours before a meal." This short reference is not sufficient to trump the clear dosing instructions that repeatedly state that the product should only be taken with food. While this information may reveal that there is improved bioavailability in the fasted stated and that the 30% reduction in the fed state may still provide treatment – i.e., there is pharmaceutically effective absorption – this is not helpful information to the prescribing physician

or the patient. Moreover, the physician is not likely to read the Patent to determine what was claimed, but will read the product monograph to inform themselves.

[913] As Dr. Yates noted, the reference to the crossover pharmacokinetic study is not part of the "Dosage and Administration" section, which is the part of the product monograph a physician and patient would look at to inform them of how to take the drug.

[914] Dr. Adachi acknowledged that the information on the Osteoporosis Canada website clearly states that ACTONEL DR should be taken "WITH breakfast" (emphasis in the original) with a full glass of water and the direction to remain upright for 30 minutes. Dr. Adachi explained that Osteoporosis Canada would not contradict product monographs, but on a day-to-day basis, patients would take it either with or without food first thing in the morning "around breakfast time" (either before, with or shortly after).

[915] I am not persuaded by Dr. Adachi's opinion that physicians treating osteoporosis would know that ACTONEL DR can be taken with or without food, as this is what the ACTONEL DR product monograph instructs and supports. While physicians may know this based on their own experience with particular patients, it is not supported by the product monograph.

[916] The experts all agree that whether taken with food or without, there will be pharmaceutically effective absorption. Apotex has conceded that its product will achieve pharmaceutically effective absorption. However, the dosing instructions do not give the patient a

real choice of when or how to take the medication. Neither ACTONEL DR nor APO-RISEDRONATE DR live up to the claims of the ‘188 Patent.

[917] Apotex’s disclosure to Health Canada regarding its request [redacted], based on the risks of exposing subjects to the risk of abdominal pain, may have [redacted]. However, this is an issue between Apotex and Health Canada. Apotex was granted [redacted] based on the risk of abdominal pain and based on labelling for use only with food.

(6) The Risk of Abdominal Pain

[918] Allergan’s submission that the risk of abdominal pain is not significant and does not deter treatment does not assist in addressing the issue of infringement. The evidence of the extent and nature of the risk of abdominal pain is mixed, but it all points to the risk of abdominal pain for some patients, to the extent that this is highlighted in both product monographs.

[919] Dr. Cremers agreed that upper GI side effects can be a problem for some patients but did not know if it was a major problem which resulted in the discontinuation of the medication. However, Dr. Cremers acknowledged that he coauthored a paper which states that upper GI side effects are the most common reason that patients are intolerant of oral bisphosphonates. He explained that the paper does not state that this is the reason a patient stopped treatment. I note that Dr. Cremers opinion is related to oral bisphosphonates more generally, not only risedronate.

[920] Dr. Adachi acknowledged that the skilled physician would understand that taking ACTONEL DR (or APO-RISEDRONATE DR) on an empty stomach could result in "slightly greater" upper abdominal pain. Dr. Adachi also agreed that taking the product with food "will lower the risk [of abdominal pain] by some amount for all patients".

(7) No Direct Infringement

[921] The Apotex product, APO-RISEDRONATE DR, does not fall within the scope of the asserted claims. Use with or without food at the choice of the patient is an essential element of the asserted claims. The Apotex product is not for use with or without food, rather it is restricted to use with food. Although the Apotex product would achieve pharmaceutically effective absorption if it were taken without food, it is not indicated for use without food. The product monograph clearly indicates this.

[922] Apotex's making, constructing and selling the oral dosage form as it proposes will not deprive Allergan of their exclusive rights and privileges arising from the Patent.

(8) No Inducement of Infringement

[923] Apotex will not induce infringement by others of the asserted claim set for use for the treatment of osteoporosis.

[924] In *Janssen 2020*, the Court addressed infringement by inducement noting, at paragraph 262, that the more recent jurisprudence has "scrupulously" applied the three part *Corlac* test. The Court noted at paras 265-266, with respect to the test, which is difficult to meet:

> [265] Where the Court has considered the test for inducement from *Corlac*, the outcome has turned on the specific references in the PM. In *Bayer*, while the PM stated that the generic company's moxifloxacin product was "compatible" with sodium chloride solutions, the PM actually recommended against the infringing co-administration of moxifloxacin and sodium chloride solutions. Conversely, in *Hospira* and *Janssen*, the PMs specifically recommended the infringing combination therapies.
>
> [266] Another important factor in all of these cases is the wording of the claims themselves. As noted by Justice Phelan in *Janssen*, to establish inducement, the alleged inducer must induce infringement of all essential elements of the asserted claims. Where the claims are directed towards a new use for a known compound, the PM must directly or indirectly instruct the new use in order to establish inducement. Similarly, where the patent claims the use of a combination, the PM must direct the infringer to use the combination in order to establish inducement.

