CITATION: Andersen v. St. Jude Medical, Inc., 2012 ONSC 3660
COURT FILE NO.: 00-CV-195906CV, Toronto
DATE: 20120626

ONTARIO

SUPERIOR COURT OF JUSTICE

BETWEEN:	)	
	)	
YVONNE ANDERSEN ON HER OWN BEHALF AND AS EXECUTRIX OF THE ESTATE OF ERIK ANDERSEN, SHARON FROST and HER MAJESTY THE QUEEN IN RIGHT OF THE PROVINCE OF ALBERTA, AS REPRESENTED BY THE MINISTER OF HEALTH AND WELLNESS	)	*Angus T. McKinnon*, *Peter W. Kryworuk*, *Russell Raikes* and *James M. Newland*, for the Plaintiffs*
Plaintiffs	)	
– and –	)	
ST. JUDE MEDICAL, INC. and ST. JUDE MEDICAL CANADA, INC.	)	*S. Gordon McKee* and *Jill M. Lawrie*, for the Defendants†
Defendants	)	
	)	**HEARD:**
	)	Evidence: February 8, 2010 to March 8, 2011 (138 days)
	)	Written Submissions: May-August 2011
	)	Oral Submissions: September 12-15, 20-23, 2011

Proceeding under the *Class Proceedings Act, 1992*

LAX J.

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* Additional Plaintiffs' Lawyers: Ed Morgan, Sandra Barton, Stephanie Montgomery, Rebecca Case, Brian P.F. Moher, Yola S. Ventresca, Louise F. Moher, Paul Hendrikx, Andrea D'Silva, Mark Hines

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SYNOPSIS

[1] This is a medical device products liability claim that was certified as a class proceeding by Mr. Justice Cullity in 2003 on behalf of a patient class and a family class and continued on to a trial of common issues before me in 2010 and 2011. The trial was about the safety of the mechanical prosthetic heart valves and annuloplasty rings with Silzone® that were designed and manufactured by the defendants and approved for sale in Canada in the late 1990s. They were implanted in Canadian patients between September 1997 and January 21, 2000, when the defendants issued a worldwide recall of all Silzone-coated products. At that time, an ongoing randomized clinical trial called 'AVERT' revealed a small, but statistically significant increase in explants due to a medical complication known as paravalvular leak (PVL) in patients who had received a Silzone implant. As a result, enrolment of patients in the AVERT study was terminated.

[2] Silzone is a proprietary term for a coating comprising layers of titanium, palladium and an outer layer of metallic silver. This was applied to the polyester (Dacron®) sewing cuff that surgeons use to attach a prosthetic heart valve to heart tissue. Silver is known as an antimicrobial in medicine and the Silzone coating was designed to inhibit the growth of the bacteria that can cause endocarditis, an infection that is a serious complication of heart valve surgery. In some forms and concentrations, silver can be cytotoxic to cells, but at the time that Silzone was developed, silver had been shown to be effective against bacteria and safe to use in applications such as wound dressings, sutures and catheters. Apart from the application of the Silzone coating to the Dacron sewing cuff, the Silzone valves were of the same design as the conventional mechanical valves that the defendants had manufactured for many years. These valves were considered to be the "gold standard" in mechanical heart valves and were favoured by many cardiac surgeons due to their reliable performance and low complication rate.

[3] The Silzone valve also enjoyed widespread use during the time it was on the market even though a few Canadian hospitals stopped using Silzone-coated devices in the year preceding the recall and in November 1999, the United Kingdom Medical Devices Agency (MDA) issued an Advice Notice to physicians warning about possible thromboembolic complications (TE events).

The MDA took no other action, but within days of this notice, Australian and New Zealand regulators withdrew approvals for Silzone products in those countries. Health Canada and the United States Food and Drug Administration (FDA), as well as the Data Safety Monitoring Board (DSMB) for the AVERT clinical trial, were well-informed about this, but they did not express concerns about the safety of the valve or take any action. The Silzone devices continued to be marketed in Canada and in the United States as well as in the United Kingdom and Europe until the recall. At the time of recall, about 36,000 valves had been sold in markets around the world.

[4] There are nine common issues to be answered, but at its core (although on a grand scale), this is a negligence claim and the evidence focused on two of its major elements: breach of duty causing injury and cause. The trial examined the defendants' conduct in designing, testing and marketing the Silzone valve (Common Issue 1) and considered questions of general causation – whether Silzone has an adverse effect on tissue healing (Common Issue 2) and whether the risk of medical complications is greater for patients with Silzone valves (Common Issue 3). The preponderance of the evidence that was adduced at trial addressed these common issues. The remaining common issues are largely concerned with entitlement to the remedies the plaintiffs seek: medical monitoring (Common Issues 4 and 5), spoliation (Common Issue 6), disgorgement of profits or 'waiver of tort' (Common Issues 7 and 8) and punitive damages (Common Issue 10(a)).[1] The trial was concerned only with liability and Common Issues 9 and 10(b) on quantum of damages were bifurcated to the end of the trial of common issues.

[5] The plaintiffs needed to establish on a balance of probabilities a "but for" negligent act or omission linking the defendants' conduct to a class-wide injury in order to move the claims of each class member forward to individual hearings. They tried to show that the defendants failed to reasonably evaluate the utility and safety of Silzone before introducing it to the market and then failed in their duty to warn of its risks. A theme was that the Silzone valve was rushed to market in view of the pending expiry of the patent for the defendants' successful bileaflet valve.

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[1] A list of the certified common issues is found in Schedule I.

The plaintiffs advanced the theory that Silzone is a toxic substance that interferes with the cells involved in tissue healing and impairs the body's ability to properly incorporate the Silzone device into the heart, thereby causing or contributing to a variety of serious medical complications for Silzone patients. As medical complications can occur with all prosthetic heart valves, a key inquiry in this trial was whether a Silzone coating on a mechanical heart valve puts patients at a *materially increased risk* of experiencing one or more of these complications.[2]

[6] There is sufficient evidence to find (and the defendants do not dispute) that Silzone probably materially increased the risk of PVL for some patients for some period of time post implant. The explanation for this is unclear. There is insufficient evidence to conclude that Silzone probably increased the risk of the other medical complications that are in issue and the plaintiffs did not succeed in proving that Silzone has an adverse effect on tissue healing. Although there is a high duty of care imposed on a medical device manufacturer, the plaintiffs did not establish that the defendants failed to exercise a reasonable degree of care in the pre-market design and testing or in the post-market surveillance of Silzone-coated products that would be expected of a reasonable and prudent prosthetic heart valve manufacturer in similar circumstances.

[7] These findings lead to the conclusion that the action must be dismissed.

INTRODUCTION

The Trial

[8] The trial was lengthy and complex. Some 2,293 documents were introduced into evidence as exhibits in electronic format with many exhibits running to hundreds of pages. The court heard testimony for 138 days from 40 witnesses, including 23 expert witnesses from 14 different disciplines in science and medicine. At the conclusion of the evidence, the parties

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[2] This wording was formulated by Mr. Justice Cullity in his reasons on the certification motion and will be discussed in Common Issue 3.

delivered voluminous written submissions over a period of several months and 18 months after the trial had commenced, it concluded in late September 2011 with eight days of closing submissions.

[9] There is a vast and challenging evidentiary record to consider and opposing expert opinions to resolve in order to arrive at the answers to those issues that the certification judge determined could be tried as common issues. To assist me, the parties provided their written submissions in electronic format with hyperlinks to the transcripts of witness testimony, the exhibits, and numerous legal authorities. Their submissions alone comprise more than 2,000 pages.

[10] The parties left no stone unturned in presenting this important case to the court and I have reviewed the extensive record many times and given careful consideration to all of it. However, if I were to discuss every argument and every detail of the evidence, this judgment would also run to thousands of pages, which I do not believe is necessary or desirable. Instead, I have tried to select the key arguments and evidence that the parties rely upon and explain how this has led to the conclusions that I have reached. Although I will not discuss everything, I hope to demonstrate that I have given careful consideration to all issues that are truly of substance. In parts of these reasons, I have used a narrative format. Unless I indicate otherwise, these are findings of fact.

[11] In preparing these reasons, I have borrowed liberally from the parties' written submissions. I have incorporated portions as my own where I considered it appropriate to do so. Without their roadmaps through 138 days of evidence as well as the additional written material that was prepared for closing submissions, my task would have been considerably more difficult. I am grateful to counsel for the invaluable assistance provided to the court at each phase of the trial process. I am also indebted to them for the exemplary manner in which they conducted the trial.

The Parties

[12] St. Jude Medical, Inc. is a global manufacturer of medical devices with its headquarters in St. Paul, Minnesota. St. Jude Medical Canada, Inc. is its wholly-owned subsidiary. St. Jude manufactured and distributed three Silzone-coated products in Canada – the St. Jude Medical

Mechanical Heart Valve SJM Masters series with Silzone (Silzone valve), the St. Jude Medical Mechanical Heart Valve SJM Regent Valve with Silzone (Regent valve) and the Sequin Annuloplasty Ring with Silzone (Sequin Ring).[3] The SJM Tailor Annuloplasty Ring with Silzone coating and the Epic valve with Silzone were also manufactured by the defendants, but they were not sold in Canada.

[13] In May 1997, St. Jude submitted applications for regulatory approval to distribute and sell the Silzone valve to Health Canada, the FDA and regulatory agencies in Europe. The application was filed as a Supplementary Notice of Compliance (SNOC) in Canada and as a Pre-Market Application Supplement (PMA Supplement) in the United States. It was approved in both countries as a modification to the Masters series valve.[4]

[14] The patient class consists of approximately 1100 Canadian residents other than residents of Quebec and British Columbia whose native aortic or mitral heart valves, or both, were replaced with a Silzone valve. At the time of certification, the plaintiff class was represented by Sharon Frost and Erik Andersen. Sharon Frost received a Silzone valve in the mitral position on April 13, 1998 that was explanted and replaced with another Silzone valve on August 20, 1998. That valve remains in place and Ms. Frost was the first witness to testify at trial in February 2010. Erik Andersen received a Silzone valve in the mitral position on May 28, 1998 that was explanted on July 27, 1998 and replaced with a second Silzone mitral valve. At the same time, Mr. Andersen's native aortic valve was replaced with a Silzone valve. Mr. Andersen died on January 15, 2005 with both Silzone valves still implanted. His widow, Yvonne Andersen, replaced him as class representative in her personal capacity and in her capacity as executrix of his estate. Mrs. Andersen was the second witness to testify at trial.

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[3] The defendants' submissions state that this device was implanted in three Canadian class members, but I was unable to find evidence to support this. The plaintiffs led no evidence about the Sequin Ring.

[4] At the time, a new prosthetic heart valve was licensed in Canada by a Notice of Compliance or NOC. In the United States, this was by way of a Pre-market Application or PMA.

