CITATION: Wise v. Abbott Laboratories, Limited, 2016 ONSC 7275
COURT FILE NO.: CV-16-550747CP
DATE: 20161123

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:	
NORMAN DOUGLAS WISE and MONIKA ELISABETH WISE Plaintiffs	*Michael Peerless, Sabrina Lombardi,* and *Eli Karp* for the Plaintiffs
– and –	
ABBOTT LABORATORIES, LIMITED, ABBOTT PRODUCTS INC. (f/k/a SOLVAY PHARMA INC. and SOLVAY PHARMA CLINICAL INC.), ABBOTT PRODUCTS CANADA INC. (f/k/a SOLVAY PHARMA CANADA INC.), and ABBVIE PRODUCTS LLC (f/k/a ABBOTT PRODUCTS LLC, f/k/a ABBOTT PRODUCTS, INC., f/k/a SOLVAY PHARMACEUTICALS, INC.) Defendants	*Neil Finkelstein, Brandon Kain, Byron Shaw,* and *Breanna Needham* for the Defendants
Proceeding under the *Class Proceedings Act, 1992*	**HEARD**: September 21, 22, 23, 26, 27, and 28, 2016

PERELL, J.

REASONS FOR DECISION

A. INTRODUCTION

[1] Pursuant to the *Class Proceedings Act, 1992*, S.O. 1992, c. 6, Norman Douglas Wise and his wife, Monika Elisabeth Wise, bring a proposed class action against Abbott Laboratories, Limited, Abbott Products Inc., Abbott Products Canada Inc., and Abbvie Products LLC (collectively, "Abbott").

[2] Abbott, which is a pharmaceutical company, manufactures a topical ointment known as AndroGel^{TM} as a treatment for hypogonadism, which is medical problem for males. Hypogonadism is indicated by low testosterone levels ("LowT") and the presence of a variety of symptoms.

[3] The Wises bring a products liability class action against Abbott. The Wises' principal allegation is that AndroGel^{TM} causes serious cardiovascular events (sometimes referred to as serious CV events), such as heart attacks (myocardial infarction or "MI") and strokes.

[4] Another major allegation made by the Wises is that AndroGel^{TM} was sold as a remedy for "LowT," which they allege is a fabricated disease made up by Abbott to sell more of its product. The Wises allege that Abbott marketed AndroGel^{TM} to aging men as a cure for feeling sad or grumpy, deterioration in the ability to play sports, falling asleep after dinner, decreased libido and decreased sexual performance, but they say LowT is not a disease and that the aging men who purchase AndroGel^{TM} to ameliorate the naturally occurring decline in testosterone, purchased a useless product and unnecessarily placed themselves at an increased risk of harm. The Wises allege that in selling AndroGel^{TM} for LowT, Abbott was "disease mongering," the selling of a drug that offers no therapeutic benefits, and, therefore, the Wises submit that Abbott has been unjustly enriched and should compensate the Class Members for their pure economic losses. The Wises also assert a waiver of tort claim.

[5] Abbot denies all claims of negligence. Abbott submits that LowT is a type of hypogonadism; i.e., Abbott disputes that it is selling AndroGel^{TM} to non-hypogonadal men, which is what, in effect, the Wises allege. Abbott argues that there is no basis for the Wises' tort claim for pure economic losses.

[6] Although the Wises' action has not yet been certified as a class action, Abbott brings a summary judgment motion to have the action dismissed.

[7] In its factum, Abbott submits that the Wises' negligence claims should be dismissed for four reasons: (1) because the Wises cannot prove general causation which is a constituent element in all of the claims; (2) because there is no evidence of negligence in design; (3) because the Wises cannot establish a breach of a duty to warn; and, (4) because there is no evidence to support the allegation that Abbott marketed AndroGel^{TM} for off-label uses. Abbott makes other attacks against the Wises' claim, and it submits that the failure of the negligence claims entails the failure of the Wises' unjust enrichment and waiver of tort claims.

[8] In response to the summary judgment motion, the Wises, who do not bring a cross-motion for summary judgment, submit that the case is not appropriate for a summary judgment - for Abbott - but they submit that the case would be appropriate for a partial summary judgment - for them - with the result that three of the five certification criteria would be satisfied (cause of action, a common issue, and representative plaintiff criteria). In other words, the Wises submit that they should be granted a partial summary judgment and that their action should move on to certification and to a common issues trial of the remaining common issues followed by assessments of damages for individual Class Members.

[9] The parties filed more than 11,000 pages in materials for the summary judgment motion, including affidavits and exhibits and transcripts (approximately 7,200 pages), factums (292 pages) and case authorities (4,025 pages). There was six days of oral argument.

B. OVERVIEW

[10] For the reasons that follow, I grant Abbott a summary judgment dismissing the Wises' action. My ultimate conclusion is that there is no genuine issue requiring a trial about general causation, which was not proven.

[11] The Wises were successful in proving that there is an "association" between AndroGel™ and serious cardiovascular events, which is to say that AndroGel™ and serious cardiovascular events occur together more frequently than one would expect by chance. Proof of association, however, is not proof of causation because there might be explanations other than cause for why AndroGel™ and serious cardiovascular events occur together more frequently than one would expect by chance.

[12] Whether AndroGel™ can cause serious cardiovascular events was neither proven nor disproven and remains to be determined. The Wises had a difficult epidemiological problem to analyze because testosterone naturally decreases as men age and old men do have heart attacks regardless of their level of testosterone. It is debated whether restoring testosterone levels increases or decreases the likelihood of a serious cardiovascular event. It remains to be determined whether the association (a type of connection) between AndroGel™ and serious CV events is a matter of cause and effect (general causation) or is matter of chance (sometimes called random error), bias (errors in the design and implementation of the epidemiological studies), or confounding (explained below).

[13] As I shall explain below, the Wises proved that it is possible that AndroGel™ might be a possible cause of serious cardiovascular events. The simultaneous occurrence of AndroGel™ and cardiovascular events might be explained - but is not necessarily explained - by AndroGel™ causing serious cardiovascular events. However, the Wises' failed to prove general causation. The point is subtle, but all that the Wises proved was the possibility of a possibility. However, the possibility of a possibility that AndroGel™ could cause a serious cardiovascular event is not proof of general causation because, as a legal matter, it is not proof on the balance of probabilities.

[14] Based on the evidentiary record now before the court, it cannot be said that Mr. Wise, who was prescribed AndroGel™ and who subsequently had a heart attack, has proved "general causation"; which is to say that he failed on the balance of probabilities to prove that AndroGel™ could be a cause of his heart attack. Thus, there is no genuine issue requiring a trial that general causation was not proven. Mr. Wise's negligence action must be dismissed because he failed to prove causation, which is a constituent element of his negligence claims.

[15] I pause here to foreshadow that in arguing that Mr. Wise failed to prove general causation and that there was no breach of a manufacturer's duty to warn, Abbott relied on the legal-epidemiological methodology employed by Justice Lax in *Andersen v. St. Jude, Medical Inc*., 2012 ONSC 3660. However, while the *Andersen v. St. Jude, Medical Inc.* decision is ultimately not harmful to Abbott's argument, Abbott misunderstands Justice Lax's treatment of material risk and her use of statistics and epidemiology.

[16] The Wises' failure to prove general causation leads also to the dismissal of the failure to warn claim. Once again, the explanation for the dismissal of his claim is subtle. About the duty to warn, Abbott argued that there can be no duty to warn based on the proven association between AndroGel™ and serious cardiovascular events and that there was no evidence that it breached any duty to warn. I disagree with this argument.

[17] In my opinion, an association between a danger and a product may give rise to a duty to warn even if the association cannot be characterized as a causal association. Notwithstanding Abbott's arguments, I conclude that there was a duty to warn in the immediate case based on the association between AndroGel™ and serious cardiovascular events. However, whether that duty

to warn had been breached by Abbott, would involve an analysis of the standard of care and the adequacy of the warnings that Abbott included in its product monograph. On this summary judgment motion, the evidence and the analysis did not go that far, although the trend of the evidence, which showed compliance to regulatory standards, tended to favour Abbott. The primary reason that the Wises' failure to warn claim fails is assuming a breach of the standard of care, Mr. Wise's claim fails just because of his failure to prove general causation. A failure to warn that causes no harm is not culpable negligence; no causation of harm, no fault.

[18] As for the Wises' claims for unjust enrichment, pure economic losses, or waiver of tort, these claims also fail. These claims are based on the allegation that AndroGel^{TM} is a worthless, non-beneficial product, and a dangerous one not worth the risk of being consumed. Mr. Wise submits that he has proven that AndroGel^{TM}, which is a dangerous drug (the product monograph does point out several dangers), is misleadingly sold for uses for which it is ineffective and for which it provides no benefit, and, thus, he and the Class Members have a legally viable claim for pure economic loss in tort or for unjust enrichment or for waiver of tort in restitution. In the discussion below, I will explain that these submissions are mistaken for several factual and legal reasons.

[19] To arrive at the above conclusions, there is a great deal of complicated factual and legal material to cover, and there are some difficult ancillary legal and evidentiary problems.

[20] In the discussion below, in addition to addressing important issues about products liability claims, the use of epidemiological evidence, causation, and unjust enrichment, I shall also address several important evidentiary and procedural issues. The evidentiary issues were associated with the testimony of expert witnesses. There was a question about how to treat the evidence of most of the expert witnesses who were accused of partisanship (non-independence, conflicts of interest, bias and impartiality). There was a question about what to do with the circumstance that the number of Abbott's expert witnesses exceeded the number that, under s. 12 of the *Evidence Act*, R.S.O. 1990, c. E.23, may testify without the leave of the court. As a procedural matter, there was a question about whether the summary judgment motion was appropriate for a judgment and about whether it was in the interests of justice that there should be a trial to determine the general causation issue and the other constituent elements of the Wises' claims.

C. EVIDENTIARY BACKGROUND

1. The Witnesses

[21] Abbott Laboratories supported its summary judgment motion with affidavits from:

- Dr. Abraham Morgentaler, sworn September 28, 2015, April 19, 2016, May 9, 2016, and August 22, 2016. He delivered four reports. Dr. Morgentaler was cross-examined.
- Dr. William J. French, sworn September 22, 2015, May 10, 2016, and August 22, 2016. He delivered three reports. Dr. French was cross-examined.
- Dr. Gerald Brock, sworn September 28, 2015, May 9, 2016, and August 22, 2016. He delivered three reports. Dr. Brock was cross-examined.
- Dr. David Greenberg, sworn September 25, 2015, May 9, 2016, and August 22, 2016. He

delivered three reports. Dr. Greenberg was cross-examined.

- Dr. Laurentius Marais, sworn September 28, 2015, April 18, 2016, and August 22, 2016. He delivered three reports. Dr. Marais was not cross-examined.
- Dr. Joel Heidelbaugh, sworn August 22, 2016. He delivered one report. He was not cross-examined.
- Anne Tomalin, sworn September 26, 2015 and April 18, 2016. She delivered two reports. Ms. Tomalin was cross-examined.
- Sylvie Brillon, sworn, February 26, 2015. Ms. Brillon was cross-examined.
- Katherine Stubits, sworn September 19, 2016. Ms. Stubits was not cross-examined.

[22] Dr. Morgentaler, is an urologist. He is Associate Clinical Professor of Surgery (Urology) at Harvard Medical School, from which he received his B.A. (biology) and his M.D. He has been involved in testosterone research since 1976. In his 25 years of practice, he has treated several thousand men suffering from testosterone deficiency. He described himself as one of the earliest physicians in the modern era to treat substantial numbers of patients with testosterone for the condition of testosterone deficiency, also called hypogonadism. He is a member of the American Urological Association, the International Society for Sexual Medicine, the International Society for the Study of the Aging Male, and the International Consultation in Sexual Medicine. He served as chairman of the first international Expert Consensus Conference on Testosterone Deficiency. Over the last two years, he has focussed his research on the issue of whether testosterone replacement treatment causes cardiovascular (CV) events or increases CV risk. He represented the American Urological Association at the March 2016 annual meeting of the European Association of Urology where he lectured on testosterone therapy.

[23] Dr. French is a cardiologist with over 40 years of practice. He is Professor of Medicine at the David Geffen School of Medicine at the University of California, Los Angeles ("UCLA"). He is a graduate of the University of New Hampshire (B.Sc., chemistry) and of University of Vermont School of Medicine (M.D.) and he is a board certified physician in cardiovascular diseases and interventional cardiology. He has written extensively on serious cardiovascular events in peer reviewed publications. He is the Director of the Cardiac Catheterization Laboratory at the Harbor-UCLA Medical Center, which has a celebrated record of research studies in cardiology. He was co-author of a comprehensive review article entitled "Testosterone and the Cardiovascular System", which was published in the *American Heart Association Journal* in 2013. He was a member of the two-person Data Safety Monitoring Board for a randomized controlled trial studying the effects of testosterone on atherosclerosis in aging men, the results of which were recently published in the *Journal of the American Medical Association* ("*JAMA*").

[24] Dr. Brock is an urologist with over 25 years of practice. He is a graduate of McGill University (B.Sc., physiology and M.D.) and is a Professor in the Department of Surgery, Division of Urology at the University of Western Ontario and Program Director for the Urology Residency Training Program at the university. He was the Secretary of the Sexual Medicine Society of North America and the Vice President (now President) of the Canadian Urology Association. He is the Scientific Chair of the Society for the Study of the Aging Male and has served as Chair of the Canadian Male Sexual Health Council. In his clinical practice, he sees 25-50 new patients monthly for complaints of testosterone deficiency. He runs a clinical research

program, which focuses on various disease states leading to sexual dysfunction, including testosterone deficiency.

[25] Dr. Greenberg is a family physician with over 25 years of practice. He is a graduate of the University of Western Ontario (M.D.). He serves on the staff of St. Joseph's Health Centre in Toronto and is a lecturer in the Department of Family and Community Medicine at the University of Toronto. He is a member of the Board of the Canadian Society for the Study of the Aging Male, which, among other things, educates Canadian physicians on low testosterone medical conditions. He is a director of the Canadian Men's Health Foundation, a non-governmental organization ("NGO") dedicated to heightening awareness and providing education to Canadian men to improve their health. He is a founding member of the American Society for Men's Health. Dr. Greenberg also edits the Men's Health Guidelines for Family Medicine.

[26] Dr. Marais is a mathematician specializing in statistics. He is a graduate of Stellenbosch University (B.Sc., mathematics and computer science) and Stanford University (M.Sc., statistics, M.Sc., mathematics, PhD., business administration and mathematics). He is the Vice President and Principal Consultant at William E. Wecker Associates, Inc., and he specializes in analyzing biostatistical and epidemiological data concerning the rates of and risk factors for health effects, including the adverse events associated with pharmaceutical medicines. He is a fellow of the Royal Statistical Society and a member of the American Statistical Association and the Society for Industrial and Applied Mathematics.

[27] Dr. Heidelberg is a family physician and a professor at the University of Michigan Medical School. He received his M.D. from the Upstate Medical University in Syracuse, New York, in 1996. Since 1999, he has been on the faculty in the Department of Family Medicine at the University of Michigan and since 2000, he has practiced family medicine at the Ypsilanti Health Center in Ypsilanti, Michigan. Neither party referred to Dr. Heidelberg's report, and for the purposes of these Reasons for Decision, I have ignored his report and did not read it.

[28] Ms. Tomalin is a graduate of York University, and holds a B.A. in English (1970) and a B.Sc. in chemistry (1980). She received a Regulatory Affairs Certification from the Regulatory Affairs Professional Society for U.S. Regulatory Affairs (1997), European Regulatory Affairs (2001), and Canadian Regulatory Affairs (2005). She is the President and Founder of TPIreg, a consulting company that provides training services to pharmaceutical companies in regulatory affairs. She has worked in-house at pharmaceutical companies (not Abbott or any of its predecessors). She teaches Regulatory Affairs at Humber College in Toronto. She served on the executive of the Pharmaceutical Sciences Group (PSG) and the Canadian Association of Professional Regulatory Affairs (CAPRA), which are industry associations focusing on regulatory issues.

[29] Ms. Brillon was formerly the Senior Manager, Regulatory Affairs & Quality Assurance at Abbott, where she began her career in 1992 after receiving her M.B.A. from McGill University and a B.A. (chemical engineering) from the École Polytechnique in Montréal.

[30] Ms. Stubits is a law clerk at McCarthy Tétrault, counsel for Abbott. She filed an affidavit that contained copies of the reports and medical literature referred to by Drs. Morgentaler, French, Brock, Greenberg, and Marais and by Ms. Tomalin.

[31] The Wises resisted the summary judgment motion with affidavits or expert's reports

from:

- Norman Wise, affidavit sworn January 12, 2016. Mr. Wise was cross-examined.
- Dr. Barbara Mintzes, affidavits sworn January 12, 2016 and April 16, 2016. Dr. Mintzes delivered two reports. Dr. Mintzes was cross-examined.
- Dr. William Milne, affidavit sworn July 14, 2016. He delivered one report. Dr. Milne was cross-examined.

[32] Dr. Mintzes is a graduate of Simon Fraser University (B.A., geography, biology) and the University of British Columbia (M.Sc., healthcare and epidemiology, PhD, healthcare and epidemiology). She is an Affiliate-Associate Professor with that university's School of Population and Public Health, and she is also a senior lecturer at the Faculty of Pharmacy and Charles Perkins Centre at the University of Sydney, Australia. The Charles Perkins Centre is a multi-disciplinary research centre with a focus on obesity, diabetes, and cardiovascular disease and Dr. Mintzes works in a unit that focuses on research integrity. Her areas of specialization are drug safety and effectiveness and the influence of pharmaceutical promotion on medicine use. Previously, she was an Assistant Professor with the Department of Anesthesiology, Pharmacology and Therapeutics at the University of British Columbia. Since 1999, she has worked with the University of British Columbia-based research group, the Therapeutics Initiative, which group has the aim of providing physicians and pharmacists with information on prescription drug therapy. She has been lead researcher on approximately 30 systematic reviews of the clinical trial evidence on efficacy and safety of newly approved prescription medicines for the British Columbia Minister of Health and the Common Drug Review. Her areas of teaching interest include pharmaceutical policy, pharmaceutical regulation, systematic review, critical appraisal of clinical trials, risk assessment, ethics of interactions between professionals and the pharmaceutical industry, and public health. She has been a peer reviewer for over 65 periodicals including *British Medical Journal, Canadian Medical Association Journal, Journal of the American Medical Association, Lancet, McGill Journal of Law and Health, PLOS ONE,* and the *New England Journal of Medicine.*

[33] Dr. Milne is an emergency physician and is a strong proponent of the practice of what is known as evidence based medicine ("EBM"). He is a graduate of the University of Calgary (M.D.) and has a B.Sc. (physiology) and M.A. (physiology) from the University of Western Ontario. He is the Chief of Emergency Medicine and Chief of Medical Staff for the South Huron Hospital Group, a small hospital (19-bed) in Exeter, Ontario. He is an academic clinician with two adjunct appointments from the University of Western Ontario, one in the Department of Family Medicine and the other in the Department of Medicine/Division of Emergency Medicine. He has been involved in research for more than 31 years with a particular interest in the critical appraisal of medical literature as part of the EBM movement, which he practices and teaches. He has published extensively in peer-review publications with over 100 publications and abstracts. He is a faculty member of the Best Evidence in Emergency Medicine group, at McMaster University, where his responsibilities have included structured critical reviews of medical literature, covering a broad range of medical specialities.

2. The Alleged Partisanship of the Experts

(a) Introduction

[34] The *Rules of Civil Procedure* set out the duty of an expert. Rule 4.1 states:

> *Duty of Expert*
>
> 4.1.01 (1) It is the duty of every expert engaged by or on behalf of a party to provide evidence in relation to a proceeding under these rules,
>
> (a) to provide opinion evidence that is fair, objective and non-partisan;
>
> (b) to provide opinion evidence that is related only to matters that are within the expert's area of expertise; and
>
> (c) to provide such additional assistance as the court may reasonably require to determine a matter in issue.
>
> *Duty Prevails*
>
> (2) The duty in subrule (1) prevails over any obligation owed by the expert to the party by whom or on whose behalf he or she is engaged.

[35] Both parties made aggressive arguments to disqualify and discredit their opponent's expert witness for breaching the duties of an expert.

[36] As I shall explain in this section of my Reasons for Decision, although there is some factual traction to these arguments, ultimately, the respective arguments are misconceived and they fail. The evidence of both sides' experts is admissible and their evidence will be judged based on its persuasiveness and not discounted on account of the witness's alleged impartiality.

(b) The Allegations that the Experts were Partisan

[37] As a factual matter, there is some traction to the respective allegations that the litigants' experts were not fair, objective, and non-partisan. (There were also allegations of want of competence, which I did not think had any merit.)

[38] The Wises submit that all of Abbott's experts are biased and partisan and that their evidence should be given little weight. They submit that Abbott's experts are not objective, independent, and non-partisan and rather are connected with industry-affiliated groups. The Wises submit that the experts' support for AndroGel™ was self-interested.

[39] About the alleged partisanship or non-independence of Abbott's expert witnesses, it is true that various testosterone manufacturers, including Abbott, have paid Dr. Morgentaler for clinical trial research, consulting and feedback on scientific advisory boards. It is also true that pharmaceutical companies that sell testosterone products or that are developing testosterone products have sought Dr. Morgentaler's expertise, and as disclosed in his expert's report, he has served as a paid consultant for pharmaceutical companies and as a member of scientific advisory board committees. It is a fact that Dr. Morgentaler advocates the use of testosterone replacement for what the Wises submit is the prescribing of testosterone for non-hypogonadal men and disease mongering, but which Dr. Morgentaler describes as a treatment for hypogonadism. Dr. Morgentaler's advocacy for testosterone replacement was advanced at an open meeting of the

United States Food and Drug Administration's advisory panel looking into testosterone and cardiovascular harms. He wrote a book entitled: *Testosterone for Life: Recharge your Vitality, Sex Drive, Muscle Mass and Overall Health*. He founded the Androgen Group, which issued press releases and petitioned journals to retract articles about risks associated with testosterone treatment, which risks he regarded as unsubstantiated.

[40] It is also fair to say that Dr. Morgentaler, Dr. Greenberg, and Dr. Brock are promoters of the use of testosterone products for aging males. In his book, Dr. Morgentaler stated that if a man presents with symptoms of low testosterone, he deserves a trial of testosterone therapy.

[41] As noted above, Dr. Greenberg is the president of what was formerly known as the Canadian Andropause Society and, as will be noted below, "andropause" is a contentious issue in the medical science community and connotes the idea of male menopause, the existence of which is strenuously disputed. Dr. Greenberg is a founding member of the American Society for Men's Health and the president of the Canadian Society for the Study of the Aging Male ("CSSAM") formerly known as the Canadian Andropause Society, and he chaired a panel that developed guidelines for primary care issues pertaining to men's health, of which testosterone deficiency was one. Although Abbott had no role in the development of these guidelines, which were drafted and commented on by expert clinicians in active practice, it agreed to sponsor the distribution of the guidelines to Canadian physicians after funding was sought from various sources. It is also true that Dr. Greenberg was invited to and attended three AndroGel™ advisory board meetings (the last in 2012) for which he received honoraria between $1,500 and $2,500 per meeting for time away from his practice. Dr. Greenberg also presented two accredited continuing health education talks to pharmacists on testosterone deficiency and received reimbursement from Abbott for travel and lodging to attend three educational meetings. With the financial support of Abbott, Dr. Greenberg attended meetings of the American Urologic Association, the International Society for Pharmacoeconomics and Outcomes Research (in Milan, Italy), and the International Society for Men's Health (in Nice, France).

[42] Dr. Brock is the treasurer of the International Society for Sexual Medicine ("ISSM"), and it is true that in in campaigning for this position he stated that close ties to industry was essential. As an expert in hypogonadism, Dr. Brock was asked to attend or chair several AndroGel™ advisory board meetings (first in 2005 and the last in 2013), and one of the topics discussed at the meetings was how to increase the sales of the drug. Dr. Brock received honoraria of approximately $2,500 to $3,500 per meeting to compensate for his time away from clinical practice. The total honoraria Dr. Brock received was in the range $11,500 to $13,500 over an eight-year period. Various testosterone manufacturers, including Abbott's competitors (but not Abbott), and non-industry sources have funded the clinical trials conducted by Dr. Brock. The funding is paid to the Western University, Department of Surgery, and Dr. Brock receives no personal compensation for any grant money for clinical trials; all the money goes to cover clinical trial costs for Dr. Brock's experiments.

[43] It is true that Dr. French received industry grants for the costs of clinical trial research conducted through the laboratory arm of his practice at UCLA. In 2013 and 2014, he received in excess of half a million dollars in grants from pharmaceutical and medical device companies. However, Dr. French has never personally received compensation of any kind from testosterone manufacturers for any of his clinical or research work on testosterone deficiency and testosterone replacement treatment.

[44] It is true that Dr. Marais is a professional witness in the sense that he has been frequently retained to provide opinions for pharmaceutical and tobacco manufacturers.

[45] It is true that Ms. Tomalin's career is about providing regulatory advice to pharmaceutical and medical device manufacturers and she has frequently been retained as a professional witness for pharmaceutical companies including other retainers from Abbott.

[46] Dr. Milne, the Wises' expert, opined that the clinical judgment and opinions of Drs. Morgentaler, Brock, and Greenberg was questionable due to conflicts of interest. The Wises submit that the physicians testifying for Abbott have built their academic, clinical, and professional practices on promoting testosterone treatments and that they have substantial intellectual and financial conflicts of interests in opining in favour of AndroGel™. Further, the Wises submit that Dr. Brock's failure to reveal his ties to Abbott and in particular his involvement with the marketing of AndroGel™ was dishonest and his evidence should be disregarded. The Wises submit that Dr. Greenberg's failure to disclose his relationship with the pharmaceutical industry was misleading and dishonest and that his evidence ought to be given no weight.

[47] For its part, Abbott submits that Dr. Milne and Dr. Mintzes are not independent experts and rather are biased and partisan witnesses. Abbott's experts challenge both the competence and the objectivity of Dr. Mintzes and Dr. Milne. In attacking Dr. Milne's qualifications as an expert witness, Abbott's witnesses were very dismissive of his credentials to comment about the treatment of low testosterone and to review the scientific literature. In attacking Dr. Mintzes' qualifications as an expert witness, Abbott submits that she has an "obvious anti-pharmaceutical agenda" and it relied on the fact that her fee for providing her opinion for this litigation was 10% of her annual income. Abbott suggested that a large portion of Dr. Mintzes' career has been dedicated to criticizing the pharmaceutical industry and the industry's direct-to-consumer advertising, and they point out she has not published a single peer-reviewed article about cardiovascular risk and that her only peer-reviewed article about testosterone, "Disease mongering and low testosterone in men", concerns the perceived negative effects of advertising. Abbott criticizes Dr. Mintzes for disclosing in her report that she made a complaint to Health Canada about Abbott's advertising of AndroGel™, but failed to disclose that the complaint was rejected.