[925] The Court noted at para 267 that the claim at issue was directed to a dosing regimen, which it found analogous to a combination. The Court applied the three part *Corlac* test, noting that the second prong was the key aspect (the "but for" test). The Court found that the proposed product monograph made more than just a subtle reference to the infringing dosing regimen, rather it was one of the recommended dosing regimens. However, the Court concluded that Teva would not induce infringement. Based on the product monograph and the evidence of the experts regarding the practices of physicians, including that they consider individual patient characteristics and do not consult generic product monographs, the Court found that infringement would not be influenced by Teva's (the generic) product monograph.

[926] Although some physicians may advise their patients – contrary to the product monograph's clear instructions – to take the product without food, this does not establish infringement by Apotex. If a physician, like Dr. Adachi, prescribes ACTONEL DR for use without food, the Apotex product monograph has not influenced that decision. If Apotex were aware of this "off label" prescribing, Apotex is not knowingly inducing such a practice.

[927] In the present case, applying the *Corlac* test, it is apparent that the Apotex product monograph clearly directs that its product only be taken with food. It is not knowingly influencing a physician to prescribe APO-RISEDRONATE DR or a patient to use it with or without food. To the contrary, it is cautioning physicians and users to take it only with food.

[928] Taking into account the clear wording of the proposed APO-RISEDRONATE DR product monograph, which instructs that the product only be taken with food and cautions against taking it without food, and the evidence of the experts, including that the physician would prescribe the brand product, and as a result, the product monograph of the generic would not influence that practice, Apotex cannot be found to induce infringement of the asserted claims.

[929] Dr. Yates opined that Apotex will not induce infringement of the use claims (the use for the treatment of osteoporosis) because the oral dosage form does not fall within the claims of the '188 Patent. Dr. Yates noted that the Apotex product monograph does not instruct or advise patients to take the product either with or without food, at their preference, rather it instructs patients and physicians to do the opposite – to only take APO-RISEDRONATE DR with food.

[930] With respect to prescribing medication, Dr. Adachi explained that a physician would prescribe the brand name of the drug (i.e., ACTONEL DR) as opposed to a generic product, although the pharmacist may provide the generic version. Therefore, the APO-RISEDRONATE DR product monograph will not influence physicians in how they prescribe the brand, ACTONEL DR.

XIII. Costs

A. *The Parties' Submissions*

[931] The parties made submissions with respect to costs before the Court issued this Judgment.

[932] The parties agree on the principles governing the Court's discretion to award costs and both point to recent jurisprudence regarding the trend to award lump sum costs, particularly in complex matters, including actions pursuant to the *PMNOC Regulations* (for example, *Apotex Inc v Shire LLC*, 2021 FCA 54 at paras 16-24 [*Shire*]; *Allergan Inc v Sandoz Canada Inc*, 2021 FC 186 at paras 19-28 [*Allergan*]; S*eedlings Life Science Centures, LLC v Pfizer Canada ULC*, 2020 FC 505 at paras 2-7 [*Seedlings*]).

[933] Both parties supported their cost submissions with affidavits and exhibits, which establish, among other things, the hourly rate of counsel and their years of experience, the time spent by counsel, paralegals and others, the fees paid to experts, and the other disbursements incurred. The Court is satisfied that the documented fees and disbursements have been incurred and are

reasonable in the circumstances, given, among other things, the complexity of this litigation, the importance of the issues to both parties, and the engagement of many experts.

[934] Allergan submits that if it is wholly successful, it should receive a lump sum award representing 45% of the actual fees it has incurred plus 100% of its disbursements. Allergan alternatively submits that if Apotex is successful on one or more issues (i.e., it does not infringe and/or the '188 is invalid), Apotex should receive a lump sum award of 30% of its fees and 100% of its disbursements (excluding fees and disbursements related to Dr. Leslie Z. Benet).

[935] Allergan points to recent jurisprudence noting that lump sum awards may range from 25% to 50% of actual fees incurred. Allergan argues that Apotex, if successful, should not benefit from a lump sum award at the higher end of the range due to its conduct in this litigation. Allergan points to, among other things: Apotex's eleventh hour change in approach on several issues resulting in wasted preparation time by Allergan; Apotex's failure to accept the qualifications of Allergan's expert witnesses; and, Apotex's mid-trial objection to read-ins, subsequently withdrawn. Allergan also notes Apotex's conduct in [redacted], regarding Apotex's submission to Health Canada that [redacted]. Allergan also takes issue with Apotex's innuendos regarding the Takeda patent, which border on allegations of fraud.

[936] Apotex submits that the successful party should be awarded a lump sum of 25% of its reasonable legal fees plus 100% of its reasonably incurred disbursements.