[15] The evidence of the representative plaintiffs occupied less than a day of the trial. In the section that follows, I introduce the other fact witnesses who were involved in the Silzone story in the 1995 – 2000 timeframe and whose evidence contributed to my understanding of Silzone from product development to recall.

The Fact Witnesses

Plaintiffs' Witnesses

[16] In 1997, Dr. Keith Butler and Dr. William Freeland held positions in the Health Protection Branch of Health Canada. Dr. Butler has a Ph.D. in physiology and was a scientific reviewer in the cardiovascular division who was assigned to the application submitted by St. Jude for Canadian regulatory approval for the Silzone valve. Dr. Freeland is a medical doctor and was the Chief, Device Evaluation Division, Medical Device Bureau. Their evidence addressed the Canadian regulatory regime for a medical device and the approval process for the Silzone valve.

[17] Jagdish Butany and Eric Butchart are physicians and were among the first to raise concerns about the Silzone valve. Dr. Butany is an internationally recognized cardiovascular pathologist at the Toronto Hospital, University Health Network (TGH) who was summoned to testify. Mr. Butchart is a senior cardiovascular surgeon at University Hospital of Wales, Cardiff, Wales and is an internationally recognized cardiothoracic surgeon, specializing in thromboembolic complications of heart valve surgery.[5]

[18] All heart valves have thrombogenic potential in that thrombus may form on the leaflets or sewing cuff that can cause a blockage either at the valve site or elsewhere in the body after breaking away and travelling through the bloodstream. In the 1990s, Mr. Butchart was conducting an ongoing study known as 'CERFS' at his Cardiff hospital to evaluate the risks of thromboembolic complications (TE events) in patients following valve surgery.[6] Patients with Silzone valves were enrolled in the study between October 1997 and July 1998. He concluded

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[5] In the United Kingdom, senior surgeons are referred to as "Mr." rather than "Dr."
[6] 'CERFS' is an acronym for Cardiff Embolic Risk Factor Study.

that there was an increased incidence of TE events in these patients. His study findings strongly influenced the MDA to issue its Advice Notice to U.K. physicians in November 1999 and this, in turn, influenced the decisions of the Australian and New Zealand regulators to cancel the registration of Silzone products in these countries. Mr. Butchart was also a key expert witness for the plaintiffs, particularly on questions of thrombogenicity and TE events.

[19] Drs. George Christakis, Ghopal Bhatnagar and Hugh Scully are cardiovascular surgeons who held staff positions at teaching hospitals in Toronto at the relevant time. They testified about their experience with the Silzone valve in their respective hospitals. Dr. Christakis was also qualified as an expert witness, mainly on the issue of medical monitoring for Silzone patients.

[20] Through the read-in process, the plaintiffs adduced evidence given at U.S. depositions or Canadian discovery from a number of St. Jude employees or former employees.

Defendants' Witnesses

[21] Dr. Katherine Tweden, Mr. William Holmberg and Dr. Alan Flory were the main fact witnesses for the defendants. Dr. Tweden holds a Ph.D. in biomedical engineering with a focus on biomaterials and was the senior scientist on the Silzone project. She conducted the initial investigations on the antibacterial potential of a silver-coated sewing cuff, evaluated the *in vitro* efficacy and safety testing, and participated in many aspects of the *in vivo* sheep studies that assessed tissue healing. William Holmberg is a mechanical engineer and was the Silzone project team leader. Among other things, he was responsible for co-ordinating the work of the team members, facilitating Design Review meetings where key aspects of the project were discussed, and reporting periodically about the status of the project to the executive group at 'goaltending' sessions. Dr. Flory is a doctor of veterinary medicine and was Vice President of Corporate, Clinical and Regulatory Affairs. He and his staff were involved in the pre-market regulatory approval process, the AVERT study design and implementation, and post-market surveillance and recall.

[22] Other St. Jude employee witnesses were Terry Shepherd, President of the Heart Valve Division until 1999 and later, Chief Executive Officer of the company, and Dr. Wenda Carlyle, a research scientist at the company between 1997 and 2000. Dr. Robert Frater is a cardiothoracic surgeon who served as Medical Director of the company from 1999.

[23] At the time that Silzone was developed, St. Jude was known as a very good company with a reputation for producing very good products. The St. Jude employee witnesses who testified struck me as very able people who individually reflected the attributes that had earned St. Jude that reputation. They demonstrated professionalism and concern for their work and I was favourably impressed with their testimony. I found each of them to be credible, forthright and honest witnesses.

[24] Spire Corporation developed the technology for the Spi-Argent coating that ultimately became Silzone. Eric Tobin is Vice-President and Chief Operating Officer of Spire Biomedical Inc., a division of Spire Corporation. During the relevant time period, he was a research scientist who worked on the development of the Spi-Argent coating.

[25] Dr. Hartzell Schaff is a cardiothoracic surgeon and Chair, Cardiothoracic Surgery Division at the Mayo Clinic in Rochester, Minnesota. Dr. Schaff was the AVERT Principal Investigator for North American sites. Dr. Lisa Kennard was a member of the Department of Epidemiology at the University of Pittsburgh. Dr. Kennard was the AVERT Study Coordinator between 1998 and 2002 when she became AVERT's co-Principal Investigator, a position she continues to occupy.

AVERT

[26] As the AVERT study figures so prominently in the trial, and in particular, in the causation analysis in Common Issue 3, I will introduce it briefly here. AVERT was a randomized control trial (RCT) sponsored and funded by St. Jude and is an acronym for Artificial Valve Endocarditis Reduction Trial. Its purpose was to study whether Silzone was clinically effective in reducing prosthetic valve endocarditis, but its protocol included the collection of data on adverse events that are complications of valve surgery. The protocol specified that the study would take four years to complete.

[27] RCTs comparing mechanical heart valves are uncommon, but during its development of the Silzone coating, St. Jude began planning for a post-approval clinical trial to establish that the Silzone coating would reduce the incidence of prosthetic valve endocarditis in patients implanted with a Silzone valve. Until this was demonstrated, the FDA did not permit St. Jude to make efficacy claims in its product labelling or marketing. AVERT was designed as a large, multi-

centre, study with the study population coming from 17 centres in North America and in Europe and with patients randomized into two groups – those who received a Silzone valve and those who received a conventional St. Jude valve. Dr. Schaff was to serve as Principal Investigator in North America and Dr. Thierry Carrel, a cardiac surgeon in Bern, Switzerland, was to serve as Principal Investigator in Europe.

[28] The Epidemiology Data Coordinating Center (DCC) at the University of Pittsburgh was selected to receive reports from the various clinical centres and maintain a database. The DCC, in turn, was to recruit members from the medical community to serve on a Data Safety Monitoring Board (DSMB). Its role was to review the AVERT data and make recommendations as to the conduct of the study having regard to the safety of enrolled patients. Its membership included specialists in cardiology, cardiac surgery, infectious disease and statistics. The DSMB was to operate independently from St. Jude as study sponsor and funder, from Drs. Schaff and Carrel as investigators, and from the DCC.

[29] The design of the AVERT study was well underway by early 1998 at a time when the Silzone valve was undergoing the regulatory review process at the FDA. The Silzone valve was not approved for sale in the United States until March 1998, some eight months after it was approved for sale in Canada. A study sample size of 4400 patients – 2200 patients in each of the Silzone and non-Silzone arms of the study – had been calculated by Dr. Gary Grunkemeier, statistical consultant for AVERT. The study was launched in the summer of 1998 with the first implant taking place in August of that year.

[30] When the DSMB recommended in January 2000 that patient enrolment in AVERT be suspended, there were a total of 807 patients enrolled – 403 in the Silzone arm and 404 who had received non-Silzone valves. It is these patient populations who continue to be comparatively followed in the AVERT study for risk of medical complications to find out whether these risks are greater for patients with Silzone valves than they are for those with the conventional St. Jude valve.

Adverse Inferences

[31] The plaintiffs provided the court with a list of individuals whom they say are material witnesses that the defendants failed to call. An adverse inference may be drawn in circumstances where a party fails to call a witness who would have knowledge of the facts and would be assumed to be willing to assist the party. It also may be drawn against a party who does not call a material witness over whom he or she has exclusive control and does not explain it away.[7] An adverse inference is not justified where the issue has been adequately covered by another witness, or by other evidence.[8] The fundamental condition for the operation of the rule is that it applies only to issues material to the determination of a case and only where the case made against the party is of such strength that it calls for a reply.

[32] The first group of witnesses the plaintiffs say should have been called includes scientists or physicians who were involved in aspects of the AVERT study – Dr. Holubkov, Dr. Grunkemeier, Dr. Davila-Roman and Dr. de la Rivière. There is no evidence that the defendants exercised exclusive control over these individuals, nor can it be assumed that they would have been willing to assist the defendants merely because they were participants in AVERT. The defendants adduced evidence from Dr. Schaff and Dr. Kennard – two key participants in the design and conduct of the AVERT study – as well as from Dr. Flory. All of the material AVERT issues were addressed by these witnesses and none of the proposed witnesses had evidence material to the determination of the case.

[33] The second group, Connie Roos, Monica Schultz and Barbara Illingworth, were St. Jude employees between 1995 and 2000.[9] There is no evidence they were employees at the time of trial and there is no reason to assume that they would have been willing to assist the defendants by reason only of their employment more than a decade earlier. The plaintiffs had access to the deposition evidence of these witnesses and by agreement, the ability to adduce the evidence of

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[7] Sopinka, Lederman & Bryant: *The Law of Evidence*, 3rd ed. (Markham, Ontario: LexisNexis, 2009) at 6.449-6.450; *Lambert v. Quinn*, [1994] O.J. No. 3 at paras. 11-15 (C.A.).
[8] *Ritchie v. Thompson*, [1994] N.B.J. No. 540 at paras. 9 and 15 (C.A.) [*Ritchie*].
[9] The plaintiffs' written submissions also include Mr. Jonas Runquist in this group, although he does not appear on the list provided to the court during oral argument. Mr. Runquist was an engineer and Product Regulation Manager who reported to Dr. Flory.

Ms. Schultz and Ms. Illingworth through the read-in process.[10] If the plaintiffs considered the evidence of Ms. Roos necessary, they could have taken their own steps to adduce her evidence. While each of these potential witnesses are out of the jurisdiction and would only be compellable to give evidence by Letters of Request, the plaintiffs had equal ability to use that process.

[34] Richard Bianco and Dr. Douglas Cameron were consultants to St. Jude and involved in the pre-market animal studies. The plaintiffs' read-in discovery evidence shows that while Dr. Cameron initially provided some information to the defendants for responses to undertakings during the Ontario discovery process, he did not continue to do this. If he would not assist the defendants during the discovery process, it is unlikely he would be willing to assist them at trial. Mr. Bianco did appear on the defendants' witness list, but months before the trial process was completed, the plaintiffs were advised that they did not propose to call him as a witness. As part of the plaintiffs' consent to resolve two outstanding motions related to Mr. Bianco, the defendants paid the plaintiffs' costs of the motions and agreed not to call him at any future time. There is no justification for drawing an adverse inference in circumstances where the defendants do not call a witness in compliance with an undertaking.