[48] Abbott suggests as an example of Dr. Mintzes' animosity toward the pharmaceutical industry is the fact that she was the lead author of a letter of complaint to the Pharmaceutical Advertising Advisory Board in June, 2011 that was copied to Health Canada. The authors of the letter, who included representatives of consumer organizations and professors of medicine, philosophy, health policy, bioethics and pharmacology from Canada, the U.S, England, and Australia, complained about an advertising campaign for AndroGel™. Dr. Mintzes objected to the advertising campaign with the headline "Lost that Loving Feeling?" that ran in the *Globe & Mail* in June and July of 2011. She contended that the ads were promoting unapproved uses of AndroGel™. Dr. Mintzes said that the advertisement was an example of disease mongering, the "widening of disease boundaries of treatable illness in order to sell a product" but Abbott pointed out that while Dr. Mintzes mentioned her letter in her opinion, she did not mention that Health Canada declined to take any action after it receiving the letter.

[49] The Wises, however, did not ask that Abbott's experts be disqualified for partisanship; rather, they just ask that no weight be given to their evidence because of partisanship. Similarly,

Abbott did not ask that the Wises' experts be disqualified for partisanship; rather, it just asks that no weight be given to their evidence because of partisanship.

[50] Thus, both parties make vigorous attacks against the impartiality of their opponent's expert witnesses and there is some factual basis for those attacks; however, both parties ask just that I simply weigh the partisanship as a factor when weighing the evidence of their opponent.

(c) Discussion and Analysis – The Alleged Partisanship of the Expert Witnesses

[51] There is no doubt that Abbott's witnesses have connections with the pharmaceutical industry and are proponents for the use of AndroGel™ as a treatment for hypogonadism, which, as I shall explain below, they expansively define. And, there is no doubt that Dr. Mintzes and Dr. Milne, who do not oppose the use of AndroGel™ for hypogonadism - narrowly defined - are advocates for protecting the interests of the consumers of pharmaceuticals and vigorously oppose the sale of AndroGel™ for LowT, which they do not accept is a form of hypogonadism and rather regard as disease mongering. There is no doubt that that the parties' respective experts vigorously oppose the views of the opposing experts, and the experts have little respect for the professional integrity and opinions of their opponents.

[52] What the court is to do about these circumstances is the question. To answer this question, it is necessary to review the law about the admission of the opinion evidence of experts including the law about the qualification to give expert evidence.

[53] As a general rule, opinion evidence is not admissible; witnesses testify as to the facts which they perceived, not as to the inferences -- that is, the opinions -- that they drew from their perceptions: *Graat v. The Queen*, [1982] 2 S.C.R. 819. There is, however, an exception for witnesses duly qualified to express an expert's opinion: *R. v. Abbey*, [1982] 2 S.C.R. 24. As confirmed by the Supreme Court of Canada in *White Burgess Langille Inman v. Abbott and Haliburton Co.*, 2015 SCC 23, there is a two-stage test for the admission of opinion evidence.

[54] In the first stage, (the threshold stage), the litigant proffering expert evidence must satisfy the four factors from *R. v. Mohan*, [1994] 2 S.C.R. 9 which are: (1) relevance; (2) necessity in assisting the trier of fact; (3) the absence of an exclusionary rule; and (4) qualification as an expert. There is a fifth factor from *Mohan* in cases in which the expert's opinion is based on novel or contested science or science used for a novel purpose, and in these cases, the reliability of the underlying science for that purpose must be established: *White Burgess Langille Inman v. Abbott and Haliburton Co., supra* at para. 23; *R. v. J.-L.J.*, 2000 SCC 51; *R. v. Trochym*, 2007 SCC 6.

[55] In the second stage, (the gatekeeper stage), the court makes a cost-benefit discretionary decision weighing the probative value of admitting the evidence against the potential adverse impacts of admitting the evidence including the consumption of time, prejudice, and the risk of confusing the trier of fact.

[56] In the immediate case, the problem of the respective attacks made on the opposing expert witnesses is associated with the fourth of the *Mohan* criteria in the threshold stage of the qualification of the witness as an expert. For the fourth criteria to be satisfied, two factors must be satisfied. First, the witness must be shown to have acquired special or peculiar knowledge through experience or study in respect of the matters on which he or she will testify: *R. v. Mohan, supra* at para. 27. Second (as codified by rule 4.1.01 in Ontario), the witness must be

independent, objective, and impartial, which non-partisanship will be assumed if the witness acknowledges his or her duties to the court. In the case at bar, the problem is about the non-partisan factor.

[57] In *White Burgess Langille Inman v. Abbott and Haliburton Co., supra,* Justice Cromwell explained that independence and impartiality of the proffered expert witness are to be considered at the threshold stage and not left as a matter going to the weight to be given to the expert's witness's testimony; i.e., it was not to be left to the assessment of the reliability of the expert's witness's testimony after the evidence is admitted. For present purposes, this is a very important point because before *White Burgess Langille Inman,* there were conflicting lines of authority about how the question of the independence and impartiality of the expert was to be treated.

[58] It seems that in the case at bar, both parties were relying on the line of authorities, which holds that except in egregious cases, the expert's independence and impartiality goes to weight rather than to admissibility. See: *Gallant v. Brake-Patten*, 2012 NLCA 23; *R. v. Klassen*, 2003 MBQB 253; *Andersen v. St. Jude Medical, Inc*., 2010 ONSC 5768; *Carmen Alfano Family Trust v. Piersanti,* 2012 ONCA 297 at para. 110; *Henderson v. Risi,* 2012 ONSC 3459. I emphasize, however, that the Supreme Court rejected this approach in *White Burgess Langille Inman*.

[59] In *White Burgess Langille Inman v. Abbott and Haliburton Co., supra,* the facts were that after the shareholders of Abbott and Haliburton Co. retained an accountant from the accounting firm of Grant Thornton LLP to audit the corporation's books, the accountant advised them that there were problems in the accounting previously done by the firm of White Burgess Langille Inman. The shareholders then sued White Burgess Langille Inman for professional negligence, and on a summary judgment motion, the shareholders proffered the expert evidence of Susan MacMillan, another accountant from Grant Thornton LLP. In a decision reversed by the Nova Scotia Court of Appeal, the motions judge ruled Ms. MacMillan was not qualified to provide independent and impartial expert evidence. Justice Cromwell, writing the judgment for the Supreme Court, affirmed the decision of the Nova Scotia Court of Appeal and held that Ms. MacMillan's opinion was admissible.

[60] Justice Cromwell's analysis was as follows. An expert witness has a special duty to the court to provide fair, objective and non-partisan assistance. This special duty is comprised of impartiality, independence, and the absence of bias. The expert must be impartial in the sense that he or she is expressing their own unbiased professional objective assessment. The expert must be independent in the sense that his or her opinion is the product of their own, independent judgment based on their own knowledge and judgment and uninfluenced by the litigant who retained them. The expert must be unbiased in the sense that he or she does not favour one litigant's position over another. The fact that an expert is paid by one of the litigants does not, standing alone, undermine the expert's impartiality, independence, or freedom from bias.

[61] Continuing his analysis, Justice Cromwell stated that a proposed expert witness who is unable or unwilling to comply with these duties of impartiality is not qualified to give expert opinion evidence and should not be permitted to do so. If a witness is unable or unwilling to fulfill their duties, he or she does not qualify to perform the role of an expert and should be excluded. Concerns about a witness's impartiality, independence, and bias should be addressed as a threshold requirement for admissibility. Absent a challenge, the expert's attestation or testimony recognizing and accepting the duty will generally be sufficient to establish that the threshold test has been met. The burden is then on the litigant opposing the admission of the

evidence to show that there is a realistic concern that the expert's evidence should not be received because the expert is unable or unwilling to comply with his or her duty. If the opponent meets this burden of showing a realistic concern, then the litigant proffering the witness must demonstrate that the expert is impartial, independent and unbiased. If this is not done, the expert's evidence, or those parts of it that are tainted by a lack of independence or by impartiality, should be excluded.

[62] In determining whether the threshold requirement is satisfied the judge must determine, having regard to both the particular circumstances of the proposed expert and the substance of the proposed evidence, whether the expert is able and willing to carry out his or her primary duty to the court. It is the nature and extent of the interest or connection with the litigation or a litigant that matters, not the mere fact of the interest or connection; the existence of some interest or a relationship does not automatically render the evidence of the proposed expert inadmissible. Finding that expert evidence meets the basic threshold, however, does not end the inquiry and at the gatekeeping stage of the two-pronged test for the admissibility of expert evidence, the judge may take concerns about the expert's independence and impartiality into account in determining whether to admit the evidence. Ultimately, the judge must be satisfied that the potential helpfulness of the evidence is not outweighed by the risk of the dangers materializing that are associated with expert evidence.

[63] Justice Cromwell summarized his approach at various stages of his judgment. He stated at paras. 10, 45, and 49:

> 10. In my view, expert witnesses have a duty to the court to give fair, objective and non-partisan opinion evidence. They must be aware of this duty and able and willing to carry it out. If they do not meet this threshold requirement, their evidence should not be admitted. Once this threshold is met, however, concerns about an expert witness's independence or impartiality should be considered as part of the overall weighing of the costs and benefits of admitting the evidence. …
>
> ….
>
> 45. Following what I take to be the dominant view in the Canadian cases, I would hold that an expert's lack of independence and impartiality goes to the admissibility of the evidence in addition to being considered in relation to the weight to be given to the evidence if admitted. …. Binnie J. summed up the Canadian approach well in *J.-L.J.*: "The admissibility of the expert evidence should be scrutinized at the time it is proffered, and not allowed too easy an entry on the basis that all of the frailties could go at the end of the day to weight rather than admissibility".
>
> 49. This threshold requirement is not particularly onerous and it will likely be quite rare that a proposed expert's evidence would be ruled inadmissible for failing to meet it. The trial judge must determine, having regard to both the particular circumstances of the proposed expert and the substance of the proposed evidence, whether the expert is able and willing to carry out his or her primary duty to the court. For example, it is the nature and extent of the interest or connection with the litigation or a party thereto which matters, not the mere fact of the interest or connection; the existence of some interest or a relationship does not automatically render the evidence of the proposed expert inadmissible. In

> most cases, a mere employment relationship with the party calling the evidence will be insufficient to do so. On the other hand, a direct financial interest in the outcome of the litigation will be of more concern. The same can be said in the case of a very close familial relationship with one of the parties or situations in which the proposed expert will probably incur professional liability if his or her opinion is not accepted by the court. Similarly, an expert who, in his or her proposed evidence or otherwise, assumes the role of an advocate for a party is clearly unwilling and/or unable to carry out the primary duty to the court. I emphasize that exclusion at the threshold stage of the analysis should occur only in very clear cases in which the proposed expert is unable or unwilling to provide the court with fair, objective and non-partisan evidence. Anything less than clear unwillingness or inability to do so should not lead to exclusion, but be taken into account in the overall weighing of costs and benefits of receiving the evidence.

[64] Coming to the case at bar, one conclusion I take from Justice Cromwell's judgment in *White Burgess Langille Inman v. Abbott and Haliburton Co.*, is that in the immediate case, the arguments of both parties are analytically misconceived. In making their respective arguments, having cocked their rifle with strident submissions that their opponent's experts are partial, dependent, and biased, the Wises and Abbott respectively do not pull the trigger to have the witnesses disqualified and excluded and rather they respectively just ask that no weight be given to their evidence because of the witnesses' partisanship.

[65] In my opinion, this approach advanced by both parties is misconceived, illogical, intellectually dishonest, and inconsistent with the trend of the modern case law, which is to tighten the admissibility requirements and not to leave evidentiary matters to the weight to be given the evidence. It strikes me as a *non-sequitur* to conclude that an expert is a partisan but then to admit his or her evidence and give it little or no weight. Having concluded that a witness is not independent, objective or neutral, it is hard to see how the court could give some weight to his or her evidence. It is a threshold requirement that the court be satisfied that a proposed expert witness be able and willing to comply with his or her duties to the court, and if a witness is unable or unwilling to fulfill their duties, he or she does not qualify to perform the role of an expert and his or her evidence should simply be excluded and it should not be put on the scales of justice.

[66] An expert's objectivity, independence, and non-partisanship are pre-conditions for admissibility: *Deemar v. College of Veterinarians Ontario,* 2008 ONCA 600; *R. v. Docherty,* 2010 ONSC 3628; *R. v. L.K.*, 2011 ONSC 2562. See, in particular, Justice Romilly's superb analysis of the issues in *United City Properties Ltd. v. Tong*, 2010 BCSC 111.

[67] To avoid misunderstanding, it is necessary to point out that if the expert passes the threshold and the gatekeeper tests and his or expert's testimony is admitted, it does not follow that the court must give it full weight and credit. There may be other reasons to give the expert witness's testimony little or no weight, including the straightforward reason that the witness was not persuasive and his or her opinion was just not helpful. And it is also necessary to point out that if the expert passes the threshold and is qualified to give evidence and does give evidence, he or she may later be revealed, possibility during cross-examination, to have become impartial and partisan and then the trial judge should give no weight to the discredited or disqualified expert's testimony.

[68] In the immediate case, given the vigorous attacks made on the qualifications of the various experts on the grounds of lack of independence, which as noted above, have some factual traction, I do not agree with the parties that I can admit the evidence and then give it diminished weight; my choices are to admit the evidence if I conclude that the expert is qualified or to exclude it in its entirety if I conclude that the expert is not qualified to give opinion evidence. This means in the case at bar that I must move beyond my conclusion that the allegations of partisanship have factual traction to determine whether the facts actually establish that the expert is not qualified to give opinion evidence.

[69] I begin that analysis by saying that none of the experts is so closely related to the litigants that there is an immediate apprehension of partisanship. In *Deemar v. College of Veterinarians of Ontario* (2008), 92 O.R. (3d) 97 (C.A.), Justice Juriansz stated at para. 21 that the court "may refuse to qualify a person of unquestioned expertise who is closely related to the tendering party". The case at bar is not a case like *R. v. Docherty*, *supra*, where defence counsel proposed to introduce a psychiatric report authored by his father, who was the psychiatrist called for the defendant. In that case, the expert's evidence could not be seen to be the independent product of the expert uninfluenced by the exigencies of litigation. See also: *Royal Trust Corp. of Canada v. Fisherman* (2000), 49 O.R. (3d) 187 (S.C.J.); *Fellowes, McNeil v. Kansa General International Insurance Co.* (1998), 40 O.R. (3d) 456 (Gen. Div.), varied (2000), 138 O.A.C. 28 (C.A.).

[70] The case at bar is the type of case that requires a factual inquiry into whether impartiality does, in fact, exist. In *United City Properties Ltd. v. Tong*, *supra,* Justice Romilly described how a judge might go about screening for impartiality. He stated at paragraph 49:

> 49. Several options are suggested for logically situating the impartiality screening in the overall expert qualification analysis: it could be subsumed into the discussion of the necessity or reliability criteria; it could be treated in the context of the trial judge's residual discretion to exclude overly prejudicial evidence; or, preferably, it could be elevated to become a fifth criterion for qualification of the expert witness. While the authors [Casey Hill et al., *McWilliams' Canadian Criminal Evidence*, looseleaf (Aurora, Ontario: Canada Law Book, 2009)] do not suggest a particular test, they do list 14 factors which might warrant consideration when ascertaining bias and impartiality. ….:
>
> > (1) the nature of the stated expertise or special knowledge;
> >
> > (2) statements publicly or in publications regarding the prosecution itself or evidencing philosophical hostility toward particular subjects;
> >
> > (3) a history of retainer exclusively or nearly so by the prosecution or the defence;
> >
> > (4) long association with one lawyer or party;
> >
> > (5) personal involvement or association with a party;
> >
> > (6) whether a significant percentage of the expert's income is derived from court appearances;
> >
> > (7) the size of the fee for work performed or a fee contingent on the result in the case;
> >
> > (8) lack of a report, a grossly incomplete report, modification or

> withdrawal of a report without reasonable explanation, a report replete with advocacy and argument;
>
> (9) performance in other cases indicating lack of objectivity and impartiality;
>
> (10) a history of successful attacks on the witness's evidence;
>
> (11) unexplained differing opinions on near identical subject matter in various court appearances or reports;
>
> (12) departure from, as opposed to adherence to, any governing ethical guidelines, codes or protocols respecting the expert witness's field of expertise;
>
> (13) inaccessibility prior to trial to the opposing party, follow through on instructions designed to achieve a desired result, shoddy experimental work, persistent failure to recognize other explanations or a range of opinion, lack of disclosure respecting the basis for the opinion or procedures undertaken, operating beyond the field of stated expertise, unstated assumptions, work or searches not performed reasonably related to the issue at hand, unsubstantiated opinions, improperly unqualified statements, unclear or no demarcation between fact and opinion, unauthorized breach of the spirit of a witness exclusion order; and
>
> (14) expressed conclusions or opinions which do not remotely relate to the available factual foundation or prevailing special knowledge.

[71] Impartiality is a question of fact. Absent an obvious partisan relationship, what the court must do is undertake a factual inquiry as to whether or not there is an actual partisan relationship. In undertaking this inquiry, courts recognize and accept that experts are called by one party in an adversarial proceeding and are generally paid by that party to prepare a report and to testify. Thus, as noted by Justice Cromwell in *White Burgess Langille Inman v. Abbott and Haliburton Co.*, *supra*, the existence of some interest or a relationship does not automatically render the evidence of the proposed expert inadmissible. The alignment of interest of an expert with the retaining party is not, in and of itself, a matter that will necessarily encroach upon the independence or objectivity of the expert's evidence: *Carmen Alfano Family Trust v. Piersanti*, *supra* at para. 106. That the proposed expert is paid or has an employment relationship or has a pre-existing relationship with a litigant is something to be examined, but it is does not necessarily entail that the witness cannot or will not comply with his duty to the court when giving expert evidence.

[72] Having reviewed the evidence in the immediate case, should I then disqualify and refuse to admit the evidence of any of the expert witnesses because I am satisfied that he or she is unable or unwilling to provide the court with fair, objective and non-partisan evidence? Having considered the above factors that are relevant to this determination, I conclude that the answer to this question is “no”.

[73] Apart from the fact, that both parties did not ask that any witnesses be treated as unqualified, I am satisfied that they all were able and willing to provide the court with fair, objective, and non-partisan evidence. Neither party met the burden of showing that there is a realistic concern that the expert's evidence should not be received because the expert was unable

or unwilling to comply with his or her sworn duty.

[74] While the opposing experts were sharply critical of their competitors' opinions, the competing opinions were not that far apart, at least in the sense that they were based on the same data and information and in the sense that there was agreement about the data that should be analyzed and general agreement about the methodology of analysis. In any event, etiology and epidemiology, which are explained below, are matters about which reasonable persons may differ.

[75] Further, in this last regard, etiology and epidemiology are ultimately matters about interpretation and reasoned argument, and in the case at bar both sides' methodologies of analysis and argument were conventional. Using the same data, there was consensus that there were limitations in all of the medical science studies of the data. Using the same data, there was a consensus that notwithstanding the limitations in the studies that an association between testosterone and serious cardiovascular events had been established, there was consensus that association is, however, not proof of general causation. Using the same data, neither side had data to work with that was overwhelmingly convincing to support their respective opinions.

[76] Moreover, there was a consensus that testosterone replacement treatments were appropriate for classical hypogonadism. There was no suggestion from any witness that AndroGel^{TM} should be recalled or removed from the marketplace and not be available for the treatment of classical hypogonadism, and the controversy narrowed to whether AndroGel^{TM} was negligently being sold for the treatment of a possibly age-related decline in testosterone. The essential dispute between the parties was about the adequacy and appropriateness of the information and warnings in AndroGel^{TM}'s product monograph beyond the product's use for classic hypogonadism.

[77] Using the same data, both parties emphasized the analysis of the regulators. In an extremely significant consensus, although the litigants differed somewhat in the significance to be given to the information, there was agreement that in providing an opinion that might be helpful to the court, the most reliable and valuable analysis was that of the regulators; i.e., Health Canada, the United States Food and Drug Administration ("FDA"), and the European Medicines Agency ("EMA"). Although both parties differed in their interpretations, they both relied heavily and borrowed extensively from what the regulators both said and did and also about what the regulators did not do about testosterone products. Given that the expertise, independence, and impartiality of the scientists working for the regulators was not doubted and given that unlike some products liability class actions, the regulator was not a party, the borrowing of the regulator's opinions diminished concerns of impartiality in the competing opinions.

[78] I was impressed with the qualifications, credentials, and experience of all of the witnesses and not impressed with Abbott's submissions that Dr. Mintzes and Dr. Milne were expressing opinions outside their areas of expertise.

[79] The scientific method is built on skepticism, and it is a good thing and not a bad thing that there are scientists like Dr. Mintzes that are sceptics about the claims made by pharmaceutical companies, who, for their part, do nothing wrong in having commercial motivations. But, if they are to be good corporate citizens, they should have the attitude of inviting and not avoiding the scrutiny of the sceptics like Dr. Mintzes.

[80] There is no necessary evil in pharmaceutical companies providing funding for research to

study the safety and efficacy of their products. For clinical researchers, there are often little to no other sources of funding, such as government grants, available for research trials, so it is understandable they would not refuse industry support in the research projects, but it is a good thing to civil society that there remain scientists like Dr. Mintzes and Dr. Milne prepared to be critics even if they are regarded as devil's advocates by the pharmaceutical industry. That said, the sceptics and critics cannot cross the line of losing their professional detachment and objectivity and must provide reasoned criticism of the industry sponsored research projects. In my assessment, Dr. Mintzes and Dr. Milne did not cross the line.

[81] Equally, provided they too do not cross the line, it is a good thing and not a bad thing that some doctors and scientists accept the funding from the pharmaceutical companies and conduct the research trials and that they serve on advisory boards for the pharmaceutical companies. In the development of drugs and medical devices, there is a push and pull relationship between the medical and scientific community, and it is not always clear who is pushing or pulling for the development of the product. The modern Hippocratic oath requires a physician to "respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow." Drs. Morgentaler, Greenberg, and Brock are promoters of the use of testosterone products for aging males. Their advocacy is not a purchased advocacy and rather appears to be a genuine belief based on clinical observation and their own study that it is in the interests of their patients to receive testosterone replacement treatments.

[82] An expert's alleged impartiality and want of independence must be scrutinized and is a matter of factual determination on a case by case basis. As already noted, in the immediate case, there is factual traction for an argument that several of the witnesses may have crossed the line and entered the forbidden territory of being advocates for the litigant who retained them, but in the end these arguments were misconceived and they did not succeed and none of the expert witnesses should be disqualified.

[83] I, therefore, shall admit the evidence of all of the experts.

3. The Multiplicity of Defendants' Experts

[84] Section 12 of the *Evidence Act* states:

> *Expert evidence*
>
> 12. Where it is intended by a party to examine as witnesses persons entitled according the law or practice to give opinion evidence not more than three of such witnesses may be called upon either side without the leave of the judge or other person presiding.

[85] Abbott delivered their first round of affidavits from each of their expert witnesses on September 30, 2015 in accordance with the scheduling order of Justice Leach, who was then case managing this action. Almost one year later, relying on s. 12 of the *Evidence Act*, R.S.O. 1990, c. E.23, the Wises objected that the number of defence experts exceeded the three permitted without first obtaining leave of the court.

[86] Candidly, I can say that had I been asked for leave before the argument of the summary judgment motions, I probably would have refused leave. With the Wises' complying with s. 12 of the *Evidence Act* with two experts and having been buried under the mound of 19 reports

delivered by Abbott's seven expert witnesses, with the benefit of hindsight that would have been the right decision. However, under s. 12, leave may be granted at any time, and, in my opinion, this is an appropriate case to grant leave notwithstanding that I would not have granted if it had been sought at the appropriate time.

[87] See *Reid v. Watkins*, [1964] 2 O.R. 249 (H.C.J.); *Burgess (Litigation guardian of) v. Wu*, [2005] O.J. No. 929 (S.C.J) for case law about s. 12. In *Burgess (Litigation guardian of) v. Wu*, Justice Ferguson described the factors to consider when a request for leave to call more than three expert witnesses is made; namely: (a) whether the opposing party objects to leave being granted; (b) the number of expert subjects in issue; (c) the number of experts each side proposes to have opine on each subject; (d) how many experts are customarily called in cases with similar issues; (e) whether the opposing party will be disadvantaged if leave is granted because the applying party will then have more experts than the opposing party; (f) whether it is necessary to call more than three experts in order to adduce evidence on the issues in dispute; (g) how much duplication there is in the proposed opinions of different experts; and (h) whether the time and cost involved in calling the additional experts is disproportionate to the amount at stake.

[88] Although in the immediate case, there was a great deal of redundant evidence and more experts than necessary from Abbott to adduce the evidence that was necessary to decide the issues on the summary judgment motion, nevertheless, I grant leave for more than three experts because, at the end of the day, I conclude that the Wises' would not be disadvantaged by granting leave and because, practically and metaphorically speaking, after a six-day hearing, it is too late and not fair to shut the evidentiary barn door and stable some of Abbott's experts or even possible to choose how many to stable. Until recently, the Wises were content to respond to Abbott's deluge of experts with just two of their own, and, therefore, I grant Abbott leave to call more than three witnesses.

D. FACTUAL BACKGROUND

1. Norman Wise

[89] On August 28, 2013, Mr. Wise, who was 67 years' old man at the time, was prescribed AndroGel™ as treatment for testosterone deficiency. Mr. Wise had cardiovascular risk factors including being overweight, high cholesterol, high blood pressure, and a past history of smoking. It was later discovered that he had severe atherosclerosis.

[90] Mr. Wise had seen a TV commercial about AndroGel™ and asked his family physician whether it might respond to his symptoms of fatigue and falling asleep early in the evening. His testosterone level was tested, and it was found to be on the low end (6.6 units) of the normal range of 6.0 units to 27 units. He was prescribed AndroGel™ and used it for one month. He did not renew his prescription because it was not making him feel better.

[91] On October 10, 2013, Mr. Wise suffered a myocardial infarction complicated by a ventricular septal defect. He underwent two operations and spent many weeks in the hospital.

[92] Mr. Wise testified that he would never have considered using AndroGel™ were it not for the misleading promises of Abbott. He said that he would not have used AndroGel™ had he been warned of its potential to cause or contribute to his having a heart attack.

[93] It was Dr. Milne's theory that the testosterone replacement therapy could have changed

Mr. Wise's coronary vascular tone and flow, destabilizing and rupturing the plaque from the atherosclerosis and contributing to Mr. Wise's heart attack.

2. The Proposed Class Action

[94] In January 2014, as described in more detail below, there was considerable media attention to the issue of whether testosterone medications increased the risk of serious adverse cardiovascular events.

[95] On June 26, 2014, the Wises commenced their proposed class action against Abbott. The action was brought on behalf of the following Class:

> (i) All persons in Canada who were prescribed and used AndroGel™ at any time, which was manufactured, marketed, sold and/or otherwise placed into the stream of commerce in Canada by the defendants; and
>
> (ii) All persons in Canada who by virtue of a personal relationship to one or more of such persons described above, have standing in this action pursuant derivative legislation in their jurisdiction (i.e., in Ontario, s. 61(1) of the *Family Law Act*).

[96] The Wises claim damages of $500,000 for each Class Member prescribed AndroGel™ plus punitive damages of $60 million. The Plaintiffs have not pleaded the existence of any contract with Abbott for the purchase of AndroGel™, and their position is that they are not asserting a negligent misrepresentation claim. Their causes of action are common law negligence and unjust enrichment. They claim waiver of tort as an alternative to damages.