[937] Apotex notes that it has excluded all costs related to the expert report of Dr. Benet, which was withdrawn shortly before trial.

[938] In anticipation of Allergan's possible arguments regarding Apotex's conduct, Apotex submits that both parties contributed to wasted time and effort and that the Court should not wade into apportioning blame. Apotex notes for example, that Allergan narrowed the asserted claims late in the litigation, disputed that BR 601 was publicly disclosed, and maintained an untenable interpretation of "with or without food or beverage intake".

B. *Costs to the Successful Party*

[939] In *Allergan*, the Chief Justice noted that the general rule is that the successful party is entitled to its costs, even if not successful on each and every argument.

[940] The Chief Justice noted, at para 31, that there were two lines of cases on the issue of "whether the successful defence of a patent infringement action, or success with respect to only some grounds of invalidity, constitutes "divided success" when the defendant in the main action is not successful with respect to one or more other allegations of invalidity". The Chief Justice noted that he was bound by the line of cases from the Court of Appeal, explaining:

> In a second line of cases, it has been explicitly held that this type of outcome does not constitute "divided success" or "mixed results" and that therefore the defendant is entitled to its costs: *Raydan*, above; *Illinois Tool Works Inc v Cobra Anchors Co*, 2003 FCA 358 at paras 10-11; *Betser-Zilevitch v Petrochina Canada Ltd*, 2021 FC 151 at para 11 [*Betser-Zilevitch 2*]; *Johnson & Johnson Inc v Boston Scientific Ltd*, 2008 FC 817 at para 4. This is so regardless of whether the defendant's allegations of invalidity were made in a defence to the main action or in a separate

> Counterclaim: *Raydan*, above, at paras 6-7; *Eurocopter FC*, above, at para 11. Notwithstanding my sympathy for the approach taken in the first line of cases, I consider myself bound by this second line of cases.

[941] In the present case, I acknowledge that Allergan successfully defended many allegations of the invalidity of the '188 Patent and a significant portion of its costs was devoted to these allegations. The '188 Patent is valid, however, the Apotex product does not infringe. If not for the jurisprudence that is binding on me, I would characterize the outcome as "divided success". However, Allergan initiated this Action for infringement and did not establish infringement. Apotex is the successful party and is entitled to costs.

[942] In the present case, both parties support the award of a lump sum. As noted above, the trend in the jurisprudence favours a lump sum cost award particularly in "complex litigation conducted by sophisticated parties" (*Seedlings* at para 4). Both parties were well matched in terms of expertise and "sophistication", had comparable teams and pursued this litigation with vigour to advance their respective positions. Both parties' fees and disbursements are comparable. The fees and disbursements are also comparable to those in similar recent litigation.

[943] With respect to the appropriate amount of a lump sum award, in *Shire*, the Court of Appeal noted the need for predictability in the range of lump sum awards (at para 24). The Court of Appeal acknowledged, at para 22, that the jurisprudence reflected awards ranging from 10% to 50% of actual fees, but found that awards between 25% and 33% are the norm, and greater amounts are exceptional.

[944] As noted, Allergan submits that if Apotex is successful, Apotex should be awarded a lump sum of 30% of its reasonable fees plus 100% of its disbursements. Apotex seeks less – that if successful, it should receive a lump sum of 25% of its costs.

[945] A lump sum award of 25% of Apotex's actual fees incurred falls well within the normal range recently clarified by the Court of Appeal and no greater amount is sought or would be justified.

[946] Apotex has established that its fees are $4,447,981.75. A lump sum award of 25% amounts to $1,111,995.44 for fees. Apotex has also established that it incurred disbursements (less those associated with Dr. Benet's report) of $492,420.64. As a result, Apotex is entitled to costs in the amount of $ 1,604,416.08.

JUDGMENT

THIS COURT'S JUDGMENT is that:

1. The Plaintiffs' infringement action against the Defendant with respect to Canadian Patent 2,602,188 is dismissed.
2. The asserted claims of Canadian Patent 2,602,188 are not invalid due to anticipation, obviousness, inutility, insufficiency of disclosure or overbreadth.
3. Allergan shall pay to Apotex a lump sum representing 25% of Apotex's fees and 100% of Apotex's disbursements, which in total amount to $ 1,604,416.08.

"Catherine M. Kane"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-794-19
STYLE OF CAUSE:	ALLERGAN INC. AND ALLERGAN PHARMACEUTICALS INTERNATIONAL LIMITED v APOTEX INC.
PLACE OF HEARING:	TORONTO, ONTARIO
DATE OF HEARING:	FEBRUARY 1-12, MARCH 2-3, 2021
CONFIDENTIAL JUDGMENT AND REASONS:	KANE J.
DATED:	FEBERUARY 23, 2022

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