[35] Dr. Tirone David is a world renowned cardiac surgeon at TGH who was conducting a prospective, randomized comparison of the St. Jude bileaflet valve to the bileaflet valve of a competitor valve manufacturer. Silzone patients were added to the study in 1997. The plaintiffs submit that Dr. David's evidence ought to have been adduced in relation to "the Toronto experience" with the Silzone valve. Dr. David was a treating surgeon for one or more class members and he is not a witness who was in the exclusive control of St. Jude. His evidence was equally available to the plaintiffs. Like Dr. Butany, he could have been summoned to testify.

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[10] At trial, the plaintiffs read in 79 excerpts from Mr. Runquist's deposition transcript, 71 excerpts from Ms. Schultz's deposition and 67 excerpts from Ms. Illingworth's deposition. In each case, they relied on portions of these read-ins in their written submissions.

[36] There are many reasons why a party may not call witnesses and drawing an adverse inference is an increasingly rare finding and one that should be exercised with "the greatest of caution".[11] This is, in part, due to the increased access to pre-trial discovery. As there is a freer exchange of documents and discovery of witnesses, it is the rare case that only one party is able to bring a witness before the court. In this proceeding, the plaintiffs also had access to deposition evidence from the U.S. Silzone litigation. This significantly broadened the scope of the discovery. The fairness considerations for drawing adverse inferences that might apply in some circumstances do not apply here.

[37] In each of the cases relied on by the plaintiffs, the missing evidence was considered of crucial importance to a key element of the case.[12] In this instance, the plaintiffs failed to identify except in the most general way the inferences that they wished the court to draw. I am hard pressed to identify any evidentiary gaps on material issues that demanded a response from the defendants. Consequently, I decline to draw any adverse inferences.

The Expert Witnesses

[38] Expert evidence is essential to resolve the standard of care question in Common Issue 1 on the adequacy of the pre-market testing as well as the general causation questions in Common Issues 2 and 3 which require an understanding of the process of tissue healing, the mechanism of action of silver and epidemiological and statistical evidence of risk. The court was privileged to hear evidence from many distinguished physicians and scientists. Schedule II is a chart listing the expert witnesses who testified at trial and their respective areas of expertise.

[39] For the most part, the defendants' experts were the more qualified experts on the issues that are before the court. Dr. Schoen is an internationally recognized cardiac pathologist who also holds a Ph.D. in materials science and has extensive experience performing pathological analysis of prosthetic heart valves. Dr. Williams, the defendants' biomaterials expert, is an

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[11] *Miller v. Carley* (2009), 98 O.R. (3d) 432 at paras. 201-202 (S.C.J.).
[12] *Levesque v. Comeau*, [1970] S.C.R. 1010 (see discussion in *Ritchie* at paras. 9-14); *Bernardi v. Guardian Royal Exchange Assurance Co.*, [1979] O.J. No. 553 at paras. 28-30 (C.A.); *Vieczorek v. Piersma*, [1987] O.J. No. 124 at para. 17 (C.A.); *Claiborne Industries Ltd. v. National Bank of Canada*, [1989] O.J. No. 1048 at paras. 47-51 (C.A.).

internationally recognized expert in biomaterials and tissue response to biomaterials, especially the biocompatibility of silver, with extensive research and experience with animal studies. He has also been involved in the design and testing of prosthetic heart valves since the mid 1990s. While Dr. Rodricks, the defendants' toxicologist, lacked experience with prosthetic heart valves, he was expert on the toxicity of metals and evaluating the safety of medical devices for toxicity.

[40] Dr. Williams and Dr. Rodricks concluded that St. Jude's testing was reasonable and in accordance with industry standards. They testified that the results of the testing as well as the scientific literature gave no indication that Silzone would cause adverse reactions in patients. Dr. Williams' opinion on the adequacy of the safety testing was supported by Diane Johnson, a former lead reviewer at the FDA of prosthetic heart valve submissions for regulatory approval. Ms. Johnson was personally involved in the drafting of the FDA's 1994 Draft Heart Valve Guidance and the ISO 5840 standard, the documents that were looked to by industry and regulators at the time when considering what testing should be done for prosthetic heart valves. Dr. Williams' interpretation of the results of the sheep studies was supported by Dr. Factor, a cardiac pathologist with recognized expertise in prosthetic heart valves, healing in heart valves implanted in sheep, and the pathology of endocarditis.

[41] On the other hand, the plaintiffs' expert, Dr. Healy, a biomaterials scientist with otherwise impressive qualifications, had no experience with silver or cardiac devices in terms of pre-market testing. The major background of Dr. McLean, one of the plaintiffs' toxicologists, was in pharmaceutical medicines rather than medical devices. Dr. Olson had done some testing of silver-coated wound dressings, but the plaintiffs called him to testify about the adequacy of the two sheep studies. He had experience with sheep studies, but no experience with sheep studies involving implanted cardiac devices, particularly prosthetic heart valves. Dr. Wilson, the plaintiffs' expert in pathology, lacked experience in sheep studies and in valve disease in adult patients.

Assessment of Scientific Evidence

[42] The plaintiffs sought to prove a causal relationship between Silzone and medical complications on the basis of a theory of silver toxicity that they supported through the evidence of their expert witnesses, principally, Drs. Healy, Wilson, Madigan Sackett and Mr. Butchart. Dr. Madigan is a statistician. Dr. Sackett is an epidemiologist. Both are highly qualified. The reliability of this evidence is central to the plaintiffs' burden of proof of causation. That burden is described by Justice Osler in *Rothwell* and I adopt his language:

> ...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.[13]

[43] The reliability of expert opinion evidence is considered both at the stage of assessing its admissibility (threshold reliability) and at the stage of determining what weight, if any, should be given to that evidence (ultimate reliability). The assessment of threshold reliability is an assessment of the principles and methodology underlying an expert's opinion to determine if they are of sufficient reliability that the opinions based upon those methods ought to be admitted into evidence. Where a scientific theory or technique is "novel", the Supreme Court of Canada held in *R. v. Mohan* that it must be subjected to special scrutiny to determine whether it meets a basic threshold of reliability.[14]

[44] In *Daubert*, the court considered a number of factors to assist it in determining whether a theory or a technique constitutes scientific knowledge and has sufficient reliability. These include: (1) whether the theory or technique has been tested, (2) whether it has been subject to peer review and publication, (3) its known or potential error rate and the existence and maintenance of standards controlling its operation, and (4) whether the theory or technique has

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[13] *Rothwell v. Raes* (1988), 66 O.R. 449, [1988] O.J. No. 1847 (H.C.J.) at para. 245 [*Rothwell*], aff'd (1990), 2 O.R. (3d) 332, [1990] O.J. No. 2298 (C.A.) [*Rothwell* (C.A.)], leave to appeal to the S.C.C. refused, [1991] S.C.C.A. No. 58.

[14] *R. v. Mohan*, [1994] 2 S.C.R. 9 [*Mohan*].

received general acceptance.[15] These criteria were adopted by the Supreme Court of Canada in *R. v. J.-L.J.* and discussed by Justice Goudge as Commissioner in the Inquiry into Pediatric Forensic Pathology in Ontario.[16]

[45] A scientific theory, method or technique that is generally accepted for some purpose, may be novel when used for a different purpose, and as such, fail to satisfy reliability criteria. For example, at issue in *J.-L.J.* was a technology that had been generally recognized by the scientific community to monitor the result of treatment for sexual pathologies. The Supreme Court of Canada found that the trial judge properly excluded opinion evidence of an expert who was using the technology as a forensic rather than therapeutic tool. The techniques the expert had employed were not novel and may have been useful in therapy to obtain information about a course of treatment for a patient, but they were not sufficiently reliable to be used in a court of law to identify or exclude the accused as a potential perpetrator of an offence.[17]

[46] The need for special scrutiny of novel science was first identified in *Mohan* to ensure that only reliable evidence would be heard by a jury, but this concern has gradually broadened. Justice Goudge observed that reliability is a fundamental organizing principle in the law of evidence and must be a constant concern of judges in their gatekeeper role, whether or not the science is novel. He also noted that the jurisprudence has been moving in the direction of recognizing the importance of reliability standards for all expert evidence, if not all evidence.[18] In assigning weight to the opinions of experts, there is no reason for a court to relax its scrutiny of the evidence even though the evidence has passed through the threshold reliability gate. This demands a rigorous evaluation of the experts' theories and methodologies (including the kind and quality of studies relied on), their application to the conclusions that the expert reached, and

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[15] *Daubert v. Merrell Dow Pharmaceuticals Inc.*, 509 U.S. 579 at 592-595 (1993) [*Daubert*].
[16] *R. v. J.-L.J.*, 2000 SCC 51, [2000] S.C.R. 600 at para. 33[*J.-L.J.*]; The Honourable Stephen T. Goudge (Commissioner), Report on the Inquiry into Pediatric Forensic Pathology in Ontario, vol. 3, (Toronto: Ministry of the Attorney General, 2008) ch. 18 ("Role of the Court") at 477-482 [The Goudge Report].
[17] *J.-L.J.*, at para. 35.
[18] The Goudge Report at 478-479.

an understanding of the purpose for which those conclusions are advanced. As to why this is needed, Judge Richard Posner is quoted as saying, "the court is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it".[19]

[47] While the court must determine the answers to the common issues before it on a balance of probabilities and scientific certainty is not the standard of proof, the underlying message of *J.-L. J.*, echoed in The Goudge Report, is that in assigning weight to individual pieces of scientific evidence, the court must pay attention to its purpose and underlying methodology and be guided by the methods and principles generally accepted and applied in the relevant scientific communities. A level of reliability that may be useful to formulate a plausible hypothesis may not be sufficiently reliable to prove causation and ascribe fault.

[48] For example, there is a generally accepted hierarchy within the scientific community of different kinds of epidemiological studies that may be helpful in investigating relationships of cause and effect.[20] At the top of the hierarchy is a RCT such as AVERT. Lower down in the hierarchy are cohort studies, case studies and case reports. There is consensus within the scientific community that a RCT, if well done, is the most reliable scientific evidence to support conclusions about causation. Studies below this in the hierarchy are generally not regarded as capable of generating evidence to support a causal relationship, although they may be useful for other purposes. As Justice Osler said in *Rothwell*:

> 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.[21]

[49] In this case, the methodology applied by some of the plaintiffs' experts called into question the reliability of their opinions on causation. Examples include Dr. Wilson's use of a clinico-pathological correlation of 18 valves in 14 patients (14 patient study) to support his

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[19] *In Re Human Tissue Products Liability Litigation*, 582 F. Supp. (2d) 644 at 690 (D.N.J. 2008) [In Re Human Tissue].
[20] See discussion in *Rothwell* at paras. 49 to 63.
[21] *Rothwell* at para. 237.

causation opinions on Silzone toxicity, Mr. Butchart's CERFS study to support his opinions on increased TE events in Silzone patients, Dr. Madigan's cohort analysis of the AVERT data to support his opinion on when risk is present and Dr. Sackett's two-part test to support his opinion on continuing harm. I will later explain why these are unreliable methodologies to support the opinions for which they were advanced.