[97] The Wises allege that Abbott represented that AndroGel™ is a safe and effective treatment of age-related hypogonadism and / or so-called "LowT", when in fact the drug causes serious medical problems, including life-threatening cardiac events, strokes, and thrombolytic events. The Wises allege that to increase sales, Abbott and other pharmaceutical companies manufacturing testosterone therapies have engaged in "disease-mongering," i.e., marketing campaigns to alert physicians and consumers about the under-diagnosis of "LowT" and associated grave health risks. The Wises allege that Abbott's marketing strategies misled consumers about the prevalence and symptoms of low testosterone and failed to protect users from serious dangers that Abbott knew or ought to have known would result from the use of AndroGel™. They allege that Abbott knew that AndroGel™ is not effective in relieving symptoms associated with aging that do not derive from genuine hypogonadism.

[98] In his Statement of Claim, Mr. Wise refers to four studies that suggest that testosterone replacement therapy in men increases the risk of cardiovascular and thrombolytic events; namely:

- (1) the Basaria Study (Shehzad Basaria, *et al*, "Adverse Events Associated with Testosterone Administration" , N. Engl. J. Med., 2010);
- (2) the Xu Study (Lin Xu, *et al*, "Testosterone Therapy and Cardiovascular Events among Men: A Systematic Review and Meta-Analysis of Placebo-Controlled Randomized Trials", BMC Medicine, 2013);
- (3) the Vigen Study (Rebecca Vigen, *et al*, "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels",

Journal of the American Medical Association 2013); and,

- (4) the Finkle Study (William D. Finkle, *et al*, "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men", PLOS One, 2014).

[99] For the summary judgment motion, the Wises' experts referred to numerous other epidemiological studies, as did Abbott's experts.

3. Hypogonadism and Testosterone Therapy

[100] Testosterone is an anabolic, androgenic, endogenous hormone. That testosterone is anabolic means that in the process known as metabolism, it brings together, i.e., synthesizes molecules to form human tissue. (In metabolism, anabolism is the chemical reaction that synthesizes molecules.) That testosterone is androgenic means it is classified as a so-called male hormone. The androgens include: testosterone, dihydrotestosterone (DHT), androstenedione, 11-ketotestosterone, and dehydroepiandrosterone (DHEA). Although it is thought of as a male hormone, testosterone is naturally produced in both men and women. Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth brought about by fusion of the epiphyseal growth centers. Testosterone is responsible for the development of male sexual characteristics. That testosterone is endogenous means that it is produced internally by a body organ. In males, that organ is the gonads (the testicles).

[101] "Hypogonadism" is a deficiency or absence of endogenous testosterone in males. Hypogonadism is characterized by a low serum testosterone level in combination with various symptoms, such as decreased libido, erectile dysfunction, reduced muscle mass and strength, and increased body fat, and weight gain.

[102] A major dispute between the parties is that they will not come to terms about the pathology of hypogonadism. The parties agree that naturally occurring testosterone is a factor in energy, strength, stamina, and mood and is responsible for male sexual characteristics and a factor in sexual desire and sexual functioning. They agree that hypogonadism is a medical condition marked by low testosterone levels and that the symptoms of hypogonadism include loss of energy, fatigue, weakness, sleep disorders, regression of secondary sexual characteristics, reduced muscle mass, increased body fat, loss of height, mood disorders, depression, irritability, decreased motivation, decreased sexual desire, erectile dysfunction, and delayed ejaculation. The parties agree that hypogonadism; i.e., low testosterone and its symptoms, can be caused by genetic disorders, Klinefelter's Syndrome, pituitary injury, or poorly functioning testicles from mumps, or damage to the testicles, which they both describe as "classic hypogonadism".

[103] For over 50 years, classic hypogonadism has been treated by testosterone replacement treatment ("TRT"), which is to say hypogonadism has been treated by administering non-endogenous (produced outside the body) testosterone to elevate the amount of testosterone to its naturally occurring level. The parties agree that this treatment is appropriate provided that adequate warnings are given about side effects and risks.

[104] Where the parties vehemently disagree is about whether low testosterone and its symptoms caused by natural aging is also a type of hypogonadism.

[105] Low testosterone and its associated symptoms caused by aging has sometimes been called secondary hypogonadism, testosterone deficiency syndrome, or "andropause," which is a

phrase coined to mean "male menopause," the existence of which is a matter of controversy. The Wises and their experts dispute that so-called andropause is pathological; rather they say andropause is a fabrication of a disease made up by pharmaceutical companies for commercial purposes. The Wises through their experts, particularly Dr. Mintzes, accuse Abbott of "disease mongering" in order to increase its sales of AndroGel™. The Wises submit that while AndroGel™ has been approved for and is effective in treating classical hypogonadism, which is an actual medical condition, AndroGel™ is neither indicated for, nor beneficial in respect of alleviating the symptoms of LowT caused by a man getting older.

[106] For its part, Abbott and the manufacturers of testosterone replacement treatments assert low testosterone along with the associated symptoms caused by aging, call it what you will, is an instance of hypogonadism. Thus, while the Wises submit that Abbott and other pharmaceutical manufacturers intentionally conflate hypogonadism with LowT or andropause, Abbott, and their expert witnesses, Drs. Morgentaler, French, Brock, and Greenberg deny any misclassification and define "hypogonadism" as synonymous with testosterone deficiency syndrome, andropause, and LowT.

[107] It is a source of all of confusion, controversy, and litigation that the parties, their experts, the regulators of the pharmaceutical industry, the scientific and medical community appear to differ on whether testosterone replacement treatment is indicated only for classical hypogonadism or whether testosterone replacement treatment is also indicated for low testosterone that occurs by natural aging. The fact that the parties disputed whether or not AndroGel™ was indicated not only for classical hypogonadism but also age-related hypogonadism, non-classical hypogonadism, testosterone deficiency syndrome, andropause, LowT, or whatever it might be called, led to disputes about whether AndroGel™ was being sold for off-label uses and about whether it had any efficacy for treating other than classical hypogonadism caused by accident or specific ailments.

[108] It is not for courts to decide what is or is not a disease or a medical syndrome, and to quote from Shakespeare, the submissions of both parties were "full of sound and fury" and there was much furious talk of no importance and little or no meaning about what is hypogonadism. I am glad to say that for the purposes of the summary judgment motion, I do not have to decide what is the pathology of hypogonadism and rather I find that doctors were not prescribing AndroGel™ for off-label indications. In other words, physicians are diagnosing their clients as having low testosterone and a set of symptoms and the physicians are prescribing AndroGel™ as the treatment for that diagnosis.

[109] For the purpose of this motion, the fundamental issue to be determined is not that of defining hypogonadism; rather the issue is whether the prescriptions of AndroGel™ can be the cause of serious cardiovascular events. For present purposes, I do need to describe the heated debate about the nature of hypogonadism because it is an actual part of the factual narrative, but I need to keep in mind that the underlying issue is not about what counts for hypogonadism but the ultimate issues are whether, as a matter of general causation, AndroGel™ can cause serious cardiovascular events and whether the sale of an allegedly useless but risky product, AndroGel™, can support a product's liability negligence claim for pure economic loss.

4. Serious Cardiovascular Events

[110] Abbott's summary judgment motion is essentially built on the argument that the Wises

have not proven on a balance of probabilities that testosterone replacement treatments, including AndroGel™, can cause serious cardiovascular events. It is, therefore, necessary to understand what is presently known about the causes of serious cardiovascular events, much of which is not controversial.

[111] Coronary artery disease is the number one cause of death. It is thought to begin with damage or injury to the inner layer of a coronary artery caused by various factors, including: sedentary lifestyle, obesity, smoking, high blood pressure, high cholesterol, diabetes, insulin resistance, and radiation therapy for cancer treatments. Once the inner wall of an artery is damaged, fatty deposits or plaque made of cholesterol and other cellular waste products tend to accumulate at the site of injury in a process called atherosclerosis. If the surface of these plaques breaks or ruptures, blood cells called platelets will clump at the site to try to repair the artery, but frequently these clumps of platelets mix with fibrin stands in the bloodstream and block the artery, leading to a heart attack.

[112] There are many known risk factors for coronary artery disease, including age, smoking, hypertension, diabetes, and obesity. Risk factors often occur in clusters and may build on one another, such as obesity leading to diabetes and high blood pressure. A family history of heart disease is associated with a higher risk of coronary artery disease especially if a close relative developed heart disease at an early age. A patient's risk is highest if their father or a brother was diagnosed with heart disease before age 55 or a mother or a sister developed coronary artery disease before age 65.

[113] In his report, Dr. French stated that low endogenous bioavailable testosterone levels have been shown to be associated with higher rates of all-cause mortality and cardiovascular-related mortality and that patients suffering from coronary artery disease, diabetes, and obesity have all been shown to have lower levels of endogenous testosterone compared with those in healthy controls. In addition, he said that the severity of coronary artery disease and heart failure correlates with the degree of testosterone deficiency.

[114] All the experts agree that testosterone replacement therapy is not an accepted treatment of cardiovascular disease. Although it is not a cure, some of Abbott's expert witnesses believe, however, that testosterone replacement therapy may help reduce the likelihood of serious cardiovascular events.

5. Epidemiology and Types of Epidemiological Studies

[115] To decide this summary judgment motion, it was necessary to have an understanding of epidemiology, most of which I gained from the evidence and arguments of the parties. I shall describe this background knowledge in this section of my reasons. In describing this necessary information, which I needed in order to understand the competing experts' opinions, I was also aided by Justice Lax's judgment in *Andersen v. St. Jude, Medical Inc*., *supra*, Justice Osler's seminal judgment in *Rothwell v. Raes*, [1990] O.J. No. 2298 (C.A.), leave to appeal refused, [1991] S.C.C.A. No. 58 and the *Reference Manual on Scientific Evidence* (3rd ed.) prepared by the United States Federal Judicial Center, in particular, by that manual's *Reference Guide on Epidemiology* and by its *Reference Guide on Statistics*.

[116] Etiology is the study of cause or causes, and epidemiology is the branch of medical science that studies the etiology of diseases and that identifies risk factors for disease or medical

conditions. Epidemiology focuses on "general causation;" i.e., whether or not an agent has the capacity to cause a disease or medical condition rather than on "specific causation;" i.e., whether or not an agent did cause a disease or medical condition to be suffered by a specific person.

[117] Using a variety of different methodologies derived from the branches of mathematics that develop techniques for organizing and analyzing information, an epidemiological study determines whether there is an "association" between an agent and a condition, state or event including a disease or syndrome. An association between an agent and a condition exists when the agent and condition occur together more frequently than one would expect by chance. If an association is established, then information in the study is examined to determine whether or not the association can be explained as causal; i.e. as a matter of general causation. To determine general causation, the researcher uses a variety of statistical methodologies, discussed in the next section, and analytical tools including professional judgment and his or her knowledge from other fields of science.

[118] There are a variety of different methodologies for epidemiological studies. Regarded as the most reliable, i.e., the gold standard, is the "randomized controlled trial" or RCT, which is also called a clinical trial or a true experiment. In a RCT, participants are randomly assigned to two groups. One group, the study or case group, will be exposed to the agent and the other group, the control group, will receive a placebo or not be exposed to the agent. The assignments can sometimes be "double blind," in which case the participants and those conducting the study are not told who is receiving the drug or a placebo. This will be revealed after the data is evaluated and the idea is that double-blinding protects the objectivity of the analysis and reduces bias, of which more will be said below.

[119] There are ethical and practical constraints that may impose limits on an epidemiological study; viz., it may be unethical to prescribe a known-to-be dangerous agent. It may be necessary to stop a study early if the experiment is causing harm to the participants. It may be necessary to substitute cadavers or animals (*in vivo* studies) or grown or fabricated human or animal tissue (*in vitro* studies) for human subjects.

[120] The selection of the participants into the study group and the control group is of fundamental importance to the design of an epidemiological study. Epidemiology borrows from mathematics the idea of random sampling from a population of participants to make probabilistic conclusions about the population in the study group and in the control group. Randomization acts to equalize the prevalence of causal factors between the groups so that observed differences between the two groups can more reasonably be attributed to the difference in the treatment of the groups, since that is the only remaining difference, other than the outcomes, between the groups.

[121] In addition to RCTs, other types of epidemiological studies are observational studies of which there are several types including: a cohort study; a case-control study; a cross-sectional study; and an ecological study. An observational study can show association, but it cannot prove causation because it does do not have the benefit of genuine randomization and, therefore, known and unknown potential causes of observed differences between groups cannot be ruled out.

[122] In a cohort study, a study population is defined without regard to the participants' disease status and then divided into two groups, a group (the exposed group) that was exposed to a particular agent and a group that was not exposed (the control group) to that agent. The cohort

may be constituted from a past group or from a present group. The disease or condition status of the cohorts is then examined prospectively over a period of time. If the agent causes the disease or condition, more of the exposed group would be expected to develop the disease. An association between the agent and the disease may be inferred if more of the exposed group have the disease than the unexposed group than would be expected by chance.

[123] In a case-control study, a study population is defined, and then the study population is divided into the group that has the disease (the study group) and the group that does not have the disease (the control group). This type of study is denoted retrospective because it commences with the fact that the injury or illness exists and it looks backwards into the history of the cases and compares them with the history of members of a control group. In a case-control study, the ratio of those with the disease who were exposed to the agent to those with the disease who were not exposed (odds that a case was exposed) to the ratio of those in the control group exposed or not exposed is calculated. The researcher then compares how the study group and the control group proportionately responded to being exposed or not exposed to the agent. If the agent causes the disease or condition, then it would be expected that the ratio of exposed to the agent would be higher in the study group than in the control group. Case-control studies, which are retrospective and, therefore, subject to significant potential biases, are regarded as providing weaker epidemiological evidence than do cohort studies.

[124] The major difference between observational cohort studies and observational case-control studies is that cohort studies examine persons exposed and not exposed to the agent for the experience of the condition and case-control studies examine persons with or without the condition for the experience of exposure to the agent.

[125] An ecological study does not gather data about individuals but rather uses population data about groups. Rates of disease for different groups are studied to identify some difference between the groups that might explain the difference in the incidence of the disease or condition. The population data may have to be adjusted for differences in the demographics of the population.

[126] The weakest kind of epidemiological study is the case report or anecdotal episodes. These examine the presence of exposure to the agent and the condition in individuals at a single point in time. This type of study provides no information about cause or effect but may indicate areas for research.

[127] Another type of epidemiological study is the meta-analysis or systemic review. The meta-review pools information from epidemiological studies and seeks to draw general conclusions. A meta-analysis is a statistical procedure for combining a set of individual results from prior studies. Systemic reviews combine evidence but are only as valid as the included studies and the quality assessment of the included trials is a critical element.

[128] An epidemiological study begins with a research methodology to determine whether there is an association between an agent and a disease or condition. If the study reveals an association between the agent and the disease or condition, then the strength and reliability of the mathematical outcome of the study is tested by the rules and theories of statistics and the study methodology is analyzed to determine whether limitations in the study could explain the association. Then, further analysis is undertaken to determine whether the association can be attributed to causation, which is the cause and effect connection.

[129] Once the data is gathered and analyzed for statistical significance, the research question becomes, relying on both an analysis of the limitations of the study and also other scientific knowledge, how plausible is the explanation for the association being that the agent can cause the condition. A popular guideline for the analysis is taken from a paper delivered in 1965 at the founding of the Industrial Medicine Section of the Royal Society of Medicine in England by Sir Austin Bradford Hill. He suggested nine factors relevant to the determination of causation, which are often referred to as the Hill factors; i.e.: (1) biological plausibility (coherence with existing health science); (2) consistency with other knowledge; (3) alternative explanations; (4) specificity of the association to a specific condition or disease; (5) temporality; (6) cessation of exposure; (7) strength of the association; (8) dose-response (ratio between extent of exposure and incidence of the condition); and (9) replication of results.

[130] Before any conclusion about association and any inference can be drawn about causation, the outcome of the study must be examined to determine whether it is a result of chance; i.e., random error; bias (errors in the design of the study that might impugn its findings including partisanship), and confounding, which is the phenomena that the agent is indeed associated with the condition, but it is another agent that explains that connection and that other agent is the true cause of the disease or condition.

[131] A positive or negative association must be interpreted by analysing the limits of the study in the light of scientific knowledge because the conclusion of the existence or non-existence of an association and any inference of causation may be a result of sampling error, confounding or bias.

[132] Bias is an effect or influence on the truth or falsity of the outcome of the epidemiological study. Bias is a source of error in the methodology. As noted above, bias includes conflicts of interest, which is to say that the objective judgment of the researcher is unduly influenced by personal interest including financial, academic, or reputational enhancement by disclosing a conclusion of causation.

[133] Bias may arise in the design of the study, in the implementation of the study, in the collection of data, and in the analysis of the data. Selection bias is an error in the selection of participants for the case group or for the control group. Information bias is an error in information about the disease status or exposure status of the participants in the study. (The validity of the findings will be influenced by the reliability of the before and after diagnosis of the members of the case group and of the control group.) Misclassification bias is the error of misclassifying the participants in the study as to their exposure and or as to their diagnosis. Recall bias is the factor that individuals with a disease tend to recall exposures more readily than individuals without the disease. Publication bias is the tendency for medical journals to prefer studies that find an effect; if negative studies are under-published, the medical literature will be biased.

[134] The presence of bias may exaggerate or understate the conclusion of the study. Sometimes the identification of bias will vitiate the outcome of the epidemiological study. In other instances, once the bias is identified, adjustments may be made to account for the bias and the study may still have probative value.

[135] The third major reason for error in epidemiological studies is confounding. Confounding occurs when another agent confuses the relationship between the agent of interest and the disease or condition of interest. If an association is established, it is critical to determine whether that

association is causal or the result of confounding. The researcher should identify other risk factors for the disease or condition under study and attempt to design the study appropriately. One technique is matching. For example, in a study to determine the association between smoking and cirrhosis of the liver, since smokers are frequently consumers of alcohol, it may be necessary to match the smokers (the study group) and the non-smokers (the control group) for alcohol consumption before determining whether there is an association that could be accounted for by smoking. Effective randomizing minimizes but does not eliminate confounding.

[136] There are analytic methodologies to account for the effect of confounding agents including stratification or multivariate analysis. Stratification evaluates the effect of a suspected confounder by subdividing the study groups based on a confounding factor. Multivariate analysis controls the confounding factor through mathematical modelling of the effect of the agent and the confounder on the increase in risk.

6. Epidemiology and Statistics

[137] The presence of an association between an agent and a condition and the strength or weakness of an association is expressed in terms of "relative risk," "attributable risk" or an odds ratio. From a positive number or ratio a conclusion of causation may be inferred. A negative association may imply that the agent prevents or cures condition. It, however, must be emphasized that association itself does not prove general causation.

[138] The incidence rate is the number of cases of the condition that develop during the study period divided by the size of the cohort being studied. Visualize, if 50 persons in a study group of 100 drug recipients developed a rash, the incidence rate would be 0.5. The relative risk is the ratio of the incidence rate of the condition in those exposed to the agent to the incidence rate to those not exposed to the agent. Visualize, if 25 persons in the control group of 100 persons who received a placebo developed a rash, the incidence rate for the control group would be 0.25 and using the above example for the study group, the relative risk would be 2.0 (0.5/0.25). It thus could be said that persons taking the drug are twice as likely to develop a rash than those not taking the drug.

[139] Attributable risk is a measure of the amount of the condition that can be attributed to the exposure to the agent. The attributable risk is equal to the incidence of the condition in the exposed group minus the incidence of the disease in the unexposed group divided by the incidence in the exposed group; i.e., using the above example, the attributable risk is 0.5 (50-25/50) "Attributable to" is used for the purposes of determining association and, once again, it does not mean causation.

[140] Statistical testing may be used to assess the extent to which an outcome may be due to chance. The researcher tries to determine whether the outcome represents a true association or is the result of chance. The two main techniques for assessing whether the outcome is a matter of chance are "statistical significance" and "confidence intervals." Data is statistically significant if it cannot be explained by chance alone. A confidence interval provides a range (interval) around the measure of risk within which the risk would, as a matter of probability, fall if the study were repeated many times.

[141] Statistical significance and confidence intervals are not about the strength or weakness of the association but about the reliability of the reported outcome not being a matter of chance

alone. Thus, for example, a study might report an association with a large value but given a small sample size the report may not be statistically significant.

[142] Procedures for testing statistical significance begin with the "null hypothesis" which posits that if the risk ratio for the agent and the condition is 1.0, then there is no association and the association has occurred by chance. The data of the study is analyzed by statistical testing to see whether it is plausible that the data disproves the null hypothesis. A statistically significant result justifies rejecting the null hypothesis. An erroneous conclusion that the null hypothesis has been disapproved is called a false-positive error (alpha error). An erroneous conclusion that the null hypothesis has been proved is a false-negative error (beta error).

[143] The size of the study is a factor in determining the reliability of its outcomes. It is a mathematical phenomenon known as the Law of Large Numbers that as the size of a sample being tested increases, the value of the average of the outcomes becomes more accurate and the role of chance diminishes. This phenomenon was explained with an example by Justice Osler in *Rothwell v. Raes*, *supra* at paras. 67-68, as follows:

> 67. The importance of chance in a particular study may vary with the size of the study and hence chance is a consideration in deciding on how large a study need be in order to be reliable.
>
> 68. A homely example given in the course of the evidence concerned the case of a barrel containing 10,000 marbles, 5,000 of which were, in fact, black and 5,000 of which were white. If one were to withdraw blindly, say 50 marbles, it could well be that something like 30 of these would be black and 20 white. If the composition of the contents of the barrel were to be reported on the basis of such a sample, it would, of course, be erroneous, given the known fact that 50% of the entire contents was composed of each colour of marble.

[144] Using Justice Osler's example, it can be appreciated that if say 100 marbles had been selected it could be that something like 55 of these would be black and 45 white. The composition of the barrel would still be reported incorrectly but the report would be more accurate as the size of the amount sampled increased. This makes common sense because as the size of the sample of marbles approaches the amount of the whole barrel, the reports become more and more accurate.

[145] Epidemiology uses a 5% level of statistical significance as the criterion by which to judge the possible effects of chance. In other words, if the probability that chance accounts for the result is less than 0.05 (5%), then the result of a study is said to have statistical significance, meaning that chance is considered to be an unlikely explanation of the result. One statistical method is the calculation of a "p-value," which is the probability that an observed positive association could result from chance even if, in truth, there was no association. The "chi-squared" and "Fisher's Exact" tests are statistical tests for detecting true associations. These tests calculate a p-value which is a number between 0 and 1. A p-value below 0.05 is labeled "statistically significant". The smaller the p-value the more likely the association is true and not a matter of chance.

[146] The size of the study can affect the calculation of the p-value, because, as noted above, the larger the size of the sample, the more reliable the report. Thus, a study comparing 100 cases and 100 controls might have a p-value of 0.07, which would <u>not</u> be a statistically significant

result, but if the study had been twice as large and reported the same outcomes, the p-value would be lower, say 0.01, which would indicate that the outcomes were statistically significant. (This example is taken from *Rothwell v. Raes, supra* at para. 70.)

[147] As an alternative to using a p-value of statistical significance, the level of accuracy of an epidemiological study can be expressed as a "confidence interval." A 95% confidence interval corresponds to statistical significance set at a 0.05 (5%) level. The confidence interval is a range of values of relative risk in which the true value of the relative risk, if any, would be found if the experiment were repeated many times. Where the confidence interval contains a relative risk of 1.0 or lower, the results of the study are not statistically significant. In other words, if the lower end of the interval is less than or equal to 1.0, then the likelihood that the results are simply a matter of chance cannot be ruled out.

7. The Evidence of Ms. Tomalin, Ms. Brillon, and Ms. Stubits

[148] Ms. Tomalin practiced exclusively in the area of Canadian regulatory affairs for 45 years and has considerable experience filing with Health Canada, New Drug Submissions (NDSs), Supplemental NDSs (SNDSs), and Notifiable Changes (NCs) relating to updates to product monographs for drug products.

[149] For this summary judgment motion, Ms. Tomalin provided a report that contained a description of the Canadian pharmaceutical regulatory regime and her comments on: the Canadian regulatory approval process for AndroGel™; the changes made to the AndroGel™ product monograph over time; and the advertising for AndroGel™.

[150] Ms. Brillon was a senior manager at Abbott, and from the perspective of Abbott, she provided evidence of the regulatory approval process in Canada for a new drug and she described the history of the introduction and marketing of AndroGel™ in Canada including post-approval regulatory submissions. She also described, from Abbott's perspective, recent Health Canada reviews and announcements about AndroGel™.

[151] As noted above, Ms. Stubits is a law clerk and she filed an affidavit that contained copies of the reports and medical literature referred to by Abbott's expert witnesses.

[152] I shall incorporate my findings about Ms. Tomalin's, Ms. Brillon's, and Ms. Stubits' evidence into the discussion below.

8. The Regulators

[153] AndroGel™ is marketed in Canada, where it was regulated by Health Canada. In the United States, it is regulated by the FDA, and in Europe, it is regulated by the EMA.

[154] Health Canada is responsible for approving drugs for sale in Canada. A drug is licensed for sale by Health Canada issuing a Notice of Compliance ("NOC") after an elaborate submission and review process. Pursuant to the *Food and Drugs Act*, R.S.C. 1985, F.27, and its regulations, the manufacturer must file a New Drug Submission ("NDS"). The NDS contains detailed information about: the chemistry of the drug; the manufacturing process; the results of pre-clinical and clinical testing; information about the proposed indications, dosage, and conditions of use; the drug's claimed therapeutic value; and warnings about potential side effects and risks.

[155] The NDS/NOC process includes an extensive review of the manufacturer's submission and a review of the proposed product monograph. The product monograph is subject to a review by Health Canada's Therapeutic Products Directorate ("TPD"). The Directorate is staffed by scientific experts with extensive clinical and or medical expertise. The product monograph provides pertinent information about the nature and uses of the drug including cautions and warnings. The product monograph summarizes the results of the studies submitted to Health Canada.

[156] The Health Canada reviewers are physicians, pharmacologists or other scientists with doctorate-level academic training and significant research experience. In determining whether to approve or reject a submission, the reviewers will scrutinize: whether the drug can be made consistently; whether the product quality can be assured; whether the efficacy of the drug is acceptable based on a randomized controlled trial(s) and whether the safety profile of the drug is acceptable based on the risk/benefit analysis.

[157] Since manufacturers of prescription drugs are not permitted to engage in direct marketing activities, such as advertising to consumers, any advertising or marketing must be specifically directed to physicians and may not make any claim that has not been approved as part of the product monograph.

[158] Health Canada is also responsible for the post-marketing surveillance of drugs once they have been marketed, including monitoring drug safety and ensuring that companies comply with the regulations, which include reporting and recordkeeping obligations about the effects of the drug on patients. For example, manufacturers are required to deliver expedited adverse drug reaction (ADR) reports of all serious adverse drug reactions that occur in Canada and all serious and unexpected ADRs that occur outside of Canada. ADRs may also be submitted by patients, health professionals or others.

[159] As new information about a drug becomes available, or as changes are made by the manufacturer, a follow-up submission to Health Canada may be required. If the manufacturer expands the indications for a drug, a SNDS must be filed. For a change to identify adverse events or to take risk management measures, the manufacturer must file a NC submission and the changes can be implemented only after Health Canada issues a No Objection Letter (NOL).

[160] Health Canada (as well as other regulators around the world) have drug safety programs in place to detect potential "safety signals" and to determine if changes to the product monograph should be made. In its *Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, the FDA defines a "safety signal" as a concern about an excess of ADRs compared to what would be expected to be associated with a product's use.

[161] The FDA stated that signals indicate the need for further investigation to determine whether a product causes an event and to determine what actions should be taken.

[162] After a drug has been approved, Health Canada's Marketed Health Products Directorate (MHPD) monitors ADRs including the required reports from manufacturers and also spontaneous reports of ADRs from healthcare professionals across Canada. If Health Canada wishes to bring a specific issue concerning a drug to the attention of health professionals, it may direct the manufacturer to issue a specific communication on the issue to all relevant healthcare professionals. Health Canada will oversee amendments to the initial NOC approval, including changes to the product monograph such as changes in indications, dosages, patient populations,

and cautions and warnings.

[163] Health Canada's MHPD also reviews the scientific literature and media reports to identify issues. The data is added to a database and continually reviewed for "signals" of potential ADRs that may be associated with a drug. An Expert Advisory Committee on the Vigilance of Health Products also exists to provide Health Canada with on-going external expert broad strategic advice on the safety of marketed health products.

[164] The MHPD may conduct a "Signal Assessment" where "signal" means a preliminary indication of a product-related safety issue.

[165] As will be seen below, the MHPD of Health Canada conducted a Signal Assessment dated May 22, 2014 for testosterone products with respect to cardiovascular risk.

9. The Regulatory and the Marketing History of AndroGel™ and the Epidemiological Study of Testosterone Replacement Treatment

(a) 2000-2004: The Original Product Monograph

[166] AndroGel™ is a topical testosterone medication that was developed by Solvay Pharma Inc. In 2010, Solvay was acquired by Abbott Products, Inc., which, in turn, became Abbott Laboratories, Inc.

[167] Testosterone administered by injection has been approved for sale in Canada for decades. AndroGel™ administers testosterone transderminally (through the skin) and as such was considered a new drug that required regulatory approval.

[168] In 2000, the FDA approved AndroGel™ for sale in the United States.

[169] On February 6, 2002, AndroGel™ was approved for sale by Health Canada.

[170] Part I (Health Professional Information) of AndroGel™'s product ponograph included: summary product information, indications and clinical use, contraindications, warnings and precautions, adverse reactions, drug interactions, dosage and administration, overdosage, action and clinical pharmacology, storage and stability, special handling instructions, and dosage forms, composition and packaging. Part II (Scientific Information) of the Product Monograph included pharmaceutical information, clinical trials, toxicology, and references. Part III was consumer information.

[171] The original product monograph of February 6, 2002 was modified on July 16, 2002, and the following excerpts from the July 2002 product monograph are relevant to determining to resolving this summary judgment motion:

PRODUCT MONOGRAPH

AndroGel™

(testosterone USP)

1% gel

THERAPEUTIC CLASSIFICATION

Androgenic Hormone

ACTIONAND CLINICAL PHARMACOLOGY

AndroGel™ (testosterone gel) contains 1% testosterone and provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen.

Testosterone and Hypogonadism:

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature, and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood disorder and depressive symptoms, regression of some secondary sexual characteristics, weakness, irritability and decreased motivation. Hypogonadism is a risk factor for depression and osteoporosis in men.

….

INDICATIONS AND CLINICAL USE

AndroGel™ (testosterone gel) is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

1. Primary hypogonadism (congenital or acquired) — testicular failure including cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels but have high gonadotropins (FSH, LH) above the normal range.

2. Secondary hypogonadism (congenital or acquired)--idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum levels but may have basal gonadotropins in the normal or low range.

3. In sexual dysfunction or for andropause when the conditions are due to a measured or documented testosterone deficiency.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate.

AndroGel™ (testosterone gel) is not indicated for, nor has been evaluated for use

in women or children.

Women, especially pregnant women, should avoid skin contact with AndroGel™ application sites in men. Testosterone may cause fetal harm, especially during early pregnancy, ….

WARNINGS

….

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

….

The treatment of hypogonadal men with testosterone esters may potentiate sleep apnea (interruption of breathing during sleep) or hypertension in some patients, especially those with risk factors such as obesity or chronic lung diseases.

….

INFORMATION FOR THE CONSUMER

….

What is ANDROGEL™?

Your body normally makes testosterone, primarily in the gonads (testicles). Your doctor has prescribed AndroGel™ therapy because your body is not making enough testosterone. The medical term for this condition is hypogonadism. Testosterone is important in the production of sperm and for the development of male sexual characteristics. Testosterone is also necessary for normal sexual function and sex drive. Low testosterone levels can result in decreased sexual desire, fatigue and loss of energy, a depressed mood, weakening of the bones, irritability, decreased motivation and strength.

AndroGel™ is a clear, colourless, fragrance free gel that delivers testosterone to your body through your skin. Once AndroGel™ is absorbed through your skin, it enters your bloodstream and helps you attain normal testosterone levels. The type of testosterone provided by AndroGel™ is the same as the testosterone produced by your testicles.

What can I expect from ANDROGEL™ therapy?

Depending on your symptoms, AndroGel™ may help improve your energy levels and mood, and increase your sexual desire. In addition, AndroGel™ may improve your body composition, which can help maintain your bone and muscle mass. To get the best results from AndroGel™, it is essential that you take it exactly as your doctor has prescribed. …

What are the possible side effects of AndroGel™?

….

- swelling due to extra fluid in the body. This can result in serious problems

for patients with heart, kidney or liver damage

- high blood pressure

….

[172] It should be noted in Canada, in the early years of its product monograph, AndroGel™ was indicated for the treatment of andropause, sexual dysfunction, and male climacteric symptoms. There was no similar indication in the product monograph in the United States.

(b) 2005-2007 – The Amendment to the Product Monograph

[173] Sometime in 2005, Health Canada's Bureau of Metabolism Oncology and Reproductive Sciences began a review of testosterone replacement therapy, and Health Canada questioned whether the science supported the therapy being indicated for andropause. Health Canada determined that there was very little data to support AndroGel™ and other testosterone replacement therapy having this indication and required that the product manual be amended to remove the indication for andropause.

[174] On June 26, 2006, Health Canada sent a letter to manufacturers of testosterone products advising them that an internal review had been conducted and had concluded that indications such as andropause and male climacteric symptoms were not supported by the available clinical data and requiring these indications to be removed from labelling of all testosterone products.

[175] In response to the notification from Health Canada, Abbott (actually Abbott's predecessor) made a 244-page submission to Health Canada prepared by its internal staff with the assistance of consultants. Before making its submission, Abbott considered whether it could justify the current indication for sexual dysfunction or andropause based on the current studies and decided that it could not. Abbott instead lobbied for language that while it removed the indication for andropause it broadened the definition of hypogonadism and preserved the therapeutic information provided by the product monograph.

[176] On August 30, 2007, the product monograph for AndroGel™ was amended.

[177] The Action and Clinical Pharmacology portion of the Product Monograph now stated:

> **ACTION AND CLINICAL PHARMACOLOGY**
>
> ANDROGEL™ (testosterone gel) contains 1% testosterone and provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen.
>
> **Pharmacodynamics**
>
> Testosterone and Hypogonadism:
>
> Testosterone and dihydrotestosterone (DHT), endogenous androgens, are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal chord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Symptoms associated with male hypogonadism include decreased sexual desire with or without erectile dysfunction, fatigue and loss of energy, mood depression/ disorder and depressive symptoms, regression of some secondary sexual characteristics, osteoporosis, weakness, irritability and decreased motivation. Although causality has not been established, there are associations between hypogonadism and depression, osteoporosis, metabolic syndrome, type 2 diabetes, cardiovascular disease and increased mortality in men. Hypogonadism is a risk factor for osteoporosis in men.

….

[178] The Indications and Clinical Use portion of the product monograph now stated:

INDICATIONS AND CLINICAL USE

ANDROGEL™ is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism).

ANDROGEL™ should not be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other etiologies responsible for the symptoms have not been excluded. Testosterone deficiency should be clearly demonstrated by clinical features and confirmed by biochemical assays (Endocrine Society Guidelines recommend two separate tests preferably in the morning) before initiating therapy with any testosterone replacement, including ANDROGEL™ treatment.

Geriatrics (>65 years of age):

There are limited controlled clinical study data supporting the use of ANDROGEL™ in the geriatric population (see WARNINGS AND PRECAUTIONS and CLINICAL TRIALS).

….

[179] The Warnings and Precautions and Clinical Trials portions of the product monograph now stated:

WARNINGS AND PRECAUTIONS

General

There is very limited data from clinical trials with ANDROGEL™ in the geriatric male (>65 years of age) to support the efficacy and safety of prolonged use. Impacts to prostate and cardiovascular event rates and patient important outcomes are unknown.

ANDROGEL™ should not be used to improve body composition, bone and muscle mass, increase lean body mass and decrease total fat mass. Efficacy and safety have not been established. Serious long term deleterious health issues may arise.

ANDROGEL™ has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk of serious adverse health effects, this drug should not be used for such purpose.

If testosterone deficiency has not been established, testosterone replacement therapy should not be used for the treatment of sexual dysfunction.

Testosterone replacement therapy is not a treatment for male infertility.

….

Special Populations

....

Geriatrics (> 65 years of age):

There are very limited controlled clinical study data supporting the use of testosterone in the geriatric population and virtually no controlled clinical studies on subjects 75 years and over.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma.

Geriatric patients and other patients with clinical or demographic characteristics that are recognized to be associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy.

Cardiovascular

Testosterone may increase blood pressure and should be used with caution in patients with hypertension.

Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Diuretic therapy may be required, in addition to discontinuation of the drug.

….

Monitoring and Laboratory Tests

The patient should be monitored (including serum testosterone levels) on a regular basis to ensure adequate response to treatment.

Currently there is no consensus about age specific testosterone levels. The normal serum testosterone level for young eugonadal men is generally accepted to be approximately 10.4-34.6 nmol/L (300-1000 ng/dL). However, it should be taken into account that physiologically testosterone levels (mean and range) decrease with increasing age. Men with levels below their laboratory's reference range and who are experiencing symptoms are candidates for testosterone replacement therapy and should be evaluated as such.

[180] The Consumer Information portion of the product monograph now stated:

ABOUT THIS MEDICATION

Your doctor has prescribed ANDROGEL™ because your body is not making enough testosterone. The medical term for this condition is hypogonadism.

What it does:

ANDROGEL™ delivers medicine into your bloodstream through your skin. ANDROGEL™ helps raise your testosterone to normal levels.

….

WARNINGS AND PRECAUTIONS

….

There is very little information from clinical trials with testosterone in the older male (>65 years of age) to support safe use for a long period of time.

You should not use testosterone in an attempt to reduce weight and increase muscle, or improve athletic performance as it may cause serious health problems.

You should not use testosterone to treat sexual dysfunction or male infertility.

Before using ANDROGEL™, talk to your doctor if you:

- have difficulty urinating due to an enlarged prostate. Older patients may have a higher risk of developing an enlarged prostate or prostate cancer;
- have prostate cancer (confirmed or suspected);
- have liver, kidney or heart disease;
- have high blood pressure (hypertension);
- have diabetes;
- have breathing problems during sleep (sleep apnea).

…

(c) 2008-2013 – Increased Use of Testosterone Products

[181] Prescriptions for AndroGel™ increased substantially between 2008 and 2013. The gross sales in 2010 were $22.4 million and the sales were continuing to increase.

[182] Between 2008 and 2012, the prescriptions of AndroGel™ to Canadian men rose approximately 40 percent. In a study of testosterone sales in 41 countries between 2000 and 2011 a 12-fold increase was noted. Advertising text included: “Lack of Energy – Low Sex Drive: Has He Lost that Loving Feeling?”; “Not feeling like the man you used to be?”; and “Low T could potentially affect an estimated 1.7 million men in Canada.” Advertisement in various medical journals promoted AndroGel™ as treatment for sexual symptoms.

[183] The Wises’ experts submit that the increase in sales was prompted by the aggressive efforts by pharmaceutical companies in selling LowT as a treatable disease.

[184] In 2013, the American Endocrine Society and the American Association of Clinical Endocrinologists noted that testosterone therapy has the potential for serious side effects and

represents a significant expense. The Society warned against overprescribing of testosterone stating that many of the symptoms attributed to male hypogonadism are commonly seen in normal male aging or in the presence of comorbid conditions.

(d) <u>2010: Basaria Study</u>

[185] In 2010, the Basaria Study was published. The primary author of this study, Dr. Basaria, declared receiving grant support from Solvay Pharmaceuticals (now Abbott) along with many others drug manufacturers.

[186] The Basaria Study was a randomized controlled trial designed to investigate whether testosterone gel provided greater muscular strength and functional benefits over placebo in a population of 209 elderly men who were all over 65 (mean age 74) who had difficulty walking two blocks or climbing ten steps.

[187] The Basaria Study was not designed to investigate cardiovascular events and many of the participants had existing cardiovascular disease and co-morbidities including obesity.

[188] The Basaria Study was stopped early by the Data and Safety Monitoring Board due to more adverse CV events in the testosterone group than in the placebo group; i.e., 23 men in the testosterone group compared to 5 in the placebo group. The Study had a very expansive definition of a cardiac event that was broader than the criteria in the Medical Dictionary for Regulatory Activities.

[189] The Basaria Study concluded that testosterone replacement treatment is associated with cardiovascular harm. Although the study was not designed to investigate cardiovascular events, the researchers adjusted the results for the study group for co-morbidities and concluded that the adverse CV events were higher for the study group than for the control group.

[190] As is the case of all studies, there were limitations on the reliability of the Basaria Study. From the perspective of its utility for determining an association between testosterone treatment and serious adverse CV events, the limitations included the small size of the cohorts and the small number of adverse events, and the circumstances that elderly men are more likely to have cardiovascular disease. In the Basaria Study, the study and control groups were unbalanced in that more patients in the treatment group had co-morbidities than the placebo group. Another criticism of this study is that the men received higher than approved doses of testosterone.

[191] The researchers observed that chance may have played a role in the outcomes but nonetheless concluded that in the group of elderly men, the application of testosterone gel was associated with an increased risk of adverse CV events.

[192] Dr. Mintzes said that the Basaria Study was a strong signal of cardiovascular harm. However, in contrast, Dr. Marais opined that if the results of the Basaria Study were confined to serious CV events, it was reduced to a finding that did not reach the conventional threshold for statistical significance, and the study did not support the Wises' claims.

[193] Dr. Milne acknowledged that the Basaria Study was not designed to investigate CV events, and that it was not possible to draw any reliable conclusions from only four serious CV events.

[194] In 2010, Canada and the FDA reviewed the Basaria Study and concluded that there was insufficient evidence to proceed further and that the existing labelling for testosterone products

was sufficient.

[195] In 2012, in response to the 2010 Basaria Study, the European Association of Urology (EAU) revised its Guidelines on prescribing of testosterone replacement therapies to recommend individualized monitoring schemes involving pre-treatment assessment by a cardiologist and close monitoring during testosterone treatment.

(e) 2013: Xu Study

[196] In 2013, the Xu Study was published. The aim of the study was to evaluate the risk of CV adverse events associated with use of testosterone treatment.

[197] The Xu Study was a meta-analysis of 27 RCTs that incidentally reported serious CV events. The results were incidental because none of the studies were designed to assess the relationship between testosterone replacement treatments (TRT) and serious CV events. In aggregate, the 27 studies included 1,733 persons who had received TRT and a control group of 1,261 subjects. The TRT group experienced 115 CV events and the control group experienced 66 CV events. CV events were defined as determined by the authors of the 27 RCTs.

[198] The Xu Study researchers concluded that TRT increases the risk of CV events. They calculated an odds ratio of 1.54 with a 95% confidence interval of 1.09 to 2.18. The researchers noted that the risk ratios were higher in the studies not funded by the pharmaceutical industry.

[199] Dr. Marais opined that the Xu Study was driven by the 2010 Basaria Study, which when adjusted to serious CV events, did not support the Wises' claims. When the Xu Study was correspondingly adjusted, then its key statistical result disappeared. Dr. Marais' opinion was that the Xu Study did not support the Wises' claims.

(f) 2013: Vigen Study

[200] In November 2013, the Vigen Study was published.

[201] The Vigen Study was a retrospective observational study of a cohort of 8,709 veterans in the U.S. Veterans Administration electronic medical record system who had coronary angiography and also had low testosterone levels. The aim of the study was to assess mortality and hospitalizations for heart attack (myocardial infarction) and stroke comparing men who started a prescription for testosterone after the angiography with those who did not take testosterone after their angiogram procedures.

[202] The study focused on testosterone treatment in general with most patients receiving testosterone patches. Only 1.1% were prescribed a testosterone gel like AndroGel™. The testosterone group had less coronary artery disease and other co-morbidities than the control group and thus the results had to be adjusted for possible confounding. Without the adjustments, the results were not statistically significant.

[203] The Vigen Study reported increased rates of death, myocardial infarction, and stroke among men treated with testosterone. With an average follow-up of just over two years, the authors found an increase in a combined outcome of death, myocardial infarction or stroke, among testosterone users of 1.3% at one year, 3.1% at two years and 5.8% at three years. After making adjustments for the co-morbidities, the researchers found an increased risk of all-cause mortality, myocardial infarction, and ischemic stroke from testosterone use. The hazard ratio

(HR) was 1.29, with a 95% confidence interval (CI, 1.05 to 1.58) and a p-value of 0.02.

[204] The researchers concluded that the use of testosterone therapy in this cohort of veterans with significant medical comorbidities was associated with increased risk of mortality, myocardial infarction, or ischemic stroke and that future studies including randomized controlled trials were needed to properly characterize the potential risks of testosterone therapy in men with comorbidities.

[205] There were limitations to this observation study, and it drew a great deal of criticism in the medical community with dozens of medical societies asking that *JAMA*, the highly-regarded peer-reviewed journal, retract the Vigen Study. A March 24, 2014 letter to the editor from 26 medical societies and 157 doctors, researchers, and clinicians recommended the study be retracted because of data mismanagement. *JAMA* published some corrections to the article but did not retract the article. One major criticism of the study was that if one ignores follow-up time, the absolute percentage of patients who died, had a stroke or a myocardial infarction was higher in the untreated group (21.2%) than the testosterone group (10.1%).

[206] Dr. Mintzes defended the Vigen Study from its critics and stated that it would be wrong to ignore follow-up time. She concluded that the Vigen Study showed an increased risk of all-cause mortality, heart attack, and ischemic stroke for those administered testosterone. She said that the Study showed an increased risk of heart attacks for the group prescribed with testosterone.

[207] Dr. Morgentaler was one of the harsh critics of the Vigen Study. He and Dr. Marais opined that the Vigen Study depended on a novel statistical method (i.e., stabilized inverse probability weighting) without accreditation in peer-reviewed literature and they concluded that the Study provided no statistically reliable support for the Wises' claims.

(g) <u>2014: Finkle Study</u>

[208] In January 2014, *PLOS ONE*, a medical journal, published the Finkle Study. This Study reported increased rates of non-fatal myocardial infarction following testosterone prescriptions.

[209] The Finkle Study was a retrospective observational study of data in a health insurance database (Truven Health MarketScan) that reported rates of non-fatal myocardial infarction in the period up to 90 days following a testosterone prescription and compared these rates to myocardial infarction rates in the previous 12 months. There was no control group, but the researchers also compared men receiving a first prescription for testosterone with men who received a first prescription for the PDE5 inhibitor erection dysfunction drugs sildenafil (Viagra and alternatives) and tadalafil (Cialis and alternatives).

[210] The Finkle Study observed an increase in myocardial infarction for patients receiving a testosterone prescription. Two comparisons were carried out: comparing the testosterone users' experiences before their initial prescription and in the 90 days post-initial prescription. For testosterone users, the ratio for myocardial infarction was 1.36 (95% CI 1.03 to 1.81) comparing experience of this cohort pre-prescription and post-prescription and the rate in men older than 65 years was 2.19. In comparison, no increase in myocardial infarction rate was noted for men who received a prescription for a PDE5 inhibitor.

[211] The researchers noted numerous limitations in their own Study, but they called for more research to assess testosterone efficacy and safety and given the growing use of TRTs, they

encouraged physicians to discuss the potential cardiovascular risks with their patients especially those with cardiovascular disease.

[212] Dr. Morgentaler was again critical of this Study and again Dr. Mintzes defended the Finkle Study from Dr. Morgentaler's criticisms, and she said that it showed an increased risk of heart attacks for the group prescribed with testosterone.

[213] Dr. Marais opined that the Finkle Study provided no statistically reliable support for the Wises' claims because it had uncontrolled biases and lacked a control group to establish a baseline of myocardial infraction. He opined that the Finkle Study did not support the Wises' claims.

(h) <u>2014: Regulatory Response</u>

[214] On January 31, 2014, after publication of the Finkle Study, the FDA announced it would investigate whether there were cardiovascular risks with the use of testosterone products. The FDA announcement stated:

> **FDA evaluating risk of stroke heart attack and death with FDA approved testosterone products**
>
> **Safety Announcement**
>
> The US Food and Drug Administration FDA is investigating the risk of stroke heart attack and death in men taking FDA approved testosterone products. We have been monitoring this risk and decided to reassess this safety issue based on the recent publication of two separate studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy. We are providing this alert while we continue to evaluate the information from these studies and other available data and will communicate our final conclusions and recommendations when the evaluation is complete.
>
> At this time FDA has not concluded that FDA approved testosterone treatment increases the risk of stroke heart attack or death. Patients should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health care professionals. Healthcare professionals should consider whether the benefits of FDA approved testosterone treatment is likely to exceed the potential risks of treatment. The prescribing information in the drug labels of FDA approved testosterone products should be followed.
>
> Testosterone is a hormone essential to the development of male growth and masculine characteristics Testosterone products are FDA approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition. Examples of these conditions include failure of the testicles to produce testosterone because of reasons such as genetic problems or chemotherapy. Other examples include problems with brain structures called the hypothalamus and pituitary that control the production of testosterone by the testicles.
>
> None of the FDA approved testosterone products are approved for use in men with low testosterone levels who lack an associated medical condition. ….

> The first publication that prompted FDA to reassess the cardiovascular safety of testosterone therapy was an observational study of older men in the U.S. Veteran Affairs health system published in the Journal of the American Medical Association (*JAMA*) in November 2013. The men included in this study had low serum testosterone and were undergoing imaging of the blood vessels of the heart called coronary angiography to assess for coronary artery disease. Some of the men received testosterone treatment while others did not. On average, the men who entered the study were about 60 years old and many had underlying cardiovascular disease. This study suggested a 30 percent increased risk of stroke heart attack and death in the group that had been prescribed testosterone therapy.
>
> A second observational study reported an increased risk of heart attack in older men as well as in younger men with pre-existing heart disease who filled a prescription for testosterone therapy. The study reported a two fold increase in the risk of heart attack among men aged 65 years and older in the first 90 days following the first prescription. Among younger men less than 65 years old with a pre-existing history of heart disease the study reported a two to three fold increased risk of heart attack in the first 90 days following a first prescription. Younger men without a history of heart disease who filled a prescription for testosterone however did not have an increased risk of heart attack.
>
> ….

[215] In the weeks that followed the FDA announcement, law firms in the United States commenced an advertising campaign stating that testosterone was associated with heart attacks, strokes, and death, and the law firms encouraged men to contact the firms if they had suffered an adverse event after the use of testosterone.

[216] On February 25, 2014, the Public Citizen, an NGO, called on the FDA to immediately add a black box warning about the increased risks of heart attacks and other cardiovascular dangers to the product labels of all testosterone-containing drugs available in the US. Relying on the Basaria, Xu, Vigen, and Finkle Studies, the Public Citizen asserted that it was clear that testosterone treatment increases the risk of cardiovascular disease.

[217] Between March 3 and 6, 2014, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) discussed cardiovascular risks for testosterone, and on April 11, 2014, it announced a review of testosterone-containing medicines for male hypogonadism over concerns about cardiovascular side effects of testosterone products raised by the studies noted by the FDA.

[218] On May 22, 2014, Health Canada conducted a Signal Assessment relating to Testosterone Containing Products and CV risk. The Signal Assessment stated:

> Marketed Health Products Directorate
>
> Health Products and Food Branch Health Canada
>
> Signal Assessment
>
> Testosterone Containing Products (ANDRODE®, ANDRIOL®, ANDROGEL™®, AXIROW, DELATESTRYL®, DEPO-TESTOSTERONE, Testim® and generics)

Cardiovascular Risk

….

1. Issue

Health Canada's Marketed Health Products Directorate (MHPD) regularly reviews published scientific literature, and in the course of that activity reviewed an article regarding the cardiovascular safety of testosterone hormone replacement therapy in 2010. Preliminary screening of the article found insufficient evidence to proceed any further with an assessment at that time and labelling for testosterone regarding cardiovascular risk was considered sufficient.

Since that time there has been a growing body of evidence calling into question the known cardiovascular safety of testosterone. A published scientific article regarding this issue from November 2013 prompted a detailed assessment.

2. Purpose

The purpose of this assessment is to retrieve and review available information regarding the cardiovascular safety of testosterone hormone replacement therapy to determine appropriate next steps, involving possible further risk mitigation measure(s).

3. Scope

Unless otherwise specified, the testosterone products referred to in this assessment are those used as testosterone hormone replacement therapy for hypogonadism (testosterone deficiency) in men in Canada ….

….

4.1.2. Testosterone

….

…. No large scale long-term clinical trials have been conducted to confirm the benefits of testosterone products. Treatment guidelines and recommendations for testosterone use in selected testosterone deficient men have been developed based on available evidence from smaller clinical trials and experience from experts in this field. The treatment guidelines developed by the International Endocrine Society based in the US in 2010 and by the European Association of Urology (EAU) in 2012 recommend testosterone therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. …. While the Endocrine Society guideline recommend against testosterone therapy in men with uncontrolled or poorly controlled heart failure, the EAU guideline does not. The EAU guideline states that testosterone therapy is not associated with the development of any unsafe cardiovascular events, and special monitoring in this respect is not needed. The EAU guideline recommends men with cardiovascular co-morbidity be assessed by a cardiologist before starting testosterone therapy and close monitoring of the cardiovascular system while on testosterone therapy's, whereas, the Endocrine Society guideline

does not.

….

4.1.3. Previous and ongoing mitigation measures Actions Taken by Health Canada

Risk communications issued

As of March 10, 2014, no risk communication has been issued by Health Canada regarding the possible risk of cardiovascular events associated with testosterone.

Product labelling updates

The current labelling regarding cardiovascular risk for testosterone products marketed in Canada includes primarily warnings for hypertension, as well as edema with or without congestive heart failure (especially in patients with pre-existing cardiac disease). …. No recent change has been made to the labelling of testosterone products regarding cardiovascular events.

Other related pharmacovigilance activities

Health Canada has been, as it does with all marketed health products, routinely monitoring new and emerging safety issues with testosterone. In 2010, an article was reviewed on the issue of cardiovascular safety. Due to insufficient evidence and labelling in Canada was considered sufficient at that time, routine monitoring of this possible risk was recommended. The growing body of available evidence (including the studies mentioned by the US Food and Drug Administration regarding this issue prompted this signal assessment.

….

4.2.1. Biological plausibility

The biological plausibility for the possible association between testosterone use and cardiovascular risks exists and possible mechanism have been proposed for arterial and venous related events. [Health Canada identified six plausible biological theories as to how testosterone might be a factor in cardiovascular risk.]