[50] I will explain in Common Issue 2 why the plaintiffs failed to demonstrate on a balance of probabilities that abnormal tissue healing is the mechanism by which (or how) Silzone causes medical complications. In Common Issue 3, I will explain why the evidence does not support an inference on causation, upon which the plaintiffs relied heavily to assist their burden of proof of causation. As I point out there, I recognize that the plaintiffs do not have to demonstrate *how* Silzone causes medical complications in order to prove *that* it does. However, reliable evidence as to how Silzone would cause medical complications would be able to support an inference that it does. That evidence was lacking.

[51] As one would expect in a trial dominated by scientific evidence, there were numerous articles from the scientific literature that were introduced into evidence as exhibits. The question arises as to their evidentiary value. Justice Osler in *Rothwell* again provides guidance:

> The principal value of the studies, and of the various articles and learned papers to which reference was made in the course of the trial, is to act as touchstones which may be used to test the opinions of the witnesses who gave *viva voce* evidence and filed their reports before the court. While my conclusions must be based upon the evidence, and that of course means that I must assess and choose between the evidence of the experts where they are not in agreement, I may use the articles and reports as one of my means of assessment. While in most cases the reports are not evidence of the truth of the facts or the validity of the opinions stated therein, they are evidence, when such is acknowledged by the appropriate witnesses, of the fact that they were published, they were circulated and they were part of what has been referred to as "... the general corpus of medical and scientific learning on the subject and can be relied upon and adopted by suitably qualified experts": *Loveday v. Renton and Wellcome Foundation Ltd.*, unreported but delivered by Stuart-Smith L.J., in the Queen's Bench Division, High Court of Justice, England, March 29, 1988.[22]

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[22] At para. 89.

[52] As the excerpt explains, there are three principal uses: (1) to act as "touchstones" to assess opinion evidence; (2) to establish the fact of publication as part of the general body of scientific learning on the subject; and (3) to form part of the opinion of the witness, but only if the witness adopts passages or relies on study data from the article. During the course of these reasons, the scientific articles I refer to are footnoted with a brief reference. A bibliography of the articles with a fuller citation is found in Schedule III. A Glossary of Medical Terms is found in Schedule IV.

Order of Determination of the Common Issues

[53] It is the defendants' position that the court's determination as to what, if any, risks materially increased as a result of the addition of the Silzone coating will have a fundamental impact on what has to be determined in respect of the other common issues. They argue that as a person who acts without reasonable care commits no tort unless his lack of care causes damage, the defendants' conduct need only be considered under Common Issue 1 on standard of care to the extent it relates to a medical complication found to be at a materially increased risk under Common Issue 3. Accordingly, they submit that the first issue the court should determine is Common Issue 3 together with Common Issue 2 on tissue healing, which they describe as a sub-question of Common Issue 3 because any effect on tissue healing would be of no consequence if it is not proven to materially increase the risk of one or more medical complications.

[54] I agree that Common Issues 2 and 3 are related to one another, but it is not clear to me that addressing causation first will allow the court to narrow its standard of care analysis. The only assistance to be derived from the authorities the parties referred to is that the court must carefully consider the interaction between standard of care and causation and that to fail to consider causation may, in some circumstances, constitute legal error.[23] There are cases such as

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[23] *Grass (Litigation guardian of) v. Women's College Hospital* (2001), 144 O.A.C. 298, leave to appeal to the S.C.C. refused, [2001] S.C.C.A. No. 372; *Meringolo v. Oshawa General Hospital* (1991), 46 O.A.C. 260.

Rothwell and *Buchan* where the court has chosen to address causation before standard of care,[24] but the cases do not establish a requirement that the parties are "entitled" to findings with respect to causation before standard of care is addressed. This is a matter for the court's discretion.

[55] As I will discuss in Common Issue 3, there is insufficient evidence to conclude that Silzone patients are at a materially increased risk of experiencing medical complications with the exception of the complication known as PVL. Although I agree with the defendants that the company's conduct need only be considered under Common Issue 1 to the extent it relates to this complication, I have not found it easy to isolate the standard of care evidence for only this complication. As a result, there is no efficiency to be gained by addressing causation first. As well, I believe that addressing standard of care first will yield a more coherent narrative of the story of Silzone. I therefore propose to review the first three common issues in order.

COMMON ISSUE 1

Did the defendants breach a duty of care owed to class members by reason of the design, pre-market testing, regulatory compliance, manufacture, sale, marketing, distribution and recall of Silzone-coated mechanical heart valves and annuloplasty rings implanted in such members?

[56] The parties addressed Common Issue 1 in two parts as Common Issue 1a – pre-market design, manufacture and testing; and Common Issue 1b – post-market surveillance, warning and recall. The defendants acknowledge that St. Jude owed a duty of care to patient class members to take reasonable care in the design and testing of its products and in its post-market surveillance. What is at issue is whether there was a breach of that duty.

[57] The existence of a duty of care is a question of law: the standard of care that applies is a factual inquiry and defines the content of the duty that is owed.[25] To establish a breach of duty, a plaintiff must demonstrate, without the benefit of hindsight, some act or omission of the defendant in the present circumstances that was inconsistent with the conduct to be expected of a

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[24] *Buchan v. Ortho Pharmaceutical (Canada) Ltd.* (1984), 46 O.R. (2d) 113, [1984] O.J. No. 3181 (H.C.J.) [*Buchan*]; aff'd (1986), 54 O.R. (2d) 92, [1986] O.J. No. 2331 (C.A.) [*Buchan* (C.A.)].
[25] *Ryan v. Victoria (City)*, [1999] 1 S.C.R. 201 [*Ryan*].

like-situated party, that is, the conduct of an ordinary, reasonable and prudent prosthetic heart valve manufacturer in similar circumstances. The measure of what is reasonable was described by the Supreme Court in *Ryan v. Victoria*:

> … what is reasonable depends on the facts of each case, including the likelihood of a known or foreseeable harm, the gravity of that harm, and the burden of costs which would be incurred to prevent the injury. In addition, one may look to external indicators of reasonable conduct, such as custom, industry practice, and statutory or regulatory standards.[26]

Common Issue 1a – Design and Testing

[58] The plaintiffs do not contest their burden to show that if Silzone materially increased the risk of any medical complication, such increased risk was attributable to some act or omission by the defendants that fell below the standard of care. The plaintiffs contend that St. Jude's testing was inadequate and did not provide a proper scientific basis to support either the efficacy of Silzone or its safety and that as a result, St. Jude did not exercise reasonable care in analyzing the risks and benefits of adding the Silzone coating to its conventional valve. The plaintiffs do not clearly articulate what level of testing they allege was required by the requisite standard of care, but suggest that different and more extensive animal and pre-market clinical studies were required before the valve was marketed.

[59] It is the defendants' position that the nature and extent of the testing they performed satisfied the standard of care as informed by industry standards and the regulatory environment, and that, in any event, the plaintiffs have failed to adduce evidence to demonstrate that, if the standard of care required further testing, this would have affected the risk utility analysis and the reasonableness of St. Jude's decision to introduce Silzone-coated products.

Risk Utility Assessment

[60] The parties agree that the standard of care applicable to St. Jude as a medical device manufacturer required it to perform a risk utility assessment and to exercise reasonable care in doing so. They disagree on (i) the degree of certainty the defendants were required to have about

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[26] *Ryan* at para. 28.

the benefits of Silzone before distributing the product, (ii) the reasonableness of the product development process including the testing undertaken and the manner in which the testing results were interpreted and, (iii) the role and impact of industry and regulatory standards and practices and regulatory approval.

[61] A risk utility assessment is a concept adopted from United States jurisprudence that is used to determine whether a manufacturer has been negligent in the design of a product.[27] It requires a balancing or weighing of foreseeable risk against the foreseeable utility of the product based on information available to the manufacturer at the time of distribution of the product and without the benefit of hindsight. Health Canada and the FDA both apply a risk benefit analysis when reviewing submissions to approve new prosthetic heart valves or modifications in order to determine whether they are safe and effective. The Health Canada witnesses both testified that this involves weighing the known and potential risks of a device against the known and potential benefits and determining whether the benefits outweigh the risks. Ms. Johnson described this in the FDA process as being reasonably assured that the probable benefits to health outweigh the probable risks.

[62] In *Rentway*, the court provides a list of seven factors to consider (only a few are relevant factors in this case) but offers little guidance on how to apply these in order to assess the reasonableness of the risk utility assessment of the manufacturer. The defendants, relying on American case law, submit that a manufacturer is required to weigh the likelihood of both the benefit and the risk offered by a product as well as the value of the potential benefit and the seriousness of the potential risks. Based on the American case law cited by the defendants as well the U.S. case law referred to by Mr. Justice Cumming in *Ragoonanan*, I find that this is the assessment that the defendants were required to undertake. Put another way, St. Jude was required to weigh both the gravity and the likelihood of the reasonably foreseeable risks posed by the Silzone valve relative to the potential extent of its utility and the likelihood that the potential utility could be realized.

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[27] *Rentway Canada Ltd. v. Laidlaw Transport Ltd.*, 1989 CarswellOnt 23 at paras. 43-46, aff'd [1994] O.J. No. 50 (C.A.) [*Rentway*]; *Ragoonanan v. Imperial Tobacco Canada Ltd.*, [2000] O.J. No. 4597 at paras. 103-104 (S.C.J.) [*Ragoonanan*].

Initial Investigations

[63] The Spi-Argent technology that ultimately became Silzone was developed in the 1990s by Dr. Piran Sioshansi, a physicist at Spire Corporation in Bedford, Massachusetts. In June 1995, Dr. Sioshansi made a presentation to St. Jude employees about Spi-Argent. Bill Holmberg, the Silzone project leader, first became involved in the early fall of 1995 when St. Jude's Director of Research and Development for mechanical valves asked Mr. Holmberg to investigate the Spi-Argent technology. Dr. Katherine Tweden had attended Dr. Sioshansi's presentation and Mr. Holmberg asked her to assist him. Initially, Dr. Tweden was a consultant to the Silzone project while working on other projects within the company, but apart from a three month maternity leave commencing mid-November, 1995, she was actively involved during the initial stages of investigation and later, during the testing phase. Her participation was formalized in early December 1996 as a member of the 'AB Cuff Team'.

[64] Through her educational and work experience, Dr. Tweden had acquired specialized knowledge in tissue healing research and had conducted animal studies, including sheep studies, working with leading surgeons, pathologists, and animal study investigators in the scientific community. Mr. Holmberg was a project engineer with the company. He was not a research scientist, but he had led or been a member of several heart device projects at St. Jude and had some training in experiment design and failure modes effects analysis. They were impressive witnesses who were both deposed as part of the Silzone litigation in the United States. Neither was successfully impeached during their many days of testimony at this trial.