….

4.2.3. Published scientific literature evidence

….

This assessment reviewed seven published studies in which cardiovascular events were specifically examined … and three case series or case reports in which cardiovascular events were reported with testosterone being the sole suspected agent. The seven studies include one small clinical trial, two larger size retrospective cohort studies, and four systematic reviews and/or meta-analyses of previously published clinical trials.

These studies have varying degrees of bias and limitations. The clinical trial, two retrospective cohort studies, and one systematic review and meta-analysis showed a greater risk of cardiovascular events in men treated with testosterone as

compared to those without; whereas, the remaining three systematic reviews or meta-analyses studies showed no statistically significant risk for cardiovascular events. Note that the four studies that showed a statistically significant cardiovascular risk have fewer limitations (e.g. better control, adjustment or assessment for the possible influence by differences in patient baseline characteristics; or larger patient population). The most recent systematic review and meta-analysis's pooled analysis of clinical trials funded by pharmaceutical companies showed no risk associated testosterone while pooled analysis of other trials not funded by the industry did. Of the four studies showing a risk of cardiovascular events associated with testosterone use, three included the intended patient population (i.e. patients with a deficiency of endogenous testosterone) in Canada and patients with underlying risk factors such as pre-existing cardiovascular diseases. Of these three, [Vigen Study], with a longer follow up period, showed that testosterone use was associated with a greater risk of all-cause mortality, MI, and ischemic stroke up to 2,000 days after coronary angiography (although the risk estimate at 2,000 days is less reliable due to smaller sample size). With a larger patient population, [Finkle Study] further stratified the patient population by age (men< 65 years and ≥ 65 years) and heart disease history. Men < 65 years showed a greater risk of cardiovascular events in those with a heart disease history; whereas men ≥ 65 years without a heart disease history showed a greater risk of cardiovascular events (the risk in those with a heart disease history did not reach statistical significance). Furthermore, this study showed a non-statistically significant risk for cardiovascular events in the comparator group (phosphodiesterase type 5 inhibitors). Note that phosphodiesterase type 5 inhibitors (such as VIAGRA®, REVATIO®, and .WCIRCA® are labelled for serious cardiovascular events such as MI, arrhythmia and stroke in Canada. Confirmation of patient testosterone deficiency was not possible in the [Finkle Study].

In addition to the above studies, 19 cases of cardiovascular events in men on testosterone therapy were reported in the published literature. ….

In summary, individually, each of the above ten articles presents varying degrees of limitations in their studies or reported case information; however, collectively, they provide evidence to support the possible association between testosterone use and the risk of serious cardiovascular events such as MI and ischemic stroke in adult men with or without pre-existing comorbidities such as heart disease.

….

6. Considerations

There have been no large scale long-term well-controlled clinical trials to confirm the benefits and adverse effects of testosterone products. However, treatment guidelines based on smaller efficacy driven clinical trials have been developed by the US based international Endocrine Society and the European Association of Urology (EAU). Health Canada's approved CPMs for testosterone products give physicians the ability to determine treatment suitability based on available guidelines and each individual patient's situation. Given these tools are available

to physicians, the appropriate diagnosis and treatment of hypogonadism using testosterone therapy relies on the attending physicians. Considering the growing body of evidence regarding the cardiovascular risk of testosterone, the current CPMs and treatment guidelines may need to be revisited to give up-to-date guidance to physicians.

7. Conclusion

The benefits and risks of testosterone therapy have not been confirmed by large (e.g. thousands of patients) randomized clinical trials. The current approved usage in Canada and worldwide treatment guidelines are based on results from small clinical trials in which data regarding usage in the elderly population was limited. With respect to cardiovascular safety, the current available evidence, including the growing number of Canadian and international cases, the emerging literature studies (e.g. clinical trial retrospective cohort studies, systematic review and meta-analysis, and case reports, albeit with some limitations), and possible biological mechanisms, supports the possibility that cardiovascular adverse events (e.g. myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, or cardiac arrhythmia related events such as tachycardia and atrial fibrillation) other than those currently labelled in the CPM may occur with testosterone therapy. Furthermore, testosterone therapy prescription usage in Canada (and worldwide) has been increasing, with the elderly population being the second most prescribed age group (after men aged 40-59 years). The majority of these prescriptions were written by family physicians or physicians without a specialty…. This raised additional concern that these products may not always be used within the approved patient population in Canada.

8. Recommendations

A. Initial Labelling Update

Given the evidence as it currently stands … indicating a possible increased cardiovascular risk beyond what is currently labelled in the CPMs of testosterone products, it is recommended that Health Canada's Therapeutic Products Directorate (TPD) consider updating the CPMs of testosterone products with the new statements described and underlined below. Further labelling may be considered as new evidence emerges and further discussion with international counterparts occurs.

….

B. Timely communication to healthcare professionals and the public

Given the number of products in question and the need to inform health care professionals and the public of the appropriate use of these products and the possible increased cardiovascular risk associated with testosterone therapy in a timely manner, it is recommended that Health Canada's Marketed Health Products Directorate (MHPD) issue a Health Canada Information Update regarding this safety issue following the issuance of advisement letters to the involved innovator market authorization holders by TPD.

….

[219] On June 11, 2014, Health Canada requested that Abbott and other testosterone manufacturers modify their product monographs.

[220] On July 7, 2014, Abbott submitted a revision to the product monograph in accordance with Health Canada's request. The updated product monograph for AndroGel™ added the following warning:

> Post-market studies suggest an increased risk of serious cardiovascular events such as myocardial infarction and stroke may be associated with testosterone therapy. Before starting testosterone therapy, patients should be assessed for any cardiovascular risk factors, (e.g., existing ischaemic heart disease) or prior history of cardiovascular events (e.g., myocardial infarction, stroke, or heart failure). Patients should also be closely monitored for possible serious cardiovascular events while on testosterone therapy.

[221] On July 15, 2014, Health Canada published a Summary Safety Review about testosterone replacement products and cardiovascular risk. The Summary Review stated:

> **Summary Safety Review – Testosterone Replacement Products - Cardiovascular Risk**
>
> **Issue**
>
> A safety review was initiated to evaluate the currently available information regarding the possible cardiovascular risk (heart and blood vessel problems) associated with the use of testosterone replacement products. In the course of its normal activities, Health Canada observed a growing body of evidence suggesting a possible association between the use of testosterone replacement products and cardiovascular risk. This evidence, and in particular a scientific article published in November 20131, prompted this detailed assessment.
>
> **Background**
>
> **Approved use of testosterone replacement products in Canada.**
>
> In Canada, there are 12 testosterone-containing products that are currently marketed for use as testosterone replacement therapy: ANDRIOL, ANDRODERM, ANDROGEL™, AXIRON, DELATESTRYL, DEPO-TESTOSTERONE, TESTIM and their equivalent generics. These products are approved for use in adult males who are experiencing medical conditions because their body cannot make enough testosterone. Testosterone replacement products should not be used in men for non-specific symptoms if laboratory tests have not been done to confirm a low testosterone level, and if other possible causes of symptoms have not been excluded.
>
> **Cardiovascular risk**
>
> Cardiovascular risk refers to the risk of a group of heart and blood vessel problems that can include, but is not limited to, heart attacks, strokes, blood clots in the lungs or legs, and an irregular heart rate. It is known that testosterone replacement therapy may cause an increase in blood pressure and fluid retention/swelling. In addition to these risks, testosterone replacement products may also cause blood vessel narrowing by promoting the build-up of fats and

other materials in the inner walls of blood vessels. This narrowing of blood vessels makes it harder for blood to flow through, and if a blood clot forms and blocks the flow of blood, it may cause a heart attack or stroke. Testosterone replacement products may also cause blood clots in the lungs or legs by affecting blood clotting processes.

At the time of this review, the Canadian product label for testosterone replacement products identified the risk of high blood pressure, as well as fluid retention/swelling (particularly in persons with underlying heart problems).

Objective

To assess the available evidence concerning the cardiovascular risk, beyond the known risks of high blood pressure and fluid retention/swelling, which may be linked to testosterone replacement products.

Key Findings

Use of testosterone replacement products in Canada

Similar to the trend in other countries, prescriptions for testosterone replacement products in Canada have been increasing. Testosterone was most commonly prescribed to men aged 40-59 years. The elderly population (65 years old and over) is the second most prescribed age group.

Canadian reports of cardiovascular problems in Canada associated with the use of testosterone replacement products.

As of Aug. 31, 2013, Health Canada received 35 reports of cardiovascular problems involving testosterone replacement products. Some of these reports described the problem as disappearing after the patient stopped using the product or as re-appearing when the patient re-started the product after having temporarily stopped it. This may support a possible link between cardiovascular risk and testosterone replacement products. Some of the reports also described patients with current, or a history of, conditions (e.g., diabetes and high blood pressure) that may also be associated with the reported cardiovascular problems. In 11 of the 35 reports, heart attack, blood clots in the lungs, or irregular heart rate were considered possibly related to testosterone therapy.

Scientific reports

Several studies conducted after marketing suggest an increased risk of serious cardiovascular problems (e.g., heart attack and stroke) that may be linked to testosterone replacement products. Although these studies have limitations, they provide evidence in support of this possible association when considered as a whole. Additional cases of cardiovascular problems, such as blood clots in the lungs and legs, have also been reported in the literature, as well as in other countries. Some of these cases also described the problem as disappearing after the patient stopped using the product or as re-appearing after the patient re-started the product after having temporarily stopped it.

> Conclusions and Actions
>
> The current available evidence suggests the possibility that cardiovascular problems, other than those already identified, may occur with the use of testosterone replacement products. The use of these products in Canada (and internationally) has been increasing and findings from a Canadian study raise additional concerns that these products may not always be used within the approved patient population.
>
> **Health Canada actions**:
>
> 1. Health Canada is working with manufacturers to update the Canadian product label for testosterone replacement products regarding possible cardiovascular risks including heart attack, stroke, blood clots in the lungs or legs, and irregular heart rate;
>
> ….
>
> Health Canada will keep Canadians informed and take action, as appropriate, if any new safety information is identified.
>
> ….

[222] Also on July 15, 2014, Health Canada published an Information Update entitled "Possible cardiovascular problems associated with testosterone products." The Information Update stated:

> OTTAWA - Health Canada is advising patients and healthcare professionals of new safety information regarding testosterone hormone replacement products and a risk of serious and possibly life threatening cardiovascular heart and blood vessel problems.
>
> ….
>
> Health Canada has recently completed a safety review on testosterone replacement products. This review found a growing body of evidence from published scientific literature and case reports received by Health Canada and foreign regulators for serious and possible life threatening heart and blood vessel problems such as heart attack stroke blood clot in the lungs or legs and increased or irregular heart rate with the use of testosterone replacement products.
>
> Health Canada is working with manufacturers to update the Canadian product labels regarding this risk. The Department continues to collaborate with foreign regulators including the United States Food and Drug Administration and the European Medicines Agency regarding this safety concern. Health Canada will keep Canadians informed and take action as appropriate if any new safety information is identified. Health Canada would like to remind the public of the following important information from the Canadian Product Monographs regarding the use of testosterone products.
>
> …

[223] Meanwhile, on July 16, 2014, the FDA denied the Public Citizen petition that requested a black box warning. The FDA concluded that none of the four identified studies reporting CV risk provided clear evidence of increased risk due to treatment with testosterone. After again

reviewing the Basaria, Xu, Vigen, and Finkle Studies, the FDA stated that there was insufficient evidence of a causal link between testosterone therapy and adverse cardiovascular outcomes to support the regulatory actions requested by Public Citizen.

[224] Following a September 17, 2014 Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, on March 3, 2015, the FDA released an announcement stating that it was requiring manufacturers to add information to labeling about a "possible increased risk of heart attacks and strokes in patients taking testosterone". The announcement stated that the FDA had concluded that there is a possible increased CV risk associated with testosterone use and that some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not.

[225] In the meantime, in Europe, the EMA, after requesting additional information from drug manufacturers, concluded there was no clear indication of increased CV risk and, therefore, determined there was no need to add a warning regarding CV risk. The EMA did, however, publish the following information in its product assessment report:

- In patients suffering from severe cardiac hepatic or renal insufficiency or ischaemic heart disease treatment with testosterone may cause severe complications characterized by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately.
- Testosterone may cause a rise in blood pressure and … should be used with caution in men with hypertension.
- There is limited experience on the safety and efficacy of the use of [name of product] in patients over 65 years of age. Currently there is no consensus about age specific testosterone reference values. However it should be taken into account that physiologically testosterone serum levels are lower with increasing age.

(i) 2015: The Etmiman Study and the Morgentaler Article

[226] In 2015, M. Etmiman, *et al* published: "Testosterone Therapy and Risk of Myocardial Infarction: a Pharmacoepidemiologic Study": *Pharmacotherapy*, 2015; 35(1):72-8 (the "Etmiman Study"), which was a retrospective observational study using data from a health plan claims database. It was an observational study of a cohort of 934,283 men aged 45 to 80 years from a large U.S. insurance database (IMS Lifelink). The study observed a total of 515 CV events in men prescribed testosterone. The authors compared the myocardial infraction rate in various groups and calculated rate ratios (RR) for men whose last testosterone prescription (of any type) was within 90 days before the index date (current users) and past users (defined as all others).

[227] The authors of the Etmiman Study did not find an association between myocardial infraction and testosterone treatment save for a statistically significant association between first-time exposure to testosterone replacement treatment and myocardial infarction, although the absolute risk was low. More precisely, the authors found an increased risk of myocardial infarction among current first-time users: RR = 1.41 (95% CI 1.06 to 1.87), but they did not find an increased risk among prevalent users. The authors of the study concluded that an association

between myocardial infarction and past or current TRT had not been found but there was a very low but statistically significant association between first-time TRT exposure and myocardial infarction. Dr. Mintzes said that the Study added to the evidence of CV risks with testosterone use.

[228] In 2015, in an article in *Mayo Clinic Proceedings*, Dr. Morgentaler and others reviewed the Basaria, Xu, Vigen, and Finkle Studies and stated that none of the four studies supported any increased serious CV risk from the use of TRT.

(j) 2015 – Revision of the Product Monograph

[229] The AndroGel™ product monograph was revised. The product monograph approved on January 28, 2015 contains the following revision under Warnings and Precautions:

> Post-market studies suggest increased risk of serious cardiovascular events such as myocardial infarction stroke and venous thromboembolic events including deep vein thrombosis and pulmonary embolism associated with testosterone therapy. Before starting testosterone therapy, patients should be assessed for any cardiovascular risk factors (e.g., existing ischaemic heart disease) or prior history of cardiovascular events (e.g., myocardial infarction, stroke, or heart failure). Patients should also be closely monitored for possible serious cardiovascular events while on testosterone therapy. If any of these serious adverse events are suspected, treatment with ANDROGEL™ should be discontinued and appropriate assessment and management initiated.

[230] The Consumer Information portion of Abbott's product monograph for AndroGel™ was revised to state:

> Before using ANDROGEL™, talk to your doctor if you:
>
> …
>
> • have heart or blood vessel problems or a history of these problems such as heart attacks, stroke, or blood clot in the lungs or legs;
>
> ….
>
> SIDE EFFECTS AND WHAT TO DO ABOUT THEM
>
> …
>
> - Increased or irregular heart rate blood clot in the lungs or legs
>
> SERIOUS SIDE EFFECTS HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms/Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Heart attack and			√

	stroke			

(k) <u>2015 – The FDA's Product Safety Announcement</u>

[231] In the U.S., on March 3, 2015, the FDA published a product safety announcement that stated:

> The U.S. Food and Drug Administration FDA cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging even if a man's symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.
>
> Testosterone is FDA approved as replacement therapy only for men who have low testosterone levels due to disorders of the testicles pituitary gland or brain that cause a condition called hypogonadism. Examples of these disorders include failure of the testicles to produce testosterone because of genetic problems or damage from chemotherapy or infection. However FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established.
>
> In addition, based on the available evidence from published studies and expert input from an Advisory Committee meeting FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. Some studies reported an increased risk of heart attack stroke or death associated with testosterone treatment while others did not.
>
> Based on our findings we are requiring labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. Health care professionals should make patients aware of this possible risk when deciding whether to start or continue a patient on testosterone therapy. We are also requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. We are encouraging these manufacturers to work together on a clinical trial but they are allowed to work separately if they so choose.

[232] In August 2015, the FDA published an article in the *New England Journal of Medicine*. The article stated:

> Testosterone products have been approved by the Food and Drug Administration FDA for replacement therapy in men with classic hypogonadism primary or secondary hypogonadism caused by specific well recognized medical conditions such as Klinefelter's Syndrome pituitary injury or toxic damage to the testicles. Treatment with testosterone to restore serum concentrations in men with classic hypogonadism has long been considered the standard of care. On the basis of this intended use the FDA has required only that testosterone products reliably bring low serum testosterone concentrations into the normal range defined as the concentrations seen in healthy young men. The FDA has not mandated that clinical trials show improvements in signs or symptoms of hypogonadism in order for testosterone product to be approved.
>
> In recent years however testosterone use has increased markedly among middle aged and elderly men for a controversial condition that the FDA calls age related hypogonadism. This condition also referred to as late onset hypogonadism is typically diagnosed in men who for no discernable reasons other than older age have serum testosterone concentrations below the normal range for healthy young men as well as signs and symptoms that may or may not be caused by low testosterone concentrations. Serum testosterone appears to decline as men age and although this decline is usually modest concentrations can fall below the normal range for healthy young men In these cases it is unclear whether coexisting nonspecific signs and symptoms such as decreases in energy and muscle mass are a consequence of the age related decline in endogenous testosterone or whether they are the result of other factors, such as coexisting conditions concomitant medications or perhaps aging itself.
>
> … prompted by the growing numbers of older men using testosterone to delay or treat a variety of signs and symptoms the Institute of Medicine formed a committee to assess the state of knowledge regarding testosterone therapy After reviewing the medical literature the committee concluded that the available evidence on the effects of testosterone therapy in older men was limited and inconclusive. To date there is no definite evidence that increasing serum testosterone concentrations in these men is beneficial and safe and the need to replace testosterone in older men who lack a distinct well recognized cause of hypogonadism remains debatable.

(l) <u>2016 – The Testosterone Trials</u>

[233] The "Testosterone Trials," was the largest RCT to date involving TRT. The report on this Study, the Snyder Study, was published in the *New England Journal of Medicine* in February 2016.

[234] The Snyder Study, "Effects of Testosterone Treatment in Older Men" reported on a randomized double-blind placebo controlled trial authored by the Testosterone Trial Investigators. The Study was designed to address benefits rather than safety. The targeted benefits were sexual function, physical function and vitality. In this Study, 790 men, over 65 years of age, received either testosterone gel or placebo for one year, with follow-up for an additional year to monitor for adverse events. In the first year of the Study, there were seven

major CV events in the testosterone group and seven events in the placebo group. In the second year, there were two major CV events in the testosterone group compared with nine in the placebo group. This Study does not evidence any increased risk for the testosterone group.

[235] The results of the Testosterone Trials showed no significant improvement from using TRT in regards to physical function. Vitality also showed no benefit. However, sexual function demonstrated a perceived benefit at three, six, and nine months but not at 12 months, compared to placebo.

10. The Evidence of Dr. Mintzes

[236] Dr. Mintzes reviewed: the Basaria, Xu, Vigen, and Finkle Studies; the safety assessments of Health Canada, the FDA and the EMA, and additional studies that had been mentioned by the regulators. Dr. Mintzes reviewed the seven epidemiological studies considered by Health Canada. She considered nine additional studies. Eight of the nine did not indicate an increased risk from testosterone replacement treatments ("TRT"). The ninth study, the Etmiman Study, indicated to her serious harm associated with testosterone use.

[237] Although she acknowledged that there were limitations in the studies, in Dr. Mintzes' opinion, there was a "strong signal" from the medical literature that testosterone products, including AndroGel™ are associated with an increased risk of serious adverse events. Relying on, in part, the Safety Review completed by Health Canada in July 2014 and the safety advisories of the FDA, Dr. Mintzes opined that "there is a strong signal from the medical literature that testosterone products, including AndroGel™ are associated with an increased risk of serious adverse events, including cardiovascular risks, blood clots (venous thromboembolic events), heart attack and stroke." She also noted that Health Canada's safety review discussed the biological plausibility for cardiovascular harm from testosterone use due to effects of testosterone on salt and water retention and she said that the signal of a potential for harm is sufficiently strong to warrant caution with use.

[238] Dr. Mintzes stated that a well-designed large-scale double-blind randomized controlled trial of several years' duration, comparing testosterone with placebo, would provide the most reliable evidence of whether testosterone use increases the risk of CV events. In the absence of such a trial, in her view, sufficient evidence existed to warrant caution with TRTs.

[239] Under cross-examination, Dr. Mintzes acknowledged that association is not causation and that she did not conclude in her report that there was a causal relationship between TRT and CV events. She conceded that there was not any strong evidence of causation.

[240] Dr. Mintzes opined that AndroGel™ ought not to have ever been indicated for andropause because andropause is not a medical condition but rather is a market-driven concept accepted by a handful of physicians as an antidote for aging.

[241] Dr. Mintzes said that the link between LowT and reduced libido, muscle strength, reduced energy, and depressed mood was weak and there was lack of evidence of LowT being a condition and rather reflected physiological changes that occur with age, obesity, or poorer health.

[242] She opined that the drug bulletins that are genuinely independent of the pharmaceutical industry that are prepared for physicians and pharmacists have judged testosterone to have very limited to no effectiveness for libido sexual function, depression, cognitive function, quality of

life, and for preventing CV events.

[243] In her second expert report dated April 16, 2016, Dr. Mintzes did not focus on the association between AndroGel™ and cardiovascular harm but rather examined whether Abbott could justify its advertised claims that AndroGel™ was a treatment for what she described as non-pathological hypogonadism; i.e. an age-related decline in testosterone and an associated experience of a decline in mood, vitality, energy, physical functioning, and sexual performance including erectile dysfunction.

[244] In her second report, she stated that AndroGel™ had been promoted by Abbott to improve mood, vitality, and sexual functioning in aging men but a review of the scientific evidence did not justify Abbott's claims. She said that there was a lack of evidence or no clear evidence of any clinically relevant benefits from treatment with testosterone. She said that such evidence as there was of modest benefits was likely affected by industry sponsorship and selective publication and that the very modest observed effects of testosterone on sexuality diminished or disappeared when these biases were taken into account.

[245] Dr. Mintzes concluded that Abbott's claimed effects on sexuality for Androgel™ in Canadian advertising were not supported by solid research evidence and the very modest differences between testosterone and placebo on libido and sexual functioning were below a threshold that would be considered clinically significant. From a temporal viewpoint, she said that when Abbott made claims in Canadian medical journal advertisements for effects of AndroGel™ treatment on sexual function, physical function, mood or vitality, it did not have substantive research evidence to back its claims and the recent studies did justify the promotional claims and the efficacy claims did not outweigh the potential for harm.

11. The Evidence of Dr. Milne

[246] It was Dr. Milne's expert opinion that: (a) there is evidence in the literature that TRT is associated with, and can increase, the risk of major CV events; (b) the regulators were correct to add additional warnings to AndroGel™ based on the recent publications demonstrating increased risk of adverse events; and (c) use of AndroGel™ by Mr. Wise could have contributed to his heart attack.

[247] Further, it was Dr. Milne's opinion from his review of the scientific data, that the benefits of TRT are not clear. Dr. Milne made a detailed review of the studies and articles relied on by Dr. Morgentaler and stated that he did not find the evidence definitive. It was Dr. Milne's opinion that there had not been a properly designed research study and that Androgel™ had not been proven to be safe. In his view, while most of the historic scientific literature suggested no increase in adverse events or harms with TRTs, this was not proof of the safety of the product and some of the industry sponsored or supported studies reflected an industry bias to under-report adverse events and harm.

[248] Dr. Milne stated that while there were limitations in the Basaria, Xu, Vigen, and Finkle Studies, as there is in all studies, these studies supported the claim that there was an increase in CV risk with TRTs. Further, the more recent Etmiman Study observed a 41% relative increase in risk of myocardial infarction by first-time users and a 49% relative risk increase in first-time topical gel users and although the absolute increase in risk was small the actual amount of harm was considerable because millions of men were potentially exposed to this treatment. He said

that patients needed to be informed of the possible increased risk of myocardial infarction especially because the evidence of any actual benefits from the treatments was very weak.

[249] In this last regard, Dr. Milne stated that low testosterone may only be a marker of general health and the purported benefits of TRT came mostly from observational studies demonstrating an association not causation. In his view, there was no convincing evidence with patient oriented outcomes demonstrating that the risks, if any, of LowT can be mitigated with TRT.

[250] Dr. Milne said that all of the studies in the testosterone literature had limitations and flaws, including lack of blinding, lack of randomization, lack of control group, inappropriate comparison group, variety of biases, limited search strategies, failure to report harm/adverse events, lack of comprehensive follow-up, loss to follow-up, short duration, subgroup analyses, reliance on p-values, lack of precision, composite outcomes, high statistical heterogeneity, statistical rather than clinical significance, and surrogate markers not patient oriented outcomes.

[251] He said of his own analysis that one strength was his lack of a conflict of interest with the material being reviewed in contrast to Abbott's experts who had multiple conflicts of interest that diminished their objectivity and obscured the truth.

[252] In his cross-examination, Dr. Milne acknowledged that association is not proof of causation and that to date only an association and a weak signal of CV risk had been shown from TRT studies. He agreed that until a clinical trial was done, it could not be said whether TRT causes CV harm.

12. The Evidence of Dr. Morgentaler

[253] It was Dr. Morgentaler's opinion that there is no scientific basis for the claim that TRT causes or contributes to CV events or increases their risk. He said that the Basaria, Xu, Vigen, and Finkle Studies were weak studies that did not provide credible evidence of increased risk. He said that the Vigen and Finkle Studies arguably demonstrated a protective effect of TRT on CV risk. He said that the posited association between testosterone treatments and serious CV events was against the likelihood of increased risk and rather suggested that the treatments reduced the risk of cardiovascular misadventures.

[254] Dr. Morgentaler was sharply critical of each of the studies that had been relied on in the Wises' Statement of Claim. He said that in contrast to the four studies reporting increased CV risk with TRT, there was an extensive body of literature accumulated over several decades that suggested exactly the opposite; i.e., that testosterone deficiency was associated with adverse CV events and TRT was beneficial and reduced the risk of an adverse CV events. He said that after the Finkle Study, there had been at least 16 publications that reported no negative effects and several that reported cardiovascular benefits from TRT.

[255] Dr. Morgentaler strongly disagreed with the position taken by the FDA that testosterone is only indicated in men with classical hypogonadism. He said that the benefits of testosterone treatment had been clear for decades for classic hypogonadism and the treatment was beneficial for other causes of hypogonadism. He stated that the symptoms and signs of hypogonadism were due to a deficiency of the testosterone hormone, regardless of its cause. He said the symptoms and signs resolve once testosterone levels return to normal levels.

[256] Dr. Morgentaler said that most well-recognized medical societies do not share the recently announced view of the FDA that testosterone is only indicated in men with classical

hypogonadism and said that the symptoms and signs of hypogonadism are due to a deficiency of the testosterone hormone, regardless of its cause. He said that there is no justification to restrict treatment to a limited number of causes based on the knowledge from more than 20-30 years ago.

[257] In 2015, for *Mayo Clinic Proceedings*, Dr. Morgentaler and his colleagues published a review of approximately 100 studies conducted between 1940 to 2014 relating to testosterone and serious CV events: A. Morgentaler *et al*, "Testosterone Therapy and Cardiovascular Risk: Advances and Controversies", *Mayo Clin. Proc.*, 2015, 90(2). It was Dr. Morgentaler's opinion that none of the studies showed any association between TRT and increased CV risk. Rather, Dr. Morgentaler reported that TRT reduced CV event risk. He said that the studies showed that: mortality was reduced, the capacity to exercise was increased, carotid intima-media thickness and epicardial fat (a marker for CV risk) was reduced, muscle mass was increased and fat was reduced, metabolic syndrome (a risk factor for CV events), was resolved; and there was improvement in blood sugar control, representing a reduction in another CV risk factor. He said that administering testosterone resulted in greater exercise capacity and peak oxygen consumption compared with placebo among individuals with heart failure.

[258] Dr. Morgentaler said that the Testosterone Trials demonstrated that men who received testosterone gel achieved statistically significant benefits in the areas of sexual desire, sexual function, physical activity, and mood. In his third report, Dr. Morgentaler said that the Testosterone Trial's information did not show any increased risk of CV risk to those patients who had been prescribed testosterone products for hypogonadism by virtue of age alone. He said that it was worth noting that the study population consisted exclusively of men 65 years and older, a population already at increased risk of CV risk by virtue of age alone and that the Testosterone Trials excluded men with classical hypogonadism.

13. The Evidence of Dr. French

[259] Dr. French joined the parade of disparaging Dr. Mintzes for not having clinical experience and of having the impudence to express an epidemiological opinion without having this experience. Once again, I found the criticism unfair and paid far more attention to what Dr. French could objectively contribute to the debate.

[260] Dr. French stated that LowT had been shown to be associated with higher rates of all-cause mortality and of cardiovascular mortality. He stated that there was a correlation between the seriousness of heart failure and the degree of testosterone deficiency and that patients suffering from diabetes and obesity had been shown to have lower levels of testosterone compared with those healthy control groups.

[261] In addition to the Basaria, Xu, Vigen and Finkle Studies, Dr. French examined the medical literature and concluded that the data indicated that TRT did not increase the risk of adverse CV events. As for the Basaria, Xu, Vigen and Finkle Studies, in his opinion, all the studies were poorly designed, poorly executed, and replete with errors in data collection and analysis. In his opinion, none of the studies provided credible evidence of an increased risk of CV events from testosterone replacement treatments.

[262] Dr. French opined that there have been multiple benefits on the cardiovascular system from the use of testosterone. TRT in men who suffer from hypogonadism had proven effective in

decreasing cardiac problems by promoting better exercise tolerance, and by reducing of central obesity or increased weight in the waist, which has been shown to be a risk factor in heart disease. In addition, he said that favorable changes have been reported in platelet aggregation with reduced formation of blood clots and fibrinolytic activity with breakdown of blood clots and reduced exercise-induced heart ischemia.

[263] Dr. French served on the Data Safety Monitoring Board for the Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) Trial, which was the largest randomized placebo-control trial to date to investigate the effects of testosterone on atherosclerosis progression in older men. In this study, the researchers evaluated cardiovascular endpoints using a placebo-control, double-blind, parallel-group randomized controlled trial involving 308 men aged 60 years or older with low or low-normal testosterone levels. 156 participants were randomized to receive 7.5 g of 1% testosterone and 152 were randomized to receive placebo gel packets daily for 3 years. On August 11, 2015, a report on the TEAAM Trial was published in *JAMA*. The authors found that there was no significant difference in common carotid artery intima-media thickness and coronary artery calcium (proxies for atherosclerosis) between the placebo and testosterone groups.

[264] Dr. French opined that the results of this trial confirm that there is no significant adverse effect of testosterone on important markers of CV risk. He said that the findings of the TEAAM Trial were consistent with other studies demonstrating the lack of any causal relationship between CV events and TRTs.

[265] Dr. French summarized the epidemiological literature on the relationship between TRT and CV events. He opined that the epidemiological studies indicated that TRT does not increase the risk of adverse CV events in men. He said that the Basaria, Xu, Vigen, and Finkle studies were flawed and did not provide credible evidence of the Wises' claims about the unsafety of testosterone replacement medications.

[266] In his second report, Dr. French reviewed the epidemiological studies identified by Dr. Mintzes and said that there was nothing there that would cause him to change his opinion. He said that there was no support for the claim that TRT causes increased CV risk and that the studies that showed an increased risk were not scientifically sound or reproducible.

[267] In his third report, Dr. French stated that while the results of large, long-term RTCs will be interesting and further advance the understanding of the benefits and risks of TRT, the evidence in the extensive testosterone literature to date was that there are clinically important benefits and no CV risks from TRT in testosterone deficient men.

[268] Dr. French said that Dr. Milne's theory that TRT could dilate the coronary arteries, increase blood flow, and make pre-existing coronary plaques unstable leading to a heart attack was not supported by any scientific evidence. It was Dr. French's opinion, as a cardiologist, that the theory was not plausible and was preposterous.

14. The Evidence of Dr. Brock

[269] In his report, Dr. Brock, who is an urologist, indicated that AndroGel™ was indicated for the treatment of hypogonadism, but it should not be used to treat symptoms suggestive of hypogonadism unless testosterone deficiency had been demonstrated and other etiologies responsible for the symptoms in the patient had been considered and excluded. He said that

based on his review of the scientific literature and through personal experience in clinical practice, he would continue to strongly recommend use of testosterone in patients who presented with symptoms of hypogonadism and who were found to have biochemical evidence of a LowT state.

[270] Dr. Brock opined that on balance, the scientific literature demonstrates that testosterone deficient men are at an elevated risk for CV events, including death. He said that the literature showed that and when men treated with testosterone are compared to untreated men, a measureable health benefit was demonstrated in many studies. He concluded from his review of the scientific literature that: (a) men with LowT are at an elevated risk of morbidity and mortality including from CV and metabolic events; (b) appropriate use of testosterone in these populations has been shown to mitigate the risks to some extent; and (c) the overwhelming existing evidence shows an overall health benefit of testosterone use in hypogonadal men.

[271] Dr. Brock was one of the researchers in a RCT examining the effects of TRT on the symptoms of hypogonadism. He was the lead author of a paper that was published in the *Journal of Urology* on May 17, 2015. The RCT was a double-blind study evaluating 715 hypogonadal men over 18 years of age for 12 weeks. The study found no significant differences in CV events between the testosterone and placebo groups. Dr. Brock deposed that the study demonstrated no change in blood pressure, heart rate, or any measureable difference in rates of stroke, myocardial infarction or serious adverse events. He said that there was no evidence found of CV risk from topical testosterone.

[272] Dr. Brock described the A. Aversa *et al*, RCT epidemiological study, "Effects of Testosterone Undecanoate on Cardiovascular Risk Factors and Atherosclerosis in Middle-Aged Men with Late-Onset Hypogonadism and Metabolic Syndrome: Results from a 24-month, Randomized, Double-Blind, Placebo-Controlled Study," which was published in *Sex Med*., 2010, 7(10). He said that the study was designed to to evaluate TRT on CV risk. While the numbers were small, the assessments were intensive and carried out over a two-year period. No CV adverse signal was noted in this intensive assessment trial; rather, there was a significant risk reduction among the men receiving testosterone observed.

[273] Dr. Brock testified that the TEAAM Trial affords "strong evidence" that TRT does not increase the risk of serious CV events.

[274] Dr. Brock reviewed 19 epidemiological studies and concluded that: men with LowT are at an elevated risk of morbidity and mortality including from CV and metabolic events; appropriate use of testosterone in these populations has been shown to mitigate these risks; and the overwhelming existing evidence shows an overall health benefit of testosterone use in hypogonadal men. He opined that TRT improves health-related quality of life of men diagnosed with late-onset hypogonadism.

[275] Dr. Brock stated that the Basaria, Xu, Vigen, and Finkle Studies were outliers going against the preponderance of the scientific literature. He said the four Studies were flawed and when the defects of these Studies were taken into account, they did not support the claim that TRT causes CV events or increased CV risk.

[276] He said that the decisions and announcements of Health Canada and the FDA did not support the claim that 1% testosterone gel causes CV events such as heart attack, stroke, thrombolytic events or death, or place LowT patients at an increased risk for these events. It was

his opinion that LowT patients who receive appropriate TRT in accordance with recognized standards of practice are not at an elevated risk of CV events; and rather treatment was likely to have a protective effect and guard against the risk of adverse CV outcomes and cardiovascular disease.

[277] Dr. Brock was dismissive of Dr. Mintzes' credentials to comment on the epidemiology of TRTs. In my view, Dr. Brock's criticism was unfair and started to move into the territory where people who live in glass houses ought not to be throwing stones. Epidemiology is not the reserve of clinicians. In my view, Dr. Mintzes was entitled to her view of the information and epidemiological studies as he was, and, as noted above, I have concluded that none of the expert witnesses should be disqualified for partisanship.

[278] Dr. Brock said that Dr. Mintzes' characterization of hypogonadism as being restricted only to certain diseases such as testicular failure, orchiectomy and Klinefelter's Syndrome was not supported by clinical practice, national and international guidelines, or the literature. Hypogonadism or testosterone deficiency syndrome was, in his view, a condition in which men with abnormally LowT exhibit symptoms that occur in patients with underlying conditions as well as in patients in many other circumstances. Dr. Brock's criticism of Dr. Mintzes manifested the problem that I alluded to earlier that while everybody agreed that testosterone was an appropriate treatment for hypogonadism, they would not come to terms on the pathology of hypogonadism.

[279] In any event, Dr. Brock disagreed with Dr. Mintzes that Health Canada's conclusion that current available evidence suggests the possibility that cardiovascular problems, other than those already identified, may occur with the use of testosterone replacement products was a strong signal. He said that regardless of how one characterizes the strength of the "signal", it is not evidence of causation. In my opinion, however, this is an example of unfair criticism because Dr. Mintzes' never claimed that causation of serious cardiovascular events had been proven.

[280] Dr. Brock was also dismissive of Dr. Milne's credentials to opinion on the risks and benefits of testosterone treatment for hypogonadism. He said that there were undoubted benefits revealed by the research literature and in decades of experience by treating physicians. He disagreed with Dr. Milne that the Basaria, Xu, Vigen, and Finkle Studies, and other studies, provide strong evidence of an association between the treatments and major CV events. He stated that none of the studies, which were seriously, flawed supported the Wises' allegations.

15. The Evidence of Dr. David Greenberg

[281] In his three reports, Dr. Greenberg discussed the nature, diagnosis, standard of care, and treatment of hypogonadism from the perspective of a primary care physician. He discussed the allegation that testosterone gel causes CV events with a focus on the perspective of the primary care physician. He reviewed the Product Monograph for AndroGel^{TM}, and commented on the appropriateness of the warnings in the Monograph over time. He commented on the allegations in the Statement of Claim regarding advertising for AndroGel^{TM}. He also responded to the reports of Dr. Mintzes and Dr. Milne.

[282] Dr. Greenberg, who as noted earlier in this decision, is a staunch proponent for testosterone replacement as a factor in men's health described how he and other treating physicians make a diagnosis of hypogonadism in older men. He said that he was guided by a

screening questionnaire known as the ADAM Questionnaire (Androgen Deficiency in the Aging Male) which was developed by John Morley, a geriatrician at St. Louis University. Dr. Greenberg acknowledged that pharmaceutical companies including Abbott used the ADAM Questionnaire to market their products.

[283] The ten questions in the ADAM Questionnaire are as follows: (1) Do you have a decrease in libido (sex drive)? (2) Do you have a lack of energy? (3) Do you have a decrease in strength and/or endurance? (4) Have you lost height? (5) Have you noticed a decreased "enjoyment of life"? (6) Are you sad and/or grumpy? (7) Are your erections less strong? (8) Have you noticed a recent deterioration in your ability to play sports? (9) Are you falling asleep after dinner? And, (10) Has there been a recent deterioration in your work performance? A positive result of the ADAM Questionnaire is defined as a "yes" to any three questions or as a "yes" to the question of diminished libido or weaker erections.

[284] In his report, Dr. Greenberg reported that he used the ADAM Questionnaire as a preliminary step in the diagnostic process and if the patient's history was consistent with what might be suspected to be hypogonadism, he would then order blood work. He said that if the testosterone level was between 12 to 35 units, he would not make a diagnosis of hypogonadism even in the presence of symptoms but below 12 units, particularly below 8 units, he would make a diagnosis of hypogonadism after considering and ruling out other causes for the patient's symptoms.

[285] Dr. Greenberg commented on the Basaria, Xu, Vigen, and Finkle Studies from his perspective as a clinician in active family practice. He found the Studies flawed and concluded that they did not demonstrate any causal relationship between TRT and cardiovascular disease. He emphasized that studies both before and after these Studies demonstrated an association between LowT, mortality, and morbidity and CV events, markers of coronary artery disease and diagnoses/disease states that are themselves risk factors for cardiovascular disease (such as obesity, glycemic control and diabetes). He agreed with Dr. Morgentaler's published review of these Studies.

[286] Dr. Greenberg reported that based on his clinical experience and after reviewing the scientific and regulatory literature, he could find no evidence that AndroGel^{TM} 1% testosterone gel, when properly prescribed, properly monitored and properly used by the appropriate patient, that is, someone with symptomatic and biochemically proven LowT, causes CV events or an increase in cardiovascular risk.

[287] In my opinion, like Dr. Brock, Dr. Greenberg was unfairly dismissive of Dr. Mintzes' qualifications to comment about the epidemiology of hypogonadism because, unlike him, she was not a physician with clinical experience. He said that while academic epidemiologists such as Dr. Mintzes are well trained on statistical methods and analysis of population data, it is important to note that the populations they observe often bear little, if any, relationship to the patient population treated in active practice. I doubt that this last comment is true, but if it was true it would go some distance in diminishing the value of Dr. Greenberg's clinical experience as making him better qualified to evaluate the epidemiological studies of persons with whom he had no clinical experience.

[288] I regard Dr. Greenberg's evidence much the same way as all of the experts' evidence should be valued. It contributed to a debate on a topic where both sides had the credentials to make a contribution to the debate.

16. The Evidence of Dr. Marais

[289] Dr. Marais analyzed the Basaria, Xu, Vigen, and Finkle Studies and opined that they did not support the Wises' claims.

[290] Additionally, Dr. Marais examined ten published meta-analyses studies of the potential association between TRT and serious CV events and reported that nine of the ten did not report a statistically significant elevation in CV risk. The sole exception was the Xu Study, which he had debunked. He examined 12 primary studies (including Basaria, Vigen, and Finkle) about the potential association between TRT and serious CV events and noted that only Basaria, Vigen, and Finkle reported a statistically significant increased risk but nine studies reported statistically significant decreases in serious CV risk. He notes that with the sole exception of the Basaria Study, all the risk ratios were less than 2.0.

[291] Dr. Marais observed that the authors of the Basaria, Xu, Vigen, and Finkle Studies did not avow causation and rather were of the view that the association between TRT and serious CV events warranted further research including a RCT.

E. DISCUSSION AND ANALYSIS

Introduction

[292] To resolve Abbott's summary judgment motion, there are four major issues; namely: (1) Is the case appropriate for a summary judgment? (2) Is there a genuine issue requiring a trial about general causation? (3) Is there a genuine issue requiring a trial about the duty to warn; and (4) Is there a genuine issue requiring a trial about the Wises' negligence or unjust enrichment claim for pure economic losses?

The Pursuit of Truth and Findings of Fact

[293] With one preliminary comment about the pursuit of truth, the legal analysis may begin with a partial summary of some of my findings of fact that will serve as the transition to and the contextualization of the legal analysis that follows. Additional findings of fact will be made in the legal analysis.

[294] By way of preliminary comment, one of the profound difficulties in the immediate case is that the court is being asked to make findings about the truth of scientific facts based on evidence from scientists who disagree about the truth of their respective findings and whose philosophy about certainty and truth is, in any event, conceptually different from the law's approach to certainty and truth.

[295] Scientists use the scientific method, which posits a tentative truth consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses. In contrast, judges in civil matters use a juristic pursuit of truth that posits a final and certain truth based on the balance of probabilities. To return to a theme mentioned earlier in these reasons for decision, one of the major difficulties in assessing the evidence and making findings of facts in this case was that it is not for courts to decide what is or is not a disease or a medical syndrome. Courts are not omniscient and as finders of fact, courts make descriptive largely retrospective findings about what counts for truth. A court's findings of fact are based on

the evidentiary record presented to the court, and subject to appeal, those findings become the certain truth of the matter. The court's findings are not tentative until the real truth comes along.

[296] In the immediate case, based on the above narrative of the factual background and based on the law's notion of the pursuit of truth, which is based on the balance of probabilities, I would summarize some of my findings of fact as follows.

[297] "Hypogonadism" is a deficiency or absence of endogenous testosterone in males. Hypogonadism is characterized by a low serum testosterone level in combination with various symptoms, such as decreased libido, erectile dysfunction, reduced muscle mass and strength, and increased body fat and weight gain. A deficiency in testosterone may be caused by disease or damage to a man's gonads but testosterone also naturally declines as a man ages. For decades and until today, when the deficiency in testosterone is caused by disease or damage to a patient's gonads and there are accompanying symptoms such as as decreased libido, erectile dysfunction, reduced muscle mass and strength, and increased body fat and weight gain, physicians will diagnose the patient as suffering from hypogonadism and physicians would prescribe artificially synthesized testosterone to elevate the patient's testosterone levels.

[298] In 2000, in the United States, and in 2002 in Canada, the regulators approved for sale AndroGel™, a drug manufactured by Abbott. AndroGel™ administers testosterone transderminally (through the skin). AndroGel™ was indicated for hypogonadism caused by disease or damage to the gonads, and in Canada but not the United States, it was also indicated for patients suffering from what was described in the product monograph "as sexual dysfunction or for andropause when the conditions are due to a measured or documented testosterone deficiency."

[299] I find that between 2002 and 2006, when Health Canada, the Canadian regulator, ordered that the indication for andropause be removed from the product monograph that Abbott thought that hypogonadism and andropause were different but closely related medical conditions for which AndroGel™ was an approved treatment. Today, Abbott's medical experts regard "classic hypogonadism" (i.e., low testosterone and associated symptoms caused by disease or damage to the gonads) and "testosterone deficiency", however it may be identified or labelled (i.e., low testosterone levels and associated symptoms caused by aging), as the same medical condition.

[300] The Canadian product monograph for AndroGel™ was amended in 2006 to remove the indication for andropause but, practically speaking, the change in the monograph did not change much. There was, and continues to be, a controversy in the medical and scientific community about whether andropause exists and whether it is a natural or pathological phenomenon, but physicians continued to prescribe AndroGel™ for patients presenting with measured LowT and symptoms of decreased libido, erectile dysfunction, reduced muscle mass and strength, and increased body fat and weight gain. I agree with Abbott that in prescribing AndroGel™ for testosterone deficient men, the treating physicians were making an on-label prescription.

[301] For the purposes of this summary judgment motion, it is not necessary to resolve the definition of hypogonadism because the underlying issue is not about what counts for hypogonadism, but whether, as a matter of general causation, AndroGel™ can cause serious CV events and whether the sale of an allegedly useless but risky product, AndroGel™, can support a product's liability negligence claim for pure economic loss.

[302] The ultimate issue is whether when Abbott sold AndroGel™ to Mr. Wise and others who

did not have hypogonadism of the clearly pathological sort, it breached a duty to warn that those taking AndroGel™ were exposed to a significant risk of a serious CV event like a heart attack, which is unfortunately what happened to Mr. Wise, who says that he never would have used the drug if properly warned.

[303] After Mr. Wise suffered his heart attack, there was a great deal of media attention and news reports that recent clinical studies had revealed an association between TRT, like AndroGel™, and serious CV events.

[304] Informed by this news and, in particular, the information available from the Basaria, Xu, Vigen, and Finkle Studies, which had prompted the media's attention, Mr. Wise commenced this class action.

[305] Abbott responded with this summary judgment motion and focused on what it perceived was the Achilles heel in Mr. Wise's products liability class action. It was Abbott's contention that a review and analysis of the regulator history of AndroGel™ marketing in Canada, the U.S., and Europe, and the myriad epidemiological studies of the positive or negative effects would demonstrate that there was no genuine issue for trial about a critical constituent element in the Wises' products liability action; namely, general causation.

[306] The summary judgment motion thus became a battle of experts about the epidemiology of hypogonadism and about the proven or not proven risks and benefits of AndroGel™.

[307] Notwithstanding a great deal of disparaging commentary, the opposing experts were in agreement about the fact that what epidemiologists regard as association is not proof of general causation; rather it is from an association that an inference of general causation can sometimes be drawn.

[308] The opposing experts and the parties were also in agreement that the best evidence to determine the issues for this summary judgment motion were the views of the regulators; namely: Health Canada, the FDA, and the EMA.

[309] The opposing experts and the parties, however, differed in what was to be learned from the regulators and the significance of the teachings. Each side cherry-picked what they thought was useful and dispositive in their favour from the regulators' statements.

[310] Thus, for example, the Wises relied on the statements in the FDA's January 31, 2014 announcement that: (a) it had been monitoring the risk of serious CV events in men taking testosterone products; and (b) it had decided to reassess the safety issue and investigate further because the Basaria and Xu Studies had each suggested an increased risk, while Abbott relied on the FDA's statements that: (a) it had not concluded that there was in fact an increased risk; (b) patients should not stop taking their prescriptions without discussing it with their doctors; and (c) their doctors should follow the prescribing information on the product monograph and should consider whether the benefits of FDA approved testosterone treatment is likely to exceed the potential risks of treatment.

[311] Thus, for another example, the Wises relied on the statements in Health Canada's May 22, 2014 Signal Assessment that: (a) since 2010, there was a growing body of evidence calling into question the cardiovascular safety of testosterone; and (b) Health Canada had reviewed seven published studies in which CV events were specifically examined and although the studies had varying degrees of bias and limitation, four of the seven showed a greater risk of CV events and three studies showed no statistically significant risk. And the Wises relied on Health

Canada's overall conclusion that the scientific literature provided evidence to support the possible association between testosterone use and the risk of serious CV events. For its part, Abbott relied on the fact that Health Canada's recommendation was to consider updating the Product Monograph to indicate a possible increased CV risk beyond what was currently described.

[312] Thus, for yet another example, the Wises relied on the statement in Health Canada's July 15, 2014 Summary Safety Review that although they had limitations, several studies suggested an increased risk of serious CV problems and provided evidence in support of a possible association between testosterone products and serious CV events. Conversely, Abbott relied on the fact that Health Canada indicated that in response to the studies, it would work with manufacturers to update the Canadian product labels and would keep Canadians informed and take action, as appropriate, if any new safety information was identified.

[313] Thus, for still more examples, Abbott relied on the fact that in the United States, the FDA denied the Public Citizen's position, but the Wises relied on the fact that notwithstanding the denial of the petition, the FDA on March 3, 2015, released an announcement stating that it was requiring manufacturers to add information to labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. The announcement stated that the FDA had concluded that there is a possible increased CV risk associated with testosterone use and that some studies reported an increased risk of heart attack, stroke, or death associated with TRT, while others did not.

1. Is the Case Appropriate for a Summary Judgment?

[314] Abbott submits that the case at bar is appropriate for a summary judgment. In response to the summary judgment motion, the Wises submit that the case is not appropriate for a summary judgment - for Abbott -, but they submit that the case would be appropriate for a partial summary judgment - for them - with the result that three of the five certification criteria would be satisfied (cause of action, a common issue, and representative plaintiff criteria). In other words, the Wises submit that they should be granted a partial summary judgment and that their action should move on to certification and to a common issues trial of the remaining common issues followed by assessments of damages for individual Class Members.

[315] Rule 20.04(2)(a) of the *Rules of Civil Procedure* provides that the court shall grant summary judgment if: "the court is satisfied that there is no genuine issue requiring a trial with respect to a claim or defence." With amendments to Rule 20 introduced in 2010, the powers of the court to grant summary judgment have been enhanced. Rule 20.04(2.1) states:

> 20.04 (2.1) In determining under clause (2)(a) whether there is a genuine issue requiring a trial, the court shall consider the evidence submitted by the parties and, if the determination is being made by a judge, the judge may exercise any of the following powers for the purpose, unless it is in the interest of justice for such powers to be exercised only at a trial:
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> 1. Weighing the evidence.
>
> 2. Evaluating the credibility of a deponent.
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> 3. Drawing any reasonable inference from the evidence.

[316] In *Hryniak v. Mauldin*, 2014 SCC 7 and *Bruno Appliance and Furniture, Inc. v. Hryniak*, 2014 SCC 8, the Supreme Court of Canada held that on a motion for summary judgment under Rule 20, the court should first determine if there is a genuine issue requiring trial based only on the evidence in the motion record, without using the fact-finding powers introduced when Rule 20 was amended in 2010. The analysis of whether there is a genuine issue requiring a trial should be done by reviewing the factual record and granting a summary judgment if there is sufficient evidence to fairly and justly adjudicate the dispute and a summary judgment would be a timely, affordable and proportionate procedure.

[317] If, however, there appears to be a genuine issue requiring a trial, then the court should determine if the need for a trial can be avoided by using the powers under rules 20.04(2.1) and (2.2). As a matter of discretion, the motions judge may use those powers, provided that their use is not against the interest of justice. Their use will not be against the interest of justice if their use will lead to a fair and just result and will serve the goals of timeliness, affordability and proportionality in light of the litigation as a whole.

[318] At para. 22 of her judgment in the companion case of *Bruno Appliance and Furniture, Inc. v. Hryniak*, *supra*, Justice Karakatsanis summarized the approach to determining when a summary judgment may or may not be granted; she stated:

> Summary judgment may not be granted under Rule 20 where there is a genuine issue requiring a trial. As outlined in the companion *Mauldin* appeal, the motion judge should ask whether the matter can be resolved in a fair and just manner on a summary judgment motion. This will be the case when the process (1) allows the judge to make the necessary findings of fact, (2) allows the judge to apply the law to the facts, and (3) is a proportionate, more expeditious and less expensive means to achieve a just result. If there appears to be a genuine issue requiring a trial, based only on the record before her, the judge should then ask if the need for a trial can be avoided by using the new powers provided under Rules 20.04(2.1) and (2.2). She may, at her discretion, use those powers, provided that their use is not against the interest of justice.

[319] *Hryniak v. Mauldin* does not alter the principle that the court will assume that the parties have placed before it, in some form, all of the evidence that will be available for trial. The court is entitled to assume that the parties have respectively advanced their best case and that the record contains all the evidence that the parties will respectively present at trial: *Dawson v. Rexcraft Storage & Warehouse Inc*., [1998] O.J. No. 3240 (C.A.); *Bluestone v. Enroute Restaurants Inc*. (1994), 18 O.R (3d) 481 (Ont. C.A.); *Canada (Attorney General) v. Lameman*, [2008] 1 S.C.R. 372 at para. 11. The onus is on the moving party to show that there is no genuine issue requiring a trial, but the responding party must present its best case or risk losing: *Pizza Pizza Ltd. v. Gillespie* (1990), 75 O.R. (2d) 255 (Gen. Div.); *Transamerica Life Insurance Co. of Canada v. Canada Life Assurance Co.* (1996), 28 O.R. (3d) 423 (Gen. Div.), aff'd [1997] O.J. No. 3754 (C.A.).