[65] Dr. Tweden agreed in cross-examination that it would have been better to have had a toxicologist on the team, but the plaintiffs' own toxicology expert, Dr. McLean, volunteered that he thought Dr. Tweden did "some very competent and thorough work". Although the plaintiffs suggested otherwise, I find that Mr. Holmberg and Dr. Tweden brought relevant knowledge, training and experience to the Silzone project and approached their work in a thoroughly competent and professional manner. As the Silzone project went forward, the team was also able to draw on the experience and knowledge of other St. Jude scientists, the Medical Director, reputable testing laboratories and medical and surgical consultants as well as the experience and knowledge of Spire and those using the Spi-Argent technology. The plaintiffs' criticisms of Dr. Tweden and Mr. Holmberg are unfounded.

[66] The initial investigations of Spi-Argent occurred in the fall of 1995 when Dr. Tweden began a preliminary literature review and consulted with external experts about the types of testing to be considered. She spoke with Mr. Bianco, Director of Experimental Surgery at the University of Minnesota and with Dr. Schoen and Dr. Fortune, who were medical consultants to St. Jude. Her note records that Dr. Schoen recommended she look into the research by Dr. Anderson and Dr. Durack on animal models for endocarditis. This led to further reading. She also became aware of the work of Dr. Rolf Bambauer who was using the Spi-Argent coating on catheters. She reviewed his articles and spoke to him personally about the results of his work.[28]

[67] Sims Deltec, a manufacturer of medical products, was also using the Spi-Argent coating on catheters. Dr. Tweden, Mr. Holmberg and Jonas Runquist spoke with Dr. Harry Puryear, a scientist at the company. Dr. Tweden's testimony, confirmed by a note made at the time, describes some of the difficulties that it encountered with testing and some of their concerns about the coating coming off, but the note also records that "it appeared to be an effective technology". Sims Deltec used a silicone rubber substrate and Dr. Tweden and Mr. Holmberg satisfactorily explained why they did not believe that the adherence concerns described by Dr. Puryear would apply to the Dacron cuff. This was confirmed by Spire's testing which showed excellent adherence of the Spi-Argent coating on Dacron.

[68] Dr. Tweden concluded that Dr. Bambauer's work assessing the Spi-Argent coating on hemodialysis catheters and catheter cuffs was particularly relevant and positive. These early enquiries were followed by a conference call with Dr. Sioshansi and Mr. Barry of Spire about the Spi-Argent coating as there were two possibilities: Spi-Argent I and Spi-Argent II. At the end of November, Mr. Holmberg and several other St. Jude employees travelled to the Spire facility in Massachusetts to look at the feasibility of the Spire technology for the Silzone project and to make a "go/no go" decision about moving forward. Before this, no decision had been made to form a project team or proceed with testing, but the information obtained from these investigations was favourable. Spire made a positive impression during the visit and the

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[28] The studies conducted by Dr. Bambauer are discussed in Common Issue 2.

technology looked promising. I am satisfied that St. Jude conducted reasonable investigations of Spire, the Spi-Argent coating and the coating process before deciding to pursue the Silzone project.

[69] Spi-Argent I that ultimately became Silzone is composed of three layers beginning with titanium which is applied to the substrate (the polyester fabric) to provide adhesion; then, palladium, which acts as an oxygen barrier; and finally, silver. The Spi-Argent I coating was selected because Spire had greater experience with it, specifically on the polyester fabric that St. Jude used on its valves. It also had higher levels of antimicrobial activity and had been the subject of the majority of Spire's biocompatibility testing. The results of that testing are found in the Spire Master File and some of it was later relied on in the regulatory submissions. It was discussed at the November meeting at Spire and reviewed at other times during the project.

[70] The Spi-Argent coating is applied using an ion beam assisted deposition or IBAD process that Mr. Holmberg and others observed during the trip to the Spire facility. Mr. Holmberg and Mr. Tobin described the process and Dr. Williams explained the advantages of the IBAD process for the Silzone coating. I attach little weight to Dr. Wilson's criticisms of the uniformity of the coating from his examination of one unimplanted valve as his opinions are based on a faulty understanding of the coating and cuff construction process. The uniformity of the coating can be observed in the high magnification photographs of the fabric and was confirmed by the evidence of Dr. Williams.[29] I am satisfied that the IBAD process produced a relatively uniform and firmly adherent coating and was an appropriate technology to use for its intended purpose. The coating was applied in conformity to St. Jude's specifications. There is nothing to criticize in St. Jude's quality assurance inspection of the fabric both before and during the assembly of the valves. When problems arose – for example, the discolouration of gloves observed by workers assembling test valves – they were appropriately investigated and resolved to ensure that the coating was adherent.

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[29] Exhibits 954 to 959.

The Silzone Project Moves Ahead

[71] Following the Spire visit, a team was formed and the Silzone project did move forward. Its development was characterized by a similar approach of reasonable investigation and assessment as the project proceeded. I do not accept the plaintiffs' description of a rushed process, implying a lack of reasonable care. It is true that Mr. Holmberg as project leader, and Mr. Shepherd as the executive leading the heart valve division, frequently stressed the importance of making progress and not getting behind schedule. At times, they conveyed a sense of urgency to team members, but there is no evidence that the timelines or goals for the Silzone project were unusual from a development perspective or that it proceeded at a pace that was at the expense of completing appropriate tasks, tests and evaluation.

[72] In forming this opinion, I have considered the evidence the plaintiffs rely on, including the request to the FDA for an expedited review (the FDA refused this), the shortening of the 20 week sheep study to 10 weeks (the FDA approved this), an early strategy to release the Silzone products first in unregulated countries (the strategy was abandoned), and references to patent expiry in various marketing documents. I agree that Mr. Runquist's May 14, 1997 letter to the FDA requesting an expedited review exaggerated the demand for the Silzone product, but as the FDA refused this request, nothing turns on this.

[73] While it would be naïve to think that the company was unconcerned about profits or protecting its intellectual property, no valve manufacturer would be in business very long if it neglected patient safety and marketed products that didn't work. It also seems unlikely that a company that didn't have a real belief in the potential benefit of Silzone, both for patients and for its shareholders, would license the Spire technology as it did in February 1996; pursue a multi-million dollar project to acquire the IBAD technology from Spire that was ongoing at the time of the recall (despite the publications of Dr. Butany and Mr. Butchart raising concerns about the safety of the valve); or put the Silzone valve into a "gold standard" RCT like AVERT. At the time, this would have been considered a bold step as there had been few RCTs comparing two mechanical heart valves and clinical efficacy data could have been obtained in other ways. The plaintiffs contend that St. Jude carried on with AVERT only to assist it with the litigation that

followed the recall. As the company had no way of knowing if AVERT would show that Silzone patients were at increased risk for other medical complications, I do not find this argument persuasive.

[74] Dr. Flory, Mr. Shepherd, and the other St. Jude witnesses who testified on this point did not dispute that patent expiry was a consideration in the development of the Silzone valve, but the evidence satisfies me that it was not a consideration that affected the amount of testing that was done or the analysis of that testing. Evidence that a business is motivated by profit cannot, without more, be treated as evidence that it fell below the standard of care. At most, the evidence demonstrates that St. Jude behaved as would be expected of a commercially-motivated party.

[75] I am also satisfied that St. Jude thoroughly investigated problems when they arose, for example, the corrosion and leaching concerns that were the subject of Mr. Holmberg's August 21, 1996 letter to Dr. Sioshansi and the excess pannus observed on two valves in the Long Term Sheep Study. Mr. Holmberg sought advice from Dr. Roger Stahle, an external corrosion specialist and consulted the fabric supplier and fabric consultants. Dr. Tweden sent the valves to Dr. Schoen to be reviewed. Mr. Holmberg understood that unless these issues were addressed satisfactorily, it would slow down or stop the project and he acted reasonably in seeking advice and finding solutions, as did Dr. Tweden. I accept that the company wanted to get the product to market quickly, but the evidence as a whole satisfies me that this was not at the expense of product safety.

[76] All of the safety issues raised in the trial – including excess pannus, dehiscence and paravalvular leak, systemic and local toxicity, increased thrombogenicity, and adherence of the coating – were formally identified as potential risks during the Failure Mode Effects and Criticality Analysis (FMECA) in December 1996 and in July 1997. The FMECA provided a structured format for the analysis of the relative risks of each potential failure and recorded the results of the testing that had been done or was ongoing that provided assurance that the addition of the Silzone coating did not create these additional risks. In order to bring a variety of perspectives to the discussion, participants included not only members of the project team, but also managers and scientists involved in other projects and from other divisions. A similar format was used for the Design Review Meetings that Mr. Holmberg led.

[77] The plaintiffs criticize FMECA as coming too late in the development process, but I accept Dr. Tweden's evidence that the identification of potential failure modes formed a part of the design and testing process and the project team began brainstorming potential failure modes informally from the beginning of the project. This is corroborated by the company's Regulatory Assessment signed April 10, 1996, which identified at an early time inadequate tissue ingrowth – one of the plaintiffs' main contentions – as a possible risk of the Silzone coating.

[78] I also accept the evidence of Dr. Tweden that over the course of the project she reviewed hundreds of articles and abstracts in the scientific literature on the biocompatibility of silver. From her review of the literature, Dr. Tweden concluded that cytotoxicity was directly related to the concentration of silver ions available. Each sewing cuff contained only a tiny amount of silver – between 17 and 50 mg – depending on the size of the valve. As silver ions from metallic silver ionize much less readily than from silver salts, she concluded that cytotoxicity would be at an acceptable level as there would be fewer silver ions available. Dr. Tweden's conclusions were confirmed by the results of the pre-market safety testing and are consistent with the published literature on the toxicity profile of silver. In Common Issue 2, I will review the scientific literature and explain why it supports Dr. Tweden's conclusions.

The Utility Assessment

Potential Utility/Benefit of Silzone

[79] The Silzone valve was designed and manufactured to directly reduce infection while having no adverse effect on tissue healing when compared to the uncoated Dacron cuff. The coating was applied to the specific area where infection often started, the sewing cuff. A starting point is to consider whether there was a reasonable basis for the company to pursue a technology to reduce the incidence of post-operative infectious endocarditis, specifically, prosthetic valve endocarditis (PVE) in St. Jude's conventional valve sewing cuffs. Experts called by both the plaintiffs and the defendants gave evidence as to the rate or incidence of endocarditis among prosthetic heart valve recipients and as to its morbidity and mortality. While varying numbers were provided, the conclusion to be drawn from the evidence from both sides is that, while PVE is relatively rare, its potential consequences are very serious. Mr. Butchart, the plaintiffs' expert,

agreed that "prosthetic valve endocarditis is the most feared complication after valve replacement surgery." Dr. Sexton, the defendants' expert and a leading authority on endocarditis, described it as a "terrible disease".