[320] The jurisdictional test for granting a summary judgment is that there is no genuine issue requiring a trial, and at the heart of this test is a judicial gut check. Although she did not put it in quite that way, in *Hryniak v. Mauldin* at paras. 49 and 50, Justice Karakatsanis noted that in the context of an adversarial system, if a judge is going to decide a matter summarily, then he or she must have confidence that he or she can reach a fair and just determination without a trial. She

expressed this sentiment, as follows:

> 49. There will be no genuine issue requiring a trial when the judge is able to reach a fair and just determination on the merits on a motion for summary judgment. This will be the case when the process: (1) allows the judge to make the necessary findings of fact, (2) allows the judge to apply the law to the facts, and (3) is a proportionate, more expeditious and less expensive means to achieve a just result.
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> 50. These principles are interconnected and all speak to whether summary judgment will provide a fair and just adjudication. When a summary judgment motion allows the judge to find the necessary facts and resolve the dispute, proceeding to trial would generally not be proportionate, timely or cost effective. Similarly, a process that does not give a judge confidence in her conclusions can never be the proportionate way to resolve a dispute. It bears reiterating that the standard for fairness is not whether the procedure is as exhaustive as a trial, but whether it gives the judge confidence that she can find the necessary facts and apply the relevant legal principles so as to resolve the dispute.

[321] Part of this confidence or gut check that a summary judgment is fair and just is achieved if the judge is satisfied that he or she can justly and fairly decide the matter without the advantages of participating in the dynamic of a trial, where witnesses testify in their own words and can be observed through the rigours of both examination-in-chief and cross-examination, and where the judge has an extensive exposure to the evidence and sees the case unfold without having to piece it together in chambers working from affidavits, transcripts, and factums. In *Hryniak v. Mauldin* at paras. 51-55, Justice Karakatsanis described how a judge might determine whether he or she was satisfied that a trial was required rather than using the forensic resources of the summary judgment rule to decide the matter summarily; she stated:

> 51. We think this "full appreciation test" provides a useful benchmark for deciding whether or not a trial is required in the interest of justice. In cases that call for multiple findings of fact on the basis of conflicting evidence emanating from a number of witnesses and found in a voluminous record, a summary judgment motion cannot serve as an adequate substitute for the trial process. Generally speaking, in those cases, the motion judge simply cannot achieve the full appreciation of the evidence and issues that is required to make dispositive findings. Accordingly, the full appreciation test is not met and the "interest of justice" requires a trial.
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> 52. In contrast, in document-driven cases with limited testimonial evidence, a motion judge would be able to achieve the full appreciation of the evidence and issues that is required to make dispositive findings. Similarly, the full appreciation test may be met in cases with limited contentious factual issues. The full appreciation test may also be met in cases where the record can be supplemented to the requisite degree at the motion judge's direction by hearing oral evidence on discrete issues.
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> 53. We wish to emphasize the very important distinction between "full appreciation" in the sense we intend here, and achieving familiarity with the total body of evidence in the motion record. Simply being knowledgeable about the entire content of the motion record is not the same as fully appreciating the

> evidence and issues in a way that permits a fair and just adjudication of the dispute. The full appreciation test requires motion judges to do more than simply assess if they are capable of reading and interpreting all of the evidence that has been put before them.
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> 54. The point we are making is that a motion judge is required to assess whether the attributes of the trial process are necessary to enable him or her to fully appreciate the evidence and the issues posed by the case. In making this determination, the motion judge is to consider, for example, whether he or she can accurately weigh and draw inferences from the evidence without the benefit of the trial narrative, without the ability to hear the witnesses speak in their own words, and without the assistance of counsel as the judge examines the record in chambers.
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> 55. Thus, in deciding whether to use the powers in rule 20.04(2.1), the motion judge must consider if this is a case where meeting the full appreciation test requires an opportunity to hear and observe witnesses, to have the evidence presented by way of a trial narrative, and to experience the fact-finding process first-hand. Unless full appreciation of the evidence and issues that is required to make dispositive findings is attainable on the motion record - as may be supplemented by the presentation of oral evidence under rule 20.04(2.2)- the judge cannot be "satisfied" that the issues are appropriately resolved on a motion for summary judgment.

[322] Although in *Hryniak v. Mauldin* the Supreme Court of Canada commanded a very robust summary judgment procedure, it did not foreclose lower courts from simply dismissing the summary judgment motion and ordering that the action be tried in the normal course: *Gubert v. 1536320 Ontario Limited*, 2015 ONSC 3294. Where there are genuine issues for trial and the court concludes that employing the enhanced forensic tools of the summary judgment procedure would not lead to a fair and just determination of the merits, the court should not decide the matter summarily: *Mitusev v. General Motors Corp*., 2014 ONSC 2342 at para. 79; *Gon (Litigation Guardian of) v. Bianco*, 2014 ONSC 65 at paras. 41-47; *Yusuf v. Cooley*, 2014 ONSC 6501; *Baywood Homes Partnership v. Haditaghi*, 2014 ONCA 450 at para. 44.

[323] In *Baywood Homes Partnership v. Haditaghi*, *supra*, the Court of Appeal held that where the motion is for a partial summary judgment, the motions judge is obliged to assess the advisability of a partial judgment in the context of the litigation as a whole. In this case, the Court of Appeal also stated that when conflicting evidence is presented on factual matters, a motions judge is required to articulate the specific findings that support a conclusion that a trial is not required. The Court noted that evidence by affidavit, prepared by a party's legal counsel, which may include voluminous exhibits, can obscure the affiant's authentic voice and make the motion judge's task of assessing credibility and reliability especially difficult in a summary judgment and mini-trial context and that great care must be taken by the motions judge to ensure that decontextualized affidavit and transcript evidence does not become the means by which substantive unfairness enters, in a way that would not likely occur in a full trial where the trial judge sees and hears it all. See also: *Trotter v. Trotter*, 2014 ONCA 841; *Gino L Arnone Professional Corp. v. Hacio*, 2015 ONSC 5266.

[324] In *Mitusev v. General Motors Corp.*, *supra*, Justice Edwards declined to allow a summary judgment motion proceed when the moving party defendant did not proffer sufficient evidence to ensure that the judge hearing the motion could be confident that he or she could fairly resolve the dispute. In that product's liability case, the plaintiff's personal injury claim arose from a single vehicle car accident allegedly caused by defects in the driver's seat in the vehicle. One of the defendants moved for summary judgment based on the submission that it was not the manufacturer of the part that was defective and that had caused the failure of the seat. Justice Edwards found, however, the defendant's evidence inadmissible and, accordingly, there was inadequate evidence to allow him to fairly and justly adjudicate the dispute.

[325] To grant summary judgment, on a review of the record, the motions judge must be of the view that sufficient evidence has been presented on all relevant points to allow him or her to draw the inferences necessary to make dispositive findings: *Ghaeinizadeh (Litigation guardian of) v. Garfinkle Biderman LLP*, 2014 ONSC 4994, leave to appeal to Div. Ct. refused, 2015 ONSC 1953 (Div. Ct.); *Lavergne v. Dominion Citrus Ltd.*, 2014 ONSC 1836 at para. 38; *George Weston Ltd. v. Domtar Inc.*, 2012 ONSC 5001.

[326] In considering whether to allow the summary judgment motion to go ahead or how it should go forward, the court should consider factors such as: (a) the nature and complexity of the issues; (b) the extent of the anticipated record; (c) the comparative prospects that the record will be sufficient to satisfy the test for a summary judgment with or without examinations for discovery; (d) whether the responding party have production and oral discovery similar to that available in the normal course; and (e) whether more efficient means could be developed to ensure the just, most expeditious and least expensive determination of the case on its merits: *George Weston Ltd. v. Domtar Inc., supra* at paras. 53-55.

[327] In *Ghaffari v. Asiyaban*, 2012 ONSC 2724, which was not a class action, Justice Ferguson stated that a summary judgment motion should only be stayed in the clearest of cases and only after the court had considered: (a) whether the party seeking a stay has put its best foot forward to show that there is a genuine issue requiring a trial or that the matter was too complicated for a judge to achieve a full appreciation of the case; and (b) whether the complexity of the matter, the nature of the issues, and the nature of the evidence indicated that the case was not amenable to a judgment without a full trial. See also *Stever v. Rainbow International Carpet Dyeing & Cleaning Co.*, 2013 ONSC 241, leave to appeal refused 2013 ONSC 1574 (Div. Ct.).

[328] The debate in the case at bar about whether the case is appropriate for a summary judgment is quite similar to the debate that took place in the British Columbia case *Player Estate v. Janssen-Ortho Inc.*, 2014 BCSC 1122, which was a proposed class action against five manufacturers of transdermal fentanyl patches, a prescription painkiller where the drug is delivered by a patch applied to the patient's skin.

[329] In *Player Estate*, the plaintiffs alleged that the defendants had designed their patches negligently. Before the certification of the action, two of the defendants, Teva Canada Limited and Sandoz Canada, whose patches were designed differently than the other three defendants, sought an order dismissing the action against them on a summary trial under British Columbia's Supreme Court Rules 9-7, 11-2. The parties filed more than 5,000 pages in materials for the application, including affidavits, exhibits, submissions and case authorities. The proposed representative plaintiffs, whose deceased husbands had died after using the defendants' type of fentanyl patch, argued that the case was not suitable for a summary trial and ought to be tried by

a full trial.

[330] Justice Bracken noted that there are a number of factors to consider in determining whether it would be appropriate and just to grant judgment at summary trial including: (a) the amount involved; (b) the urgency of the matter; (c) the complexity of the matter; (d) whether credibility was a critical factor in the determination of the dispute; (e) any prejudice likely to arise by reason of delay; (f) the costs of litigation; (g) the cost of taking the case forward to a conventional trial in relation to the amount involved, (h) the course of the proceedings; and (i) the undesirability of piecemeal litigation. See also: *Inspiration Management Ltd. v. McDermid St. Lawrence Ltd.*, [1989] B.C.J. No. 1003 (B.C.C.A.); *Dahl v. Royal Bank of Canada*, 2005 BCSC 1263 at para. 12, aff'd 2006 BCCA 369; *Gichuru v. Pallai*, 2013 BCCA 60 at para. 31.

[331] Justice Bracken stated that while in some cases the fact that the summary trial was heard before certification and therefore would not bind the potential class members might be a reason to deny the application for a summary trial particularly if the issue was idiosyncratic to the proposed representative plaintiffs, this was not the general rule for cases where the application concerns the defendant's liability to the class as a whole. Justice Bracken noted that, practically speaking, it is very unlikely that where the defendant is successful on a dispositive issue at a summary trial pre-certification, that class counsel could enlist another class member to take on the enormous litigation risk of reprising the proposed class action.

[332] Justice Bracken listed a number of decisions where summary judgments were granted in pre-certification proceedings; see: *Azevedo v. Legal Services Society (British Columbia)* (1998), 49 B.C.L.R. (3d) 45 (C.A.) (breach of contract for payment of legal aid fees); *Pfeiffer v. Pacific Coast Savings Credit Union*, 2000 BCSC 1472, var'd on other grounds, 2003 BCCA 122 (interpretation of mortgage contract); *Royster v. 3584747 Canada Inc. dba Kmart Canada Ltd.*, 2001 BCSC 153 (mass wrongful termination of employees); *Dahl v. Royal Bank of Canada, supra* (failure by the banks to disclose credit card charges); *Consumers' Association v. Coca-Cola Bottling Company*, 2006 BCSC 863, aff'd 2007 BCCA 356 (claim for refunds on recyclable beverage containers); *Blackman v. Fedex Trade Networks Transport & Brokerage (Canada), Inc.*, 2009 BCSC 201 (breach of *Business Practices and Consumer Protection Act*).

[333] Justice Bracken concluded that notwithstanding the voluminous amount of material, the essential facts and issues were not as complex as the amount of material might suggest, and that although there were conflicts in the expert evidence, the evidence had been thoroughly canvassed and could be fairly assessed. He said that the evidence that had been presented was adequate to come to a full appreciation of the facts that were essential to the determination of the plaintiffs' action. He concluded that the case was suitable for a summary determination.

[334] With the enhancements to Ontario's summary judgment motion jurisdiction as interpreted by *Hryniak v. Mauldin*, it's regime is quite similar to British Columbia's summary trial regime, which is meant to expedite the early resolution of cases by allowing parties to put forward their evidence via affidavits and other written materials, rather than by *viva voce* testimony, and the Wises' Trumpian arguments in the immediate case to resist a summary determination - unless they were the winner - are similar to the arguments made by the plaintiffs in *Player Estate v. Janssen-Ortho Inc.* that were rejected by Justice Bracken.

[335] In my opinion, the case at bar is an appropriate case for a summary judgment. There is no doubt that I have sufficient evidence on all relevant points to allow me to make dispositive findings and both sides have put forward sufficient evidence to make their respective arguments

about the dispositive issues. Although there was a voluminous amount of evidence, I am satisfied that I can justly and fairly decide the matter without the advantages of participating in the dynamic of a trial. The adjudicative process of reviewing and studying the evidence might have been less demanding for the adjudicator if stretched out over a trial, but a trial adjudicator would also have had also to address not only general causation but also some very difficult duty of care and standard of care issues and ultimately the trial judge would be left to explore and analyze the expert's material outside of the courtroom in the same way that I have.

[336] Having regard to the litigation as a whole, dealing with the matter of general causation is efficient and proportionate, and while the Wises wished to hedge with the argument that a summary judgment would be appropriate only for them, this hedging belies the notion that it would not be in the interests of justice to decide the issue of general causation immediately one way or the other. This is not a case like *Baywood Homes Partnership v. Haditaghi*, *supra,* where relying on affidavits and transcripts of cross-examinations are a medium for substantive fairness. I have decided above that the experts from both sides are qualified to give opinions and that their opinions are admissible. In the discussion below, I will determine how persuasive or helpful those opinions were, but I am confident that I can fairly and justly decide the issues to be determined by summary judgment. The case at bar is an appropriate case for a summary judgment.

2. Is There a Genuine Issue Requiring a Trial about General Causation?

(a) Products Liability Claims

[337] The issue of whether there is a genuine issue requiring a trial about general causation and also the issues about the duty to warn and about pure economic losses in negligence arise in the context of the branch of negligence law known as products liability. The discussion of whether there are genuine issues requiring a trial can therefore begin with the general nature of negligence claims and of products liability negligence claims, of which there are four established categories.

[338] The elements of a claim in negligence are: (1) the defendant owes the plaintiff a duty of care; (2) the defendant's behaviour breached the standard of care; (3) the plaintiff suffered compensable damages; (4) the damages were caused in fact by the defendant's breach; and, (5) the damages are not too remote in law: *Mustapha v. Culligan of Canada Ltd*., 2008 SCC 27 at para. 3.

[339] There are four categories of products liability negligence claims. First, manufacturers have a duty of care to consumers to see that there are no defects in manufacture that are likely to give rise to injury in the ordinary course of use: *Donoghue v. Stevenson*, [1932] A.C. 562 (H.L.). Second, manufacturers have a duty of care to warn consumers of dangers inherent in the use of the product of which the manufacturer has knowledge or ought to have knowledge: *Hollis v. Dow Corning Corp.*, [1995] 4 S.C.R. 634 at para. 20; *Lambert v. Lastoplex Chemicals Co.*, [1972] S.C.R. 569 at p. 574; *Bow Valley Husky (Bermuda) Ltd. v. Saint John Shipbuilding Ltd.*, [1997] 3 S.C.R. 1210. Third, manufacturers have a duty of care in designing the product to avoid safety risks and to make the product reasonably safe for its intended purposes: *Ragoonanan v. Imperial Tobacco Canada Ltd.* (2000), 51 O.R. (3d) 603 (S.C.J.); *Rentway Canada Ltd. v. Laidlaw Transport Ltd.*, [1989] O.J. No. 786 (H.C.J.), aff'd [1994] O.J. No. 50 (C.A.). The

underlying argument in a design negligence action is that a manufacturer has a duty of care not to design a product negligently because the manufacturer should and can fairly be held responsible for the choices it makes that affect the safety of the product. The manufacturer has a duty to make reasonable efforts to reduce any risk to life and limb that may be inherent in its design: *Gallant v. Beitz* (1983), 42 O.R. (2d) 86 (H.C.J.) at p. 90; *Rentway Canada Ltd. v. Laidlaw Transport Ltd., supra*. Fourth, there is a pure economic loss claim in negligence because manufacturers have a duty of care to compensate consumers for the cost of repairing a dangerous product that presents a real and substantial danger to the public: *Winnipeg Condominium Corporation No. 36 v. Bird Construction Co. Ltd.*, [1995] 1 S.C.R. 85.

[340] As explained by Justice Huddart of the British Columbia Court of Appeal in *Harrington v. Dow Corning Corp*., 2000 BCCA 605, affg. [1996] B.C.J. No. 734 (S.C.), leave to appeal to S.C.C. ref'd. [2001] S.C.C.A. No. 21, at paras. 42 to 46, typically, the four steps in a products liability class action are: (1) determining whether the product is defective or whether although non-defective, the product has a propensity to injure; (2) determining what the manufacturer knew about the dangerousness of its product; (3) determining the reasonableness of the warning whether direct or to a learned intermediary given the state of the art and the extent of the risks inherent in the product's use; and (4) determining individual causation and damages. The first step, known as the general causation step, determines whether the product is capable of causing harm. The second step is part of determining whether the manufacturer had a duty of care not to sell the product or to sell it only with an appropriate warning. The third step focuses on the adequacy of the warning. The fourth step will determine individual causation and the quantification of the compensation for the consequent harm.

(b) <u>General Causation</u>

[341] The fundamental issue in this summary judgment motion is the matter of general causation in the context of a medical device or pharmaceutical products liability claim. It is a constituent element of the tort of negligence that the defendant's negligence caused the plaintiff's injuries.

[342] There are two aspects to causation. The first aspect is "general causation," which concerns the aspect of whether the defendant's misconduct has the capacity to cause the alleged damage and the second aspect is "specific causation," which concerns the aspect of whether the capacity to harm was actualized in the particular case. In the immediate case, the issue is thus whether it has been proven that AndroGel™ can cause serious CV events. If this is proven, it would remain for Mr. Wise to prove that his use of AndroGel™ did cause his heart attack.

[343] As noted by Justice Myers in *Baghbanbashi v. Hassle Free Clinic*, 2014 ONSC 5934, in many cases, general causation is not an issue and the case will turn on specific causation because general causation will be obvious. However, in other cases, general causation cannot be assumed and must be proven. Justice Myers stated at para. 9 of his decision:

> 9. Court decisions in tort cases usually do not mention general causation because it is often obvious. Evidence is not needed, for example, to prove that being hit by a moving car can cause broken bones. The issue in most cases is simply whether, in that particular case, the car accident in issue broke the plaintiff's bones; i.e., whether there is specific causation. General causation is often assumed. In vaccination cases however, general causation cannot be assumed. Before a

> plaintiff shows that her particular injury was caused by the vaccination she received, she first must establish that the vaccine can cause that type of injury that she suffered. ….

[344] In *Clements v. Clements*, 2012 SCC 32 at para. 8, the Supreme Court of Canada set out the test for causation as follows:

> 8. The test for showing causation is the "but for" test. The plaintiff must show on a balance of probabilities that "but for" the defendant's negligent act, the injury would not have occurred. Inherent in the phrase "but for" is the requirement that the defendant's negligence was necessary to bring about the injury — in other words that the injury would not have occurred without the defendant's negligence. This is a factual inquiry. If the plaintiff does not establish this on a balance of probabilities, having regard to all the evidence, her action against the defendant fails.

[345] In the case at bar, Abbott submits that there is no genuine issue requiring a trial about general causation because having regard to all the evidence, the Wises cannot demonstrate on a balance of probabilities that AndroGel™ can cause serious CV events. Abbott submits that all of the scientific evidence only establishes association and that it is acknowledged by the Wises' experts that association is not proof of general causation, and so Abbott submits that there is no genuine issue requiring a trial about general causation and, therefore, the Wises' action should be dismissed.

[346] As a factual matter, I agree that as a matter of scientific proof, causation has not been proven. However, as a legal matter, although I agree with the conclusion of Abbott's argument that the Wises' action should be dismissed, I do not agree with its argument, and, in my opinion, its argument is not doctrinally sound.

[347] My different line of argument leading to the conclusion that the Wises' action should be dismissed is that in the immediate case, there is a genuine issue about causation. However, moving on to the second stage of the *Hryniak v. Mauldin* analysis to use the powers under rules 20.04(2.1) and (2.2), I conclude that that having regard to all the evidence, including the proof of an association between TRTs and serious CV events and also the proof that there is a biological plausibility for that association, nevertheless, the Wises cannot demonstrate on a balance of probabilities that AndroGel™ can cause serious cardiovascular events.

[348] On a balance of probabilities, the case at bar is not a case that permits the inference of general causation to be drawn from the evidence of association and biological plausibility.

[349] To begin the elucidation of this argument, I emphasize that the test for general causation used in legal cases differs from the rigorous standards of causation applied by science. A plaintiff's proving general causation to a scientific standard would be sufficient, but it is not necessary that a plaintiff prove general causation to the scientific standard. This very important point is demonstrated by the recent decision of the Supreme Court of Canada in *British Columbia (Workers' Compensation Appeal Tribunal) v. Fraser Health Authority*, 2016 SCC 25.

[350] In the *Fraser Health Authority* case, Katrina Hammer, Patricia Schmidt and Anne MacFarlane were employees at a hospital laboratory in British Columbia. There were 63 employees at the facility and seven of them, including Mesdames Hammer, Schmidt and MacFarlane, were diagnosed with breast cancer. Pursuant to British Columbia's *Workers*

Compensation Act, R.S.B.C. 1996, c. 492, which sets a lower standard of proof of causation than does civil tort law, they applied for compensation on the basis that their cancers were an "occupational disease," which, under the statute, was to say that their employment had "causative significance" in the development of their illnesses.

[351] Their claim for compensation was denied, but they appealed to the Workers' Compensation Board, which then had to decide the etiology of their breast cancers. There were three expert reports for the Board to consider. The experts reviewed the scientific literature on factors associated with the risk of breast cancer, did an epidemiological analysis of the cancer cluster among workers in the laboratory, and a field investigation into possible exposure among laboratory technicians to potentially carcinogenic substances. The three experts were in agreement that the incidence of cancer in the laboratory represented a statistically significant cluster, but they could not come to "scientific conclusions to support the association between work-related exposures and breast cancer in this cluster". The experts were unable to establish the basis for an etiological hypothesis based on scientific evidence of causal mechanisms for breast cancer and did not find any scientific evidence for the plausibility of a laboratory work-related etiological hypothesis regarding breast cancer. The scientists speculated that the increased incidence of breast cancer among laboratory employees may have been due to: (1) a cluster of reproductive and other known, non-occupational, risk factors; (2) past exposures to chemical carcinogens and less likely to ionizing radiation, and (3) a statistical anomaly. One of the experts went further and opined that that non-occupational factors were the cause of the breast cancer. Notwithstanding these expert opinions, the Board granted the claims for workers' compensation.

[352] Judicial review proceedings followed, and the proceedings worked their way to the Supreme Court of Canada, where Justice Brown (Chief Justice McLachlin and Justices Abella, Moldaver, Karakatsanis, and Wagner, concurring, Justice Côté dissenting) in addition to addressing the administrative law aspects of the appeal, upheld the decision of the Board and in doing so, he made several legal findings about proof of causation. At para. 33 of his judgment, Justice Brown said that: "the central problem in the handling of causation in the courts below arose not in their failure to have appropriate regard to the less stringent standard of proof required by [the legislation], but from their fundamental misapprehension of how causation -- irrespective of the standard of proof -- may be inferred from evidence." At para. 38 of his judgment, Justice Brown stated that a trier of fact is not confined to the evidence of the expert's in inferring causation; he stated:

> 38. The presence or absence of opinion evidence from an expert positing (or refuting) a causal link is not, therefore, determinative of causation (e.g. *Snell*, at pp. 330 and 335). It is open to a trier of fact to consider, as this Tribunal considered, other evidence in determining whether it supported an inference that the workers' breast cancers were caused by their employment. This goes to the chambers judge's reliance upon the Court of Appeal's decisions in *Sam and Moore* and to Goepel J.A.'s statement that there must be "positive evidence" linking their breast cancers to workplace conditions. Howsoever "positive evidence" was intended to be understood in those decisions, it should not obscure the fact that causation can be inferred -- even in the face of inconclusive or contrary expert evidence -- from other evidence, including merely circumstantial evidence. This does not mean that evidence of relevant historical exposures followed by a statistically significant cluster of cases will, on its own, always suffice to support

> a finding that a worker's breast cancer was caused by an occupational disease. It does mean, however, that it may suffice. Whether or not it does so depends on how the trier of fact, in the exercise of his or her own judgment, chooses to weigh the evidence.

[353] In *Miller v. Merck Frost Canada Ltd.*, 2015 BCCA 353, leave to appeal to the Supreme Court of Canada refused [2015] S.C.C.A. No. 431, where the issue at a certification motion was the extent to which the plaintiff had to show a methodology to prove causation in order to satisfy the criteria for certification, at para. 59 Justice Savage succinctly made the point that legal degrees of proof are not mathematical probabilities but legal or epistemic likelihoods and there are no hard and fast rules for inferring causation in any given case.

[354] In *Laferrière v. Lawson*, [1991] 1 S.C.R. 541, the Supreme Court of Canada considered causation in the context of physician's negligence case and Justice Gonthier for the majority of the Court (Lamer C.J. and L'Heureux-Dubé, Sopinka, Cory and McLachlin JJ. concurring; La Forest, J., dissenting) in discussing causation wrote at para. 156:

> 156. Cases in which the evidence is scarce or seemingly inconclusive present the greatest difficulty. It is perhaps worthwhile to repeat that a judge will be influenced by expert scientific opinions which are expressed in terms of statistical probabilities or test samplings, but he or she is not bound by such evidence. Scientific findings are not identical to legal findings. Recently, in *Snell v. Farrell*, [1990] 2 S.C.R. 311, this Court made clear (at p. 328) that "[c]ausation need not be determined by scientific precision" and that "[i]t is not . . . essential that the medical experts provide a firm opinion supporting the plaintiff's theory of causation" (p. 330). Both this Court and the Quebec Court of Appeal have frequently stated that proof as to the causal link must be established on the balance of probabilities taking into account all the evidence which is before it, factual, statistical and that which the judge is entitled to presume. ….

[355] In *Rothwell v. Raes*, *supra*, Justice Osler heard a 74-day products liability negligence trial that was ultimately decided on the grounds that the plaintiff had failed to prove general causation. It was a very sad case. Within six months of his birth, Patrick Rothwell, who was an otherwise healthy infant, was immunized with DPTP vaccine, which included vaccination for pertussis or whooping cough, which is an extremely dangerous disease. Within days, he suffered brain damage that blinded him and left him seriously mentally and physically handicapped. The issue for the trial was whether there was a causal connection between the pertussis component of the vaccine and severe, permanent brain damage. Justice Osler noted that even the expert witnesses who opined that there was a causal relationship readily acknowledged that the relationship was a rare one, which did not bode well for the determination of specific causation, but the plaintiffs, Patrick's parents, failed in even establishing general causation in their action against the drug manufacturer.

[356] Justice Osler stated at paras. 237 and 245 of his judgment that the onus of proving general causation is on the plaintiff; he stated:

> 237. It is important to remember that the plaintiffs must prove their case and in medical and scientific matters it is not sufficient to show that a cause and effect sequence is theoretically possible. For the plaintiffs to discharge their onus they must show on the balance of probability that a cause and effect relationship does

> exist.
>
> ….
>
> 245. While one dislikes in a case of such serious import to rely excessively upon the principle of onus, it cannot be forgotten that the onus does lie upon the plaintiffs to establish, if only by the slimmest balance of probability, that a named cause is likely. To demonstrate a possibility is not enough; probability must be established.

[357] Justice Osler's decision was affirmed by the Court of Appeal, which stated at para. 8:

> 8. We cannot agree that the judge failed to apply the proper standard in deciding the factual questions raised by the general causation issue or by the specific causation issue. Nor can we agree with the submission that he ought to have concluded that the onus was satisfied merely by the possibility that, in admittedly rare cases, pertussis vaccine might be a cause of brain damage. While the judge made clear that the onus could be satisfied by "the slimmest balance of probability" on the facts as he found them, he could not be satisfied that it is more likely than not that the vaccine caused or was a material factor in causing the harm. We agree with the trial judge that the onus is not met simply by demonstrating that there is a possibility of some causal connection. ….

[358] I now come to *Andersen v. St. Jude Medical Inc.*, *supra,* about which there was a great deal of, analysis, argument, and discussion in the immediate case about its teachings about general causation.

[359] In this case, the defendant St. Jude, the manufacturer of a mechanical prosthetic heart valve, introduced a new model that added a Silzone coating (a coating with silver metallurgy) designed to inhibit the growth of a lethal bacterial infection which was a very serious known complication of heart valve replacement surgery. Sometime after the introduction of the new model, St. Jude recalled the heart valves because a RCT revealed a statistically significant complication known as paravalvular leak ("PVL").

[360] The Representative Plaintiff Yvonne Andersen commenced a class action in 2000 that ended in 2012 after an 18-month trial. Justice Lax dismissed the action. Justice Lax held that the evidence established a material risk in increase of PVL but that Ms. Andersen had not proven any breach of duty regarding pre-market testing and post-market surveillance of products.

[361] In *Andersen v. St. Jude Medical Inc.*, common issue 3 was: "Does Silzone coating on heart valves, or annuloplasty rings, materially increase the risk of various medical complications including, but not limited to, PVL, thrombosis, thromboembolism, stroke, heart attacks, endocarditis or death?" This common issue was an issue of general causation but the issue was made enormously more complicated by the addition of the word "materially" by Justice Cullity when he certified the action as a class action; see: *Andersen v. St. Jude Medical Inc.* (2003), 67 O.R. (3d) 136 (S.C.J.). The inclusion of the notion of materially of risk led to über-complex debate between the parties largely made in mathematical terms about whether the ratio of increased risk should be set. Ms. Andersen argued that the risk ratio must be at least 1.33 and St. Jude argued that it must be at least 2.0. As I regard this debate, which was repeated in the case at bar, it was a more a debate about the commonality and the utility of a finding of general causation to the subsequent determinations of specific causation than it was about a finding of

general causation.

[362] The extreme complexity of the debate and Justice Lax's explanation for her decision to use a risk ratio of 2.0 is revealed by paras. 530 - 538 of her judgment, which are set out below. I have added emphasis to the statements that reveal that the problem that Justice Lax was addressing was more about the utility and commonality of an answer of a risk ratio of less than 2.0 than it was about what mathematical ratio may yield a finding of general causation. Justice Lax was addressing the interrelationship of a finding of general causation to the determination of specific causation.

> *The Defendants' Doubling of the Risk Standard for Materiality*
>
> 530. The defendants argue that a risk ratio of 2.0 should be adopted as the standard for materiality under this common issue. As I will now explain, the defendants' argument in this regard flows from the nature of the "but for" test, and requires an understanding of some arithmetic ….
>
> 531. The defendants note that at the individual stage of these proceedings each class member will have the onus of proving on a balance of probabilities that but for the presence of Silzone on his/her heart valve, the complication that was suffered would not have occurred. They further note that there exists a "background rate" for each complication at issue in this trial. That is, all of the complications at issue occur with conventional valves as well as with Silzone valves. The "background rate" for a complication is the risk of that complication associated with the conventional valve. **In order for class members to prove individual causation, they must prove that they would not have suffered the complication if they had been implanted with a conventional valve - that their complication was not an occurrence associated with the background rate**. This is simply a logical extension of the application of the "but for" test to the Silzone valve.
>
> 532. I will briefly explain the arithmetic behind the defendants' argument that I should adopt a risk ratio of 2.0 as the standard of materiality under this common issue. I will start with an example for illustrative purposes. A risk ratio of 1.6, for example, would indicate that the rate of occurrence of a complication for the Silzone valve is 1.6 times the rate for the conventional valve. Given two groups of patients of equal size - one with Silzone valves and one with conventional valves - if 100 patients in the conventional group suffered the complication then 160 in the Silzone group would suffer the complication. I**n this scenario, using the "but for" test, Silzone could be said to have caused the complication in 60 out of the 160 patients who experienced the complication in the Silzone group. The other 100 patients would have been expected to suffer the complication despite the Silzone valve, because we know that 100 patients in the conventional group suffered the complication.** In other words, the background rate would result in 100 patients suffering the complication, so for 100 of the 160 Silzone patients who suffered the complication, the complication would be attributable to the background rate, and not to Silzone. As such, for those 100 patients in the Silzone group, one could not say that Silzone was a "but for" cause of their complications.

533. This scenario presents **a conundrum in determining causation in each individual case in the Silzone group**. If Silzone can be said to have caused only 60 of the 160 complications in the Silzone group, then, in the absence of any other evidence, for each of those 160 individuals it can only be said that there is a 37.5% probability that Silzone caused the complication in their particular case (60/160 = 37.5%). Since this is below 50%, it cannot be said that, on a balance of probabilities, Silzone caused the complication in *any* of the 160 instances. So while in this scenario i**t is apparent that Silzone increases the risk of the complication, it cannot be said on a balance of probabilities that it caused the complication in any given patient**.

534. The defendants note that this problem is solved when the risk ratio is greater than 2.0. For example, in the above scenario, if the Silzone group had experienced 201 complications (a risk ratio of 2.01), then 101 out of those 201 patients would not have suffered the complication "but for" the presence of Silzone on their valves. Thus, the likelihood that Silzone caused the complication in any one of those patients would be 101/201 = 50.2%. So on these facts, *all* of the 201 patients would be able to demonstrate that Silzone caused their complication on a balance of probabilities.

535. A peculiar outcome would result from the strict application of the concept described above. If no other evidence was considered other than the risk ratio, then in the former scenario none of the 60 patients who would not have suffered the complication but for the presence of Silzone on their heart valve would be able to demonstrate causation in their particular case. On the other hand, in the latter scenario, *all* of the 201 patients would be able to do so despite the fact that Silzone was a "but for" cause of the complication in only 101 of them. ….

536. Nevertheless, the defendants argue that a risk ratio of 2.0 should be adopted as the standard for materiality under Common Issue 3. The parties agreed that it was necessary to establish a materiality standard for the purposes of causation, but I was presented with only two alternatives. ….

537. As I stated above, by inserting the word "materially" Justice Cullity intended to ensure that findings with respect to whether Silzone increases the risk of complications would be sufficiently meaningful that they would be indicative of something more than a remote possibility of causation. The defendants' standard achieves this objective. As the discussion above demonstrates, whether a risk ratio for a complication is above or below 2.0, in the absence of any other evidence, is determinative of whether it is more likely than not that an occurrence of that complication **in an individual** can be attributed to the Silzone valve. **Thus, the defendants' standard satisfies Justice Cullity's intention that the word "materially" should increase the probability that a finding of an increased risk may actually translate into a finding of [individual] causation.**

538. **I therefore adopt the defendants' doubling of the risk standard as the standard for materiality under this common issue. However, as I will detail below, I disagree with the defendants' position in terms of how this standard ought to be applied.**

[363] Justice Lax went on in paras. 539 to 544 of her judgment to explain how a 2.0 risk ratio could be used as a presumptive threshold to prove specific causation. This is possible because as a mathematical-epidemiological proposition, a risk ratio of 2.0 implies that 50% of the cases studied are associated with the condition. But two points must be emphasized. First, this use of a 2.0 risk ratio as a convenient presumptive threshold for specific causation has little to do with what is the risk ratio threshold for proof of general causation. Second, the proof of causation, be it general causation or specific causation, is not confined to the mathematics.

[364] For present purposes, I need not discuss any further this movement from a finding of general causation to the determination of specific causation. For present purposes, I rather note that Abbott cannot successfully rely on Justice Lax's judgment in *Andersen v. St. Jude Medical Inc.*, *supra* to advance the argument that there is no genuine issue requiring a trial about general causation because the associations that were identified so far between AndroGel™ and serious CV events did not raise to equal to or greater than a 2.0 risk ratio.

[365] As I understand, Abbott's argument it is that in order to meet the legal standard of proof based on the balance of probabilities no lesser risk ratio will do to prove general causation. I disagree with this argument because as demonstrated by: *British Columbia (Workers' Compensation Appeal Tribunal) v. Fraser Health Authority*, *supra*; *Miller v. Merck Frost Canada Ltd.*, *supra*; *Laferrière v. Lawson*, *supra*, and *Rothwell v. Raes*, *supra*, although a judge will be influenced by statistical probabilities he or she is not bound by such evidence.

[366] Such being the state of the law about general causation and applying that law to the circumstances of the immediate case where epidemiological evidence plays a prominent role, I conclude on a balance of probabilities that the use of AndroGel™ does not as a matter of general causation cause serious CV events.

[367] In its current state of development, at best, the scientific evidence does establish an association between AndroGel™ and serious CV events, but from the scientist's perspective, association is not proof of general causation unless the scientists are prepared to draw that inference based on a variety of factors such as those described by Sir Austin Bradford Hill and noted above.

[368] In the immediate case, neither Dr. Mintzes nor Dr. Milne were prepared to go beyond the fact of association to make the inference of general causation and not surprisingly Abbott's experts opined that given what they would describe as weak evidence of association there was no basis to proceed with inference drawing.

[369] Dr. Mintzes and Dr. Milne, quite fairly, acknowledged that proof of association is not proof of general causation. And, quite fairly, they did not draw the inference of causation, but rather they said that the scientific evidence was sufficient to justify stronger warnings about the use of AndroGel™ for patients who had LowT particularly those patients who were not suffering from classic hypogonadism and the current state of knowledge justified further and better RCTs to definitively determine whether the association was a cause and effect connection.

[370] I will return to the matter of whether the scientific evidence of association was sufficient to justify better warnings but foreshadow to say that using a drug's association with a serious medical condition to justify stronger warnings is a very different matter than using a drug's association with a serious medical condition to draw an inference of causation. It appears that the regulators were alert to the distinction between an association and scientific evidence that would

justify a finding of causation and an association that would justify amending the indications and warnings in a product monograph.

[371] In any event, from a legal perspective, in the immediate case, as revealed by the above cases, I am not bound to follow a scientist's conclusions about general causation. The law's approach is to apply a "but-for" test on a balance of probabilities and there is no guaranteed symmetry between a scientist's conclusions and a judge's conclusions about general causation. In any particular case, the evidence may satisfy a judge that a relationship is causal notwithstanding the skepticism of some or all of the scientists or conversely a judge may decide on a balance of probabilities that a relationship is not causal because he or she has not been persuaded by the evidence of the experts.

[372] In the immediate case no expert and no regulator was prepared to commit to the opinion that the association between AndroGel™ and serious CV events was causal. Notwithstanding the Wises' arguments that a partial summary judgment should be granted to them, I am not convinced on a balance of probabilities that AndroGel™ is a cause of heart attacks and other serious CV events. In the immediate case, there is no genuine issue requiring a trial about general causation.

3. Is there a Genuine Issue Requiring a Trial about the Duty to Warn?

[373] On this summary judgment motion, about the duty to warn, Abbott argued that there can be no duty to warn based on the proven association between AndroGel™ and major CV events because proof of association is not proof of causation of harm. I disagree with Abbott's duty to warn argument.

[374] In my opinion, an association between a product and a dangerous condition may give rise to a duty to warn even if the association has not been demonstrated to be causal. Notwithstanding Abbott's arguments, I conclude that there was a duty to warn in the immediate case. In *Hollis v. Dow Corning Corp.*, *supra*, at para. 21, Justice La Forest explained the rationale for a manufacturer's duty to warn. He stated:

> The rationale for the manufacturer's duty to warn can be traced to the "neighbour principle", which lies at the heart of the law of negligence, and was set down in its classic form by Lord Atkin in *Donoghue v. Stevenson*, [1932] A.C. 562 (H.L.). When manufacturers place products into the flow of commerce, they create a relationship of reliance with consumers, who have far less knowledge than the manufacturers concerning the dangers inherent in the use of the products, and are therefore put at risk if the product is not safe. The duty to warn serves to correct the knowledge imbalance between manufacturers and consumers by alerting consumers to any dangers and allowing them to make informed decisions concerning the safe use of the product.

[375] The manufacturer's duty to alert consumers about dangers associated with the use of a product is a continuing duty, requiring manufacturers to warn not only of dangers known at the time of sale, but also of dangers discovered after the product has been sold and delivered: *Hollis v. Dow Corning Corp., supra*, at para. 20; *Rivtow Marine Ltd. v. Washington Iron Works*, [1974] S.C.R. 1189, at p. 1200. In the case of medical products, given their substantial risk of harm from improper use, the standard of care is correspondingly high and there will almost always be a

heavy onus on the manufacturer to provide clear, complete and current information concerning the dangers inherent in the ordinary use of its product: *Hollis v. Dow Corning Corp., supra*, at para. 23.

[376] As the immediate case and a review of the case law demonstrates, the demonstration of an association between a drug and an adverse medical condition and even something less than an association such as adverse event reports is enough to energize a regulator to signal that the warnings and indications on an already approved product monograph may need to be changed including new warnings or more intensive alarms.

[377] As the factual background discussed above reveals, in the immediate case, the AndroGel™ Product Monograph was amended several times in response to the growth of scientific knowledge and the numerous epidemiological studies. Particularly, given the serious subject matters of some of the associations being studied, there is little doubt that Abbott had a duty to warn and for present purposes, I need say no more than that the Wises have reasonable arguments that Abbott breached its duty to warn and that Abbott has reasonable arguments that it met the standard of care and breached no duty to warn. In other words, in the immediate case, I find that Abbott had a duty to warn about any dangers associated with AndroGel™, but I make no finding about whether or not that duty to warn was breached.

[378] Whether the duty to warn had been breached by Abbott would involve more analysis of the standard of care and more analysis of the adequacy of the warnings that Abbott included in its product monographs as they changed from time to time. On this summary judgment motion, the evidence and the analysis did not go that far, although the trend of the evidence, which showed compliance to regulatory standards, tended to favour Abbott's position that its warnings were adequate having regard to the state of knowledge from time to time. However, I repeat that I make no finding one way or the other about whether the duty to warn was breached in the immediate case.

[379] The primary reason that the Wises' failure to warn claim must fail is, assuming a breach of the standard of care, they failed to prove general causation. A failure to warn that causes no harm is not culpable negligence.

[380] Given that I have found as a fact that there is an association between AndroGel™ and serious CV events and given that I do not agree with Abbott that proof of an association between AndroGel™ and serious CV events without proof of causation is insufficient to trigger action on its part to alert consumers about the association and given that both sides have reasonable arguments about the breach of the duty to warn, it would seem to follow that Abbott cannot succeed in its argument that the Wises' duty to warn claim should be summarily dismissed. However, that is not the case and their claim should be dismissed for the reasons expressed above about their failure to show that there is a genuine issue requiring a trial about general causation.

[381] This conclusion follows because assuming the Wises were successful at trial or on this summary judgment motion in establishing that Abbott breached its duty to warn, the breach would be legally inconsequential because the breach would not have caused any harm, or more precisely, the ~~Abbotts~~ Wises cannot prove that any harm was caused by the breach of the duty to warn. Visualize; assuming Mr. Wise proved that Abbott breached its duty to warn and that but for being encouraged by its advertising to use AndroGel™, he would not have purchased the product, his subsequent heart attack would be an unfortunate coincidence and he would not have

proven that his injuries had been caused by the AndroGel™. (Incidentally, it may be noted that had he established general causation, there would still have to be a trial to determine whether specific causation had been proven.)

[382] No harm, no foul; causation is a constituent element of the Wises' negligence claim, be it a duty to warn claim or a negligent design claim, and there is no genuine issue requiring a trial about general causation. It follows that the negligence claims should be summarily dismissed.

4. Is there a Genuine Issue Requiring a Trial about the Wises' Negligence or Unjust Enrichment Claim for Pure Economic Losses?

[383] This brings me to the Wises' claim for unjust enrichment and its claim that Abbott should compensate the Class Members for their pure economic losses. This claim also fails.

[384] The Wises' claim for what are pure economic losses is based on the allegation that AndroGel™ is a worthless, non-beneficial product, and a dangerous one not worth the risk of being consumed. Mr. Wise submits that he has proven that AndroGel,™ which is a dangerous drug (the Product Monograph does point out several dangers), is misleadingly sold for uses for which it provides no benefit, and, thus, he and the Class Members have a legally viable claim for pure economic loss in tort or for unjust enrichment in restitution.

[385] In my opinion, however, the Wises' pure economic loss claim fails both factually and also legally.

[386] As a factual matter, putting aside for the moment, the matter of who bears the onus of proving that AndroGel™ is a beneficial product, on the evidentiary record produced for this summary judgment motion, I have already determined that general causation of harm from AndroGel™ has not been proven, but that conclusion begs the question of whether the harmless AndroGel™ is beneficial or productive of some good and thus worthy of a consumer purchasing the product or whether the harmless AndroGel™ serves no useful purpose and thus is a useless product that is not productive of any good, and thus unworthy of a consumer purchasing it.

[387] Without begging the question of whether AndroGel™ is worthy or unworthy for purchase, there is no dispute that it is worthy of purchase for classical hypogonadism, where it's utility has been recognized for decades. Thus, the question narrows to whether AndroGel™ is not worthy of purchase for what the Wises would describe as a treatment for LowT, which the Wises deny is a type of hypogonadism.

[388] The Wises' arguments are that selling AndroGel™ as a cure for a non-disease is to sell a worthless good and in any event selling AndroGel™ as a cure for LowT has no beneficial results. In my opinion, these arguments fail because, as I explained above, physicians were diagnosing their clients as having LowT on a set of symptoms and they were prescribed AndroGel™ as the treatment for that diagnosis, and thus almost by definition it cannot be said that a worthless good was being sold. But more to the point, the evidence established that while benefits of a prescription of AndroGel™ in ameliorating the symptoms were modest, there was some benefit at least for a short period of time and the evidence left open the truth of the opinions of some of the experts that AndroGel™ had some more substantial benefits including even the possibility that there was a negative association between TRT and serious CV events; i.e., there was some evidence that AndroGel™ diminished the likelihood of serious CV events.

[389] The Wises are the plaintiffs in this products liability action, and as a factual matter, the onus of proving that AndroGel™ is a harmful product is on the Wises. If they had proven general causation of harm, then Mr. Wise's and the Class Members' claims would not be claims for pure economic losses. Putting aside for the moment, whether as a legal matter, Mr. Wise and the Class Members have a claim for pure economic losses, in my opinion, the onus of proving that Mr. Wise purchased a useless worthless product is also on the Wises. On the evidentiary record presented on this summary judgment motion, the Wises failed as a factual matter to meet this onus of proof.

[390] I appreciate that, practically speaking, putting the onus of the Wises to prove worthlessness is to burden them with proving a negative, but that is the burden they took on once they built their case on the notion that Abbott was disease mongering by selling AndroGel™ for LowT.

[391] The onus of proving their case on the balance of probabilities did not change for the Wises because Abbott brought a summary motion challenging whether there was a genuine issue requiring a trial. As noted above, on a summary judgment motion, both parties are taken to have stepped forward with their evidence to prove their claim or defence. In any event, if the onus was on Abbott to prove on the balance of probabilities that AndroGel™ was worth something, then it met that burden sufficiently to shift an evidentiary burden on the Wises to show that there was a genuine issue requiring a trial about Mr. Wise's pure economic losses.

[392] I conclude from an assessment of the evidence on this motion that as a factual matter, the Wises have not proven that Mr. Wise purchased a useless product. That conclusion disposes of the Wises' unjust enrichment, pure economic loss, and waiver of tort claims on a factual basis, but the claims are also not legally tenable even if it were established that AndroGel™ was a non-beneficial useless product sold for LowT.

[393] As a legal matter, it is necessary to emphasize that the Wises' do not advance a breach of contract claim nor do they advance a negligent misrepresentation claim. The predicate wrongdoing that underlies their proposed class action is a common law products liability negligence claim. If the Wises were to establish that negligence claim, then they could waive the tort, and advance a restitutionary claim or they would have the basis for an unjust enrichment claim. Mr. Wise's claim is essentially that he outlaid money for goods that had no value for him because they provided him with no benefit. The point to emphasize is assuming that the Wises do not have a negligence claim for damages for personal injuries, then for the unjust enrichment and waiver of tort claims, they must have a negligence claim for a pure economic loss.

[394] While there is a pure economic loss claim for negligently misrepresenting the qualities of a product, there is no pure economic loss negligence claim for selling worthless or shoddy goods that are not dangerous for the uses for which they are sold: *Arora v. Whirlpool Canada L.P.*, 2013 ONCA 657, aff'g 2012 ONSC 4642, leave to appeal to the S.C.C. refused, [2013] S.C.C.A. No. 498.

[395] The Wises' claim is for the financial loss from purchasing a product that caused neither their person or their property any physical harm. The law is that although the categories are not closed, there are only limited circumstances where damages for economic loss absent physical or property harm may be recovered: *Martel Building Ltd. v. Canada*, [2000] 2 S.C.R. 860.

[396] Five descriptive categories of economic loss cases involving different policy

considerations have been identified: (1) negligent misrepresentation; (2) negligent performance of a service; (3) relational economic loss; (4) the special liability of statutory public authorities; (5) negligent supply of shoddy goods or structures for the cost of repairing their dangerous defects.

[397] In *Arora v. Whirlpool Canada L.P., supra,* the Ontario Court of Appeal held that the Supreme Court of Canada in *Winnipeg Condominium Corp. No. 36 v. Bird Construction Co.*, [1995] 1 S.C.R. 85 had left open the issue of whether there should be no recovery for pure economic loss where goods are shoddy, but not dangerous, but the Court of Appeal then went on to decide the issue by deciding that the plaintiff's claim had no reasonable prospect of success.

[398] In the immediate case, AndroGel™ is not a shoddy good and the dangers in use, as far as they are known to exist, have been disclosed and warnings provided. As was the case, in *Arora v. Whirlpool Canada L.P., supra* the sale of non-dangerous but useless goods is a circumstance where there is no public policy that would engage tort law and Mr. Wise should be left with his contractual, negligent misrepresentation, or statutory consumer law remedies, if any.

[399] As for the Wises' waiver of tort claim, I will repeat what I said in the lower court decision in *Arora v. Whirlpool Canada L.P., supra* at paras. 297-99, which was approved by the Court of Appeal in its decision in the *Arora* case; that is:

> 297. The last cause of action to consider is the claim of waiver of tort. One could write a lot about this topic, but for present purposes I can be brief. Historically, the doctrine of waiver of tort provided the victim of certain types of tortious wrongdoing with the option of foregoing (waiving) tort compensation measured by the damages suffered by the victim and claim instead disgorgement of the tortfeasor's ill-gotten gains. The traditional view was that waiver of tort was a remedy available for certain torts.
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> 298. Without deciding the point, *Serhan v. Johnson & Johnson* [(2006), 85 O.R. (3d) 665, [2006] O.J. No. 2421 (Div. Ct.), leave to appeal to C.A. refused, Oct. 16, 2006, leave to appeal that denial of leave to S.C.C. refused, [2006] S.C.C.A. No. 494], initiated a debate about whether waiver of tort was not just a remedial choice but rather a cause of action available for more than the traditional short list of torts for which it had been available as a remedy or perhaps for wrongdoing generally. In other words, there has been a debate about the doctrinal nature of waiver of tort and the range of its availability. There, however, has been one point beyond debating. Whether a remedy or a cause of action, for waiver of tort to be available, the defendant must have done something wrong.
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> 299. In *Aronowicz v. Emtwo Properties Inc.* [(2010), 98 O.R. (3d) 641, [2010] O.J. No. 475, 2010 ONCA 96], at para. 82, Justice Blair stated about the waiver of tort doctrine:
>
> > Whether the claim exists as an independent cause of action or whether it requires proof of all the elements of an underlying tort aside, at the very least, waiver of tort requires some form of wrongdoing. The motion judge found none here. No breach of contract. No breach of fiduciary duty, or duty of good faith or confidentiality. No oppression. No misrepresentation. No deceit. No conspiracy. As counsel for Mr. Grinshpan put it in their

> factum, "its eleventh hour insertion into the statement of claim does not provide the appellants' claim with a new lifeline given that the record discloses no wrongful conduct on the part of the respondents in respect of any of the causes of action pleaded."

[400] In the case at bar, for the reasons discussed earlier, because general causation has not been established, there is no predicate wrongdoing upon which to base a plea of waiver of tort. All of the proposed causes of action lack a constituent element, and thus there is no predicate wrongdoing to support a claim of waiver of tort be it a remedy or a cause of action.

[401] I conclude that there is no genuine issue requiring a trial about the Wises' negligence or unjust enrichment claim for pure economic losses.

F. CONCLUSION

[402] For the above reasons, I grant Abbott's summary judgment motion, and I dismiss the Wises' action.

[403] If the parties cannot agree about the matter of costs, then they may make submissions in writing beginning with Abbott's submissions within 20 days from the release of these Reasons for Decision followed by the Wises' submissions within a further 20 days.

[404] I alert Abbott that I am inclined to substantially reduce any costs award because of its failure to seek the leave of the court earlier to call more than three expert witnesses.

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Perell, J.

Released: November 23, 2016

CITATION: Wise v. Abbott Laboratories, Limited, 2016 ONSC 7275
COURT FILE NO.: CV-16-550747CP
DATE: 20161123

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

NORMAN DOUGLAS WISE and MONIKA ELISABETH WISE

Plaintiffs

– and –

ABBOTT LABORATORIES, LIMITED, ABBOTT PRODUCTS INC. (f/k/a SOLVAY PHARMA INC. and SOLVAY PHARMA CLINICAL INC.), ABBOTT PRODUCTS CANADA INC. (f/k/a SOLVAY PHARMA CANADA INC.), and ABBVIE PRODUCTS LLC (f/k/a ABBOTT PRODUCTS LLC, f/k/a ABBOTT PRODUCTS, INC., f/k/a SOLVAY PHARMACEUTICALS, INC.)

Defendants

REASONS FOR DECISION

PERELL J.

Released: November 23, 2016