[80] Dr. Sexton testified that there are different rates of morbidity and mortality at different medical centres, but that a blended average would be that about half of patients who have PVE require reoperation and roughly one third die as a consequence of the infection. In the late 1990s, approximately 70,000 of the defendants' valves were implanted each year. Applying a PVE rate of 1% per patient year, approximately 2800 patients would contract PVE. Of these, approximately 1400 would require reoperations and 930 would die over the anticipated four year period of the AVERT trial that was to assess the clinical efficacy of Silzone. Although these numbers are not large, PVE was a serious enough issue that some surgeons, including those at the Mayo Clinic, were dipping valve sewing rings in antibiotics prior to implantation in an attempt to minimize the risk of PVE without any evidence that this was effective.

[81] PVE is treated with a heavy course of antibiotics. The expert testimony confirmed that in the 1995-1997 timeframe, the medical and scientific communities were increasingly concerned about antibiotic resistance, and at the same time, silver was gaining popularity as an antimicrobial agent. Device infection is often caused by biofilms which are more resistant to commonly used antibiotics and very difficult to treat with systemic antibiotics. Silver has the unique ability to stop the initial phase of bacterial attachment that leads to formation of a biofilm. As well, endocarditis is caused by a number of different organisms and there is no single antibiotic with as broad a spectrum of activity against microbes as silver. Dr. Williams, the most knowledgeable expert on the biocompatibility of silver, testified that there was a reasonable scientific basis to use the Silzone coating for the purpose of reducing endocarditis. Dr. Hancock, a microbiologist and the most knowledgeable expert on infectious organisms and the behaviour of bacterial cells, agreed.

[82] Dr. Christakis downplayed the desire of the medical community for a heart valve with antimicrobial properties stating that there was no "clamour" for such a product, but St. Jude was not alone in investigating the use of antimicrobial coatings. Dr. Butany recalled that at the time, "everybody was trying to develop sewing cuffs which would prevent endocarditis". Dr. Errett,

Chief of Cardiovascular and Thoracic Surgery at St. Michael's Hospital in Toronto, described the efforts of two competitors who were also investigating impregnating sewing cuffs with antimicrobial agents, including a project similar to Silzone that applied silver to the pledgets in addition to the sewing cuff.

[83] It seems unlikely that St. Jude and its competitors would be interested in developing a product that the medical community was not going to use. In fact, all of the surgeon witnesses called by the plaintiffs, including Dr. Christakis, used the Silzone valve when it became available. It was used by leading medical centres in Canada, the United States and Europe, including the 17 centres participating in AVERT. Mr. Butchart, who later was extremely critical of the valve's performance, felt at the time that it had potential benefits for patients and agreed to include it in CERFS, the study he was conducting at his hospital in Cardiff, Wales. In my view, this is strong evidence that a mechanical heart valve with antimicrobial properties did meet a perceived need and corroborates the testimony of Mr. Shepherd and Mr. Holmberg that they understood there was support within the medical community for St. Jude to develop a product that had the ability to reduce the risk of PVE. That other manufacturers were also interested in developing a similar product is further corroboration of their evidence.

[84] The conclusion to be drawn from the evidence is that a mechanical heart valve with antimicrobial properties did meet an important need and the potential utility of Silzone was considerable for this group of patients. Although the risk of developing endocarditis was very small, the consequences were very serious. As discussed in Common Issue 2, the state of knowledge at the time was supportive of the use of silver in medical products to reduce the incidence of infection and promote healing. There was a reasonable basis for St. Jude to pursue a technology using silver to reduce the incidence of PVE.

<u>The Efficacy Testing Program</u>

Animal Efficacy Studies

[85] As I have already mentioned, at an early stage in the Silzone project, Dr. Tweden began to consult with external experts, including Mr. Bianco and Dr. Schoen about the type of testing they might recommend. Her note of September 13, 1995, records a conversation with Mr. Bianco who was highly regarded by Dr. Tweden for the work he had done in development of animal

models for testing prosthetic heart valves. Based on these discussions and her reading, Dr. Tweden concluded that there was no established animal challenge model for PVE that could be used. She became aware of an animal model for native valve endocarditis, but I accept her explanation that this model was not suitable for a prosthetic heart valve.

[86] The challenges involved in performing an animal efficacy study were outlined in St. Jude's letter to the FDA on December 29, 1995 when Mr. Runquist notified the FDA of the proposed mechanical heart valve project with Silzone and explained why the company did not plan to pursue pre-market animal efficacy studies. Instead, St, Jude proposed to the FDA that it submit relatively limited labelling claims based on Spire's *in vitro* data and then pursue post-approval efficacy studies over several years. The FDA's agreement with this approach is consistent with Dr. Wustenberg's opinion that in the 1995-2000 timeframe, the FDA wanted animal data for antimicrobial devices if it could get it, but allowed approval of devices without this data. In that event, it did not allow manufacturers to claim clinical efficacy. As a result, the FDA approved a label for Silzone products that was also reviewed by Health Canada and read: "The Silzone coating has been shown *in vitro* to reduce attachment and colonization of microorganisms frequently associated with endocarditis". That the Silzone valve enjoyed widespread use based only on *in vitro* efficacy claims is further evidence that the medical community supported the development of this product and believed it had potential benefit for patients even though clinical efficacy had not been shown.

[87] The challenges of an animal efficacy study that St. Jude described in the letter to the FDA were confirmed by the expert testimony of Dr. Hancock and by Dr. Wustenberg, the defendants' expert on industry standards for animal testing. Their opinions support the conclusion of Dr. Tweden and the project team not to pursue pre-market animal efficacy studies. Dr. Hancock testified that he had reviewed the literature and had been unable to find any previous studies using an endocarditis model in a large animal. Among other issues, such a study would have required large numbers of animals, raising ethical concerns, and it was questionable whether the animal data would apply to humans. Dr. Hancock explained that even if a challenge model could be developed, it would still be of doubtful validity to the clinical situation because these models cannot recreate the conditions of endocarditis infection found in people with replacement heart valves. St. Jude's post-submission attempt to inoculate the sewing rings of valves with bacteria

before they were implanted in sheep did not proceed past the method development stage. A systemic inoculation large animal model was also proposed but the institution where the study was to be conducted rejected it due to animal welfare concerns.

[88] Dr. Wustenberg described the technical difficulties manufacturers encountered at that time in obtaining reliable and repeatable results for antimicrobial coatings on long-term implantable devices. Virtually all of the testing was done by implanting materials infected with various infectious agents under the skin of small animals. St. Jude ultimately experienced all of these difficulties in their post-submission attempts to develo*p in vivo* efficacy models in rabbits and guinea pigs. These failed attempts support the opinion of the defendants' experts that there was no animal model available at that time for testing antimicrobial coatings that would provide repeatable results that could be extrapolated to humans. Neither Health Canada nor the FDA raised any concern that an animal efficacy study had not been conducted. I find that St. Jude's decision not to pursue pre-market animal efficacy testing was reasonable and in accordance with industry standards at the time.

In Vitro Testing

[89] The evidence that bears on this comes from Dr. Tweden and Dr. Hancock. Although the plaintiffs' expert, Dr. Olson, is also a microbiologist, the plaintiffs did not seek to qualify him to give opinion evidence on this subject. Dr. Hancock was the only microbiologist to testify at trial. He is Professor of Microbiology and Immunology at the University of British Columbia, the Director of the Centre for Microbial Diseases and Immunity Research, and a Canada Research Chair in Microbiology.

[90] St. Jude relied on tests that were performed using the Dow Corning Flask and NYS63 methods of testing. Dr. Hancock confirmed that these were standard efficacy tests and that the four microorganisms that were tested are major causes of endocarditis. The results showed that Silzone was effective against all four endocarditis-causing infectious agents. Dr. Hancock also explained and put into context some of the inconsistent test results such as the Dow assay on April 10, 1996 that the plaintiffs emphasize in their submissions. He agreed that this was a flawed result corroborating Dr. Tweden's conclusion that there were problems in the laboratory on that experimental day and that it was appropriate to repeat the test.

[91] After reviewing all of the results, including the inconsistent data, Dr. Hancock concluded that these tests demonstrated that Silzone had the potential for clinical efficacy to reduce endocarditis in patients. No expert criticized the company for not having a "pass/fail" criterion for the microorganism reduction tests and the plaintiffs did not cross-examine Dr. Hancock on this issue. Dr. Hancock's uncontradicted evidence that these tests provided strong evidence of Silzone's ability to kill the bacteria that cause endocarditis and prevent bacterial colony formation corroborates Dr. Tweden's view that the results of the testing were promising. Dr. Hancocks' opinions addressed each of the plaintiffs' arguments about the efficacy testing and support the defendants' position that there was a reasonable scientific basis for the company's belief that Silzone had the potential to reduce the incidence of endocarditis.

[92] St. Jude also performed parallel streak tests on the Silzone fabric and obtained inconsistent results. While the parallel streak test is a standard efficacy test, Dr. Tweden concluded that it was not appropriate for the Dacron fabric due to the fabric's three-dimensional nature. In order to have a meaningful test, organisms needed to be seated on the interstices of the fibres. Mr. Tobin testified that Spire had reached a similar conclusion because the silver did not come off the surface at high enough rates to set large zones of inhibition and, therefore, did not have that much sensitivity or usefulness for the Spi-Argent coating. Dr. Hancock agreed that it would have been inappropriate for St. Jude to draw conclusions about the antimicrobial activity of Silzone based on these tests because it was not an appropriate assay to test a surface-associated substance that does not diffuse rapidly. However, the results did confirm the low rate of ionization of the silver ions.

[93] The plaintiffs rely on the fact that that these tests, and also those done by Spire, showed that Silzone set a zone of inhibition, or "kill-zone", against certain microorganisms demonstrating that Silzone "leached" from the fabric. They suggest that this showed that Silzone was capable of inhibiting cellular growth and destroying cells not in direct contact with the fabric. Dr. Hancock reviewed the zone of inhibition testing reported in the Spire Master file as well as the testing performed on behalf of St. Jude by NAmSA, a reputable testing laboratory. He confirmed that there was an indication of a small zone of inhibition in a couple of test results for one particular organism and none against other organisms, but he agreed with St. Jude's conclusions that the most that could be concluded from these tests was that not much silver was

diffusing away from the surface of the fabric. In response to the plaintiffs' argument on cell destruction, he testified that whether or not there was a zone of inhibition, the results of this kind of testing with bacteria and fungi do not provide useful information about the effects on human cells as zone of inhibition testing is not a standard assay for measuring the killing of human cells as opposed to bacterial cells. Dr. Hancock was the most qualified to discuss this and his testimony on this point was not challenged.

[94] At the time the valve was distributed, St. Jude had not established that an antimicrobial coating would be clinically effective against PVE. Instead, St. Jude decided to seek regulatory approval for the valve with limited labelling claims as to efficacy based on *in vitro* testing, relying on AVERT to subsequently demonstrate clinical efficacy. It is the plaintiffs' position that St. Jude could not establish the efficacy of Silzone with the appropriate degree of certainty through *in vitro* testing and should have delayed introducing the Silzone valve until it had completed a pre-market clinical trial. The main reason they advance is that Silzone was an unproven modification to St. Jude's "gold standard", low complication rate, conventional valve. Their argument appears to be that as the conventional valve was a safer alternative, the standard of care required the defendants to show that Silzone was effective in patients and posed no additional risk in order to be able to conclude that the Silzone valve truly represented a benefit over the conventional valve that outweighed its risks.

[95] The availability of safer products to meet the same need is a factor in the risk utility analysis, but the plaintiffs' argument ignores that PVE was a known risk with the conventional valve that the Silzone valve had the potential to address. Every heart valve patient who received a conventional St. Jude valve was at a small but serious risk of experiencing this complication that is difficult to treat and associated with high morbidity and mortality. This was the need that was being addressed. The risk utility analysis did not require St. Jude to assess whether the benefits of the Silzone valve outweighed the benefits of the conventional valve relative to their risks. Rather, it was required to consider whether the potential benefits associated with the addition of Silzone outweighed the potential risks of Silzone.

[96] As well, the plaintiffs' argument is premised on the assumption that there was an increased risk with the Silzone valve over the conventional valve. In January 2000, the AVERT data showed that some Silzone valve recipients were at an increased risk of explant due to PVL, but this was not known or foreseeable at the time the valve was distributed. While in some cases the existence of a safer alternative to meet the same need can be a relevant factor in the risk utility analysis, in the circumstances of this case, this reasoning imports a hindsight analysis. In any event, the conventional valve did not meet the same need as the Silzone valve because it did not address the risk of PVE.

Regulatory Submissions

[97] Although the plaintiffs' experts did not criticize the efficacy testing or the reporting of the test results, the plaintiffs contend that St. Jude did not fairly report the efficacy testing results in the regulatory submissions and, as a result, the FDA and Health Canada were not in a position to adequately assess the test results. The essence of the evidence from Dr. Butler and Dr. Freeland was that, while Health Canada was relying on the information received from a medical device company, they expected the manufacturer to exercise judgment about what to include in a submission and did not expect information that was not scientifically relevant or reliable. If there was difficulty replicating results, Dr. Butler expected contradictory information to be resolved. In my view, this is what St. Jude did. Dr. Hancock testified that St. Jude's submission included a fair representation of the test results and fairly and accurately summarized the testing and the company's interpretation of the results. This evidence was uncontested and I agree with it.

[98] The plaintiffs also allege that the SNOC submission was misleading with respect to the sufficiency of the pre-market efficacy testing as it failed to disclose St. Jude's plans to conduct a post-market clinical efficacy study or an animal challenge study "and thereby cast doubt upon the regulators' ability to weigh the respective risks and benefits of the Silzone product". I must say I have difficulty understanding this argument. However, it was clear from the submission that a clinical trial to demonstrate efficacy had not yet been conducted. While the *in vitro* efficacy testing supported the potential benefits of Silzone, Health Canada understood the limitations of that evidence. As Dr. Butler said:

> [St. Jude Medical] did prove efficacy in the fact that this valve worked in animals. The animals would have died if this valve wasn't effective ... you know, as a valve, it was effective. That – the animal study proved it. The valve could be implanted, the valve worked, it didn't leak. So in other words the valve was proven to be effective as a valve. But they did not prove that the Silzone coating prevented infection.

[99] The plaintiffs point to the uncontradicted evidence from AVERT that Silzone was not effective in reducing the incidence of infective endocarditis as evidence that St. Jude's claims that Silzone would be beneficial "were proven false". Clinical efficacy was not proven in AVERT, but as the trial was stopped prematurely, it may never be known whether a study of 4400 patients rather than 800 patients would have shown a reduction in the rate of infectious endocarditis.

[100] The evidence as a whole shows that St. Jude's view of the potential efficacy of Silzone was reasonable at the time. The *in vitro* efficacy testing demonstrated that Silzone was effective against infectious agents that commonly cause endocarditis. Products on the market at that time, such as treatments for wounds and burns, showed silver to be effective against bacteria and promote healing. Dr. Bambauer's experience with the Spi-Argent coating on catheter devices in a blood-contacting environment showed that it reduced infection in patients. The scientific literature (to be discussed in Common Issue 2) reported the effectiveness of silver in killing bacteria and preventing them from attaching to surfaces. It was reasonable for the defendants to conclude that a Silzone coating had potential benefits and could be clinically effective in reducing the incidence of PVE.

The Risk Assessment

Industry Standards for Safety Testing

[101] Compliance with regulatory and industry standards can be useful evidence of reasonable conduct, although this is not necessarily co-extensive with the standard of care.[30] As manufacturers often play a role in setting the industry standards that they are required to meet, the court must consider whether the industry standard is one that requires an appropriate degree

[30] *Ryan* at para. 29.

of care and, if met, will discharge the manufacturer's duty of care. Industry standards can be reflected in commonly accepted industry guidelines and also by the steps that other companies in the same industry take in designing and testing similar products in order to address reasonably foreseeable risks associated with the use of these products.

[102] It is common ground that at the time the Silzone valve was developed, the industry standards for pre-market testing of a modification to an approved prosthetic heart valve included reference to written standards for pre-market testing in the FDA's Draft Heart Valve Guidance and ISO 5840 and ISO 10993, which are standards published by the International Standards Organization (ISO). The drafting of the Heart Valve Guidance was a collective effort between the FDA, heart valve manufacturers, the medical community, academics, and public stakeholders. The ISO publishes consensus standards which are developed from committees composed of industry participants, academics and representatives from regulatory agencies from around the world.

[103] Dr. Butler of Health Canada identified the Heart Valve Guidance and ISO 10993 as standards that Health Canada reviewers consult when reviewing Notices of Compliance (NOCs) and SNOCs for heart valves. The plaintiffs led no evidence at trial of Canada-specific industry standards and they acknowledge that the FDA's Guidance document and ISO standards are relevant in determining whether St. Jude met industry standards.

[104] Neither the Heart Valve Guidance nor ISO standards prescribe mandatory testing. Instead, they outline recommended testing and suggest the kinds of tests that might be done. The Heart Valve Guidance specifically contemplates that manufacturers may achieve the same testing objectives by other means, or may justify not performing the recommended tests where a justification or explanation is provided to the FDA. The plaintiffs' toxicology expert, Dr. McLean, testified that "[ISO standards] give guidance to people who are doing safety testing … by giving them advice which comes from experienced toxicologists and with very large input from industry. … [b]ut it is up to experienced, knowledgeable investigators to decide which tests are applicable for the particular device, material and site of implantation".

[105] As the Heart Valve Guidance and ISO standards were intended for new prosthetic valves, their application to modifications of existing valves required some interpretation on the part of the manufacturer as to the sections of the written standards that applied and, if they applied, the extent to which they needed to be followed to perform adequate safety testing for the modification in issue. Ms. Johnson testified that a manufacturer's assessment of how the written standards would be applied was frequently reached through informal communication with the FDA prior to submission for approval. St. Jude's proposal to shorten the 20 week sheep study recommended in the Heart Valve Guidance to 10 weeks is an example. A December 15, 1997 conference call among Mr. Runquist, Dr. Flory and FDA personnel to discuss the FDA's request for further information following the FDA's non-approvable letter is another example.

[106] While the plaintiffs acknowledge the relevance of the Heart Valve Guidance and ISO standards, they dispute that there is any industry standard or practice to measure the defendants' conduct against because it is left to the manufacturer to determine which guidelines apply and the manner in which to comply with these guidelines. In the circumstances of the introduction of a completely new medical device or the modification of an existing device incorporating a never before used material, the plaintiffs argue that it is difficult, if not impossible, to identify a recognized industry standard. I do not agree. If this were the case, industry practice would be irrelevant for every new product.

[107] The prosthetic valve industry was well-established at the time the Silzone valve was developed. Industry and regulators had acquired considerable experience in addressing modifications to previously approved valves. In fact, the predicate device – the Masters series mechanical heart valve without Silzone – itself had been approved in 1995 by way of a submission for a SNOC. The Masters series valve modified the St. Jude standard valve by adding a rotatable cuff feature. The St. Jude standard valve had originally been approved by way of a Notice of Compliance and itself received a number of SNOCs for modifications prior to the development and approval of the Masters series. While it is true that the specific tests manufacturers perform may vary depending on the nature of the modification, the experts on both sides considered industry practice in reaching conclusions about how to measure the defendants' conduct in regard to the Silzone modification.

Expert Witnesses

[108] The most probative evidence on industry standards comes from the expert witnesses. As I mentioned earlier, Ms. Johnson was the drafter of the FDA's 1994 Heart Valve Guidance, a former FDA lead reviewer of regulatory submissions for prosthetic heart valves from 1990 to 1995, and the voting member from the FDA for the 1996 version of ISO 5840. She had worked with and/or trained the reviewers at the FDA who later evaluated St. Jude's PMA Supplement. She was clearly the most knowledgeable witness about the Heart Valve Guidance and the FDA's process for approval of a new heart valve or a modification. Ms. Johnson's testimony on industry practice was based largely on her experience at the FDA in the period immediately before the development of the Silzone valve. While she conceded there was no specific industry standard for pre-market testing of a valve with a silver-coated cuff, she described the industry standards for testing of prosthetic valves generally, and specifically for modifications to prosthetic heart valves, and provided her opinion that St. Jude met those standards.

[109] I also touched on the qualifications of Dr. Williams earlier. He has carried out many studies investigating the cytotoxicity of metallic materials, particularly silver. He has extensive experience investigating the effects of biomaterials in animal models and specific experience with prosthetic heart valves. I expand on this and review the qualifications of Dr. Rodricks, the defendants' toxicologist, in Common Issue 2.

[110] The defendants' experts provided clear and unequivocal opinions that the pre-market testing to assess the safety of applying Silzone to the sewing cuff was reasonable and in accordance with industry standards. The plaintiffs sought to neutralize the impact of their evidence by arguing that none of the defendants' witnesses had any experience in the pre-market testing of a silver-coated permanently implantable medical device that required adequate tissue healing to function safely. This is merely a variation of the argument that there can never be an industry standard for the testing of a heart valve or modification because there is no other device that is identical. Collectively, these witnesses have relevant and extensive knowledge and experience in biomaterials, biocompatibility and toxicity testing, and in the written standards and industry practices that apply to testing of modifications to prosthetic heart valves.

[111] Dr. McLean, the plaintiffs' toxicologist, was certainly qualified to discuss the toxicity testing. In fact, Dr. McLean evaluated the same testing protocols that are now in issue in the trial in 1999 in his role as a consultant to the MDA in the United Kingdom. He prepared a report to the MDA on the sufficiency of the defendants' testing and the potential toxicology issues concerning the Silzone valve.[31] He described the kinds of tests that were appropriate for devices containing blood and tissue, and concluded:

> … It is therefore noted that SJM have sponsored all of the aforementioned standard studies except for carcinogenicity bioassays and that all of these appear to have been performed satisfactorily to GLP standards.

[112] In contrast, Dr. McLean in his testimony at trial criticized the fibroblast and hemolysis tests as well as a washout study that assessed the potential loss of silver ions from the coating. His explanation in cross-examination was that he had not made it clear in his report to the MDA that St. Jude conducted "the wrong tests". If the testing methodology he proposed at trial was important to obtaining reliable test results, it is reasonable to think that this would have been discussed in his report to the MDA. His testimony is also inconsistent with his evidence that ISO standards allow discretion on the tests and methodology that can be used. His failure to satisfactorily explain these inconsistencies impaired the credibility of his evidence.

[113] His evidence was further weakened by his admission that he had read only the regulatory submissions and had not reviewed internal company documents that discussed the reasons for the selection of tests that were used to evaluate the biocompatibility of Silzone. Finally, he admitted that he had no experience with the Dacron fabric and was therefore not in a position to know if the alternative tests he proposed would be suitable for a woven fabric. In view of these shortcomings in his testimony, where the opinions of Dr. McLean conflict with those of Dr. Rodricks and Dr. Williams, I prefer their evidence.

[114] The plaintiffs tendered Dr. Olson as an expert on industry standards for the animal testing. He offered opinions on the use of power calculations to determine the number of animals to be included in an animal study, the role of Good Laboratory Practices (GLP) in the conduct of

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[31] Exhibit 335.

animal studies, and whether the defendants' study complied with ISO 5840. Dr. Olson had designed and conducted numerous animal studies, including sheep studies, but prior to this litigation, Dr. Olson had never worked with the Heart Valve Guidance or done a study using ISO 5840. Over the objections of the defendants, I ruled his evidence admissible, but I attach less weight to it.[32]

The Safety Testing

[115] The nature and quality of the testing a manufacturer performs will normally satisfy the standard of care so long as it meets industry standards and those standards are reasonable. The plaintiffs do not claim that the industry standards are unreasonable. They submit that Silzone valve patients were exposed to unnecessary risk as a result of a poorly designed and poorly executed pre-market testing strategy that was "inadequate and rushed". I have said earlier that I am not persuaded that the pre-market testing program was rushed at the expense of safety. Inadequate testing may be the basis for finding a breach of the standard of care if testing would have resulted in a reasonable decision not to manufacture the product in light of its inherent hazard. Otherwise, the failure to test will not normally result in liability because the failure does not cause the loss.[33]

[116] The plaintiffs allege that St. Jude conducted only the minimum *in vitro* tests, abbreviated the sheep studies, and conducted a limited clinical study (LIMRA), and that this amounted to inadequate testing. They referred me to two Superior Court decisions in which the court found the defendants' testing to be inadequate.[34] In *Willis*, the court held that one year of testing was insufficient, but provided no guidance in determining the measure of adequate testing. In *Alie*, the industry had established guidelines that recommended that before fly-ash supplemented

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[32] *Andersen v. St. Jude Medical*, 2010 ONSC 2436.
[33] Dean F. Edgell, *Product Liability in Canada* (Markham, Ont.: Butterworths Canada, 2000) at 55.
[34] *Willis v. FMC Machinery & Chemicals Ltd.*, [1976] P.E.I.J. No. 38 (S.C.) [*Willis*]; *Alie v. Bertrand & Frere Construction Co.*, [2000] O.J. No. 1360 (S.C.J.) at paras. 132 -155 [*Alie*], findings on liability aff'd, [2002] O.J. No. 4697 (C.A.).

cement was poured, it had to be sampled and tested. In that case, the defendant manufacturer, Lafarge, did not carry out these tests or arrange for the concrete mixer to do so. The court concluded that the defendant's protocol for testing did not meet the requirements of the standard.

[117] A failure to meet industry guidelines for testing is a relevant factor in the standard of care analysis, but in this case, the evidence shows that standard tests were performed that met the testing recommended by the Heart Valve Guidance and ISO standards. The essence of the plaintiffs' position is that St. Jude should have performed different tests or used alternative methods of testing or performed more tests, but there is no direct evidence that this testing was necessary or that it would have changed anything. It is not sufficient to claim that the defendants should have done more testing without also showing (a) that such tests were possible, and (b) that this would have affected the risk utility assessment and made it unreasonable for St. Jude to manufacture and market Silzone products. This evidence was lacking on both counts.

[118] Dr. Williams concluded that the pre-market testing was reasonable and performed in accordance with the Heart Valve Guidance and industry standards. Ms. Johnson concluded that the testing, as described in the regulatory submissions, met industry standards. Dr. Rodricks evaluated the toxicity testing and concluded that St. Jude had exercised a thorough and reasonable approach and conducted reasonable and appropriate testing. A review of the testing supports their opinions.

In Vitro and Small Animal Studies

[119] The potential for toxicity or cytotoxicity was evaluated in a series of laboratory tests and small animal studies with mice and rabbits that Spire had performed on the Spi-Argent I fabric as well as in additional fibroblast tests that St. Jude conducted. Fibroblasts are a type of cell involved in tissue healing. The toxicity testing investigated local and systemic toxicity, including differences in tissue reactions, direct cellular changes and cell death. St. Jude also conducted a washout study as well as testing for fabric performance and corrosion.

[120] The defendants acknowledge that generally, it is preferable that all testing for medical devices be performed on the finished product, but the ISO standards – which are umbrella standards for biocompatibility testing – do not preclude testing on representative samples from the final product or material. The testing performed for Spire was done in reputable laboratories

using standard protocols and no expert criticized St. Jude for relying on Spire's test results. The FDA asked St. Jude to justify this and St. Jude's rationale for using the Spire testing was explained in a December 1997 Amendment to the PMA Supplement that the FDA accepted.

[121] St. Jude performed testing to assess the potential loss of silver ions from the cuff in the form of galvanic corrosion testing and a washout study. Galvanic corrosion is a standardized test appropriate for evaluating a valve with metal components and is referenced in both the Heart Valve Guidance and ISO 5840. The first results showed very high values, but once the surface area of the fabric was correctly estimated, the corrosion rates were very low: 5 to 95 angstroms per year.

[122] In the washout study, two samples of the fabric and two assembled valves were tested. The washout study performed on the valve showed a larger release of silver in the first few days, which then dropped over time. Dr. McLean testified that the test solution in the washout study became saturated and only showed a levelling off in the amount of silver in serum. Dr. Rodricks researched the saturation point for silver salts and found that it was far above the concentrations seen in the washout study. Dr. Williams agreed with the conclusions of St. Jude that the washout study showed that silver ions would be released from the Silzone coating at a very low rate and at rates far lower than the silver concentrations seen in the literature where patients experienced toxic effects. He testified that neither test raised any safety concerns.

[123] St. Jude conducted fibroblast testing in accordance with methods recommended in ISO 10993 and also developed a human fibroblast test using a technique called a "Live Dead" assay. This test measured the potential for a toxic effect by observing fibroblasts exposed to the Silzone fabric for cell changes and for whether they remained alive or died. The results were published in an article co-authored by Dr. Tweden in the *Journal of Heart Valve Disease*.[35] Dr. Williams and Dr. Rodricks analyzed the human fibroblast testing performed by St. Jude. Dr. Williams testified that the results were consistent with what was known about silver ions (i.e. that they can produce toxicity at some level). He opined that the lack of toxicity seen until the concentration of the

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[35] Tweden et al. (1997), "Biocompatibility..." [JHVD article].

solution reached 1200 ppb indicated that it was unlikely that Silzone would exert any "consequences as far as healing and performance of tissues" adjacent to the coating was concerned.

[124] Dr. McLean and Dr. Healy each criticized the indirect method of fibroblast testing used by St. Jude, although for different reasons, but neither offered a clear opinion that St. Jude's testing did not meet industry standards. Dr. Williams testified that while a direct contact test was possible, it would be more difficult to derive meaningful data due to the complex weave of the Dacron fabric. Dr. McLean acknowledged he had no experience with the Dacron fabric. Further, both Drs. Williams and Rodricks testified that there was no benefit or scientific reason to employ a direct contact method, that industry standards permitted both methods, and that the defendants' choice of an elution or indirect method was appropriate.

[125] Dr. McLean also criticized the hemolysis testing performed on the Silzone-coated fabric. This was a standard screening test to determine if red blood cells would be 'lysed' or ruptured. An indirect hemolysis method was used and the fabric was found to be non-hemolytic. After the valve was approved in Canada, it was retested using a direct *in vitro* hemolysis method and some of the values were found to be elevated. This testing was done because of the results seen in the testing of the Epic valve which passed the indirect, but not the direct test.

[126] Dr. Williams pointed out that all mechanical heart valves cause some hemolysis and the factor that St. Jude wanted to measure was whether there was any additional hemolysis for the silver ions released from the coating. In his opinion, the most appropriate way to measure this was with the indirect method, although industry standards permit either method. No hemolytic effect was seen in the sheep implanted with the Epic valve and St. Jude concluded that based on all of the data, the Silzone-coated fabric was not hemolytic. Dr. Hirsh, an internist and haematologist, reviewed the results of the hemolysis testing and agreed with the company's conclusion. I conclude that the hemolysis testing was appropriately performed.

[127] Dr. McLean testified that the lysis seen in the Epic study is indicative of damage that could occur to fibroblasts or other cells involved in tissue healing, although the three fibroblast tests showed no significant toxic effect. The only study he could think of to support his opinion that silver metal might lyse fibroblasts was the work of Dr. Williams published in a 1989 paper

that I will discuss in Common Issue 2. Dr. Williams explained that Dr. McLean's conclusions were incorrect because he wrongly assumed that the form of silver used in Silzone was sintered silver, which is a different material. Further, as Dr. Rodricks testified, if hemolysis testing could be predictive of toxicity to other types of cells, the scientific community would be using the test for this purpose. Dr. Rodricks was not aware of any toxicology textbook that listed hemolysis testing as a screen for cell toxicity. He testified that the only inference that can be drawn from a positive *in vitro* hemolysis test is to follow up with *in vivo* testing in animals. To the extent that Dr. McLean concluded that broken red blood cells would alter the tissue healing process, his opinion is not well-founded and I reject it.

Sheep Studies

[128] St. Jude considered the most important safety issues to be whether the addition of the Silzone coating would negatively affect healing as well as the amount of silver that would be released from the cuff when implanted. The sheep studies were of great significance in evaluating both.

[129] St. Jude conducted two *in vivo* implant studies using the sheep model. The Short Term, or 4 to 5 week sheep study, was conducted between June and October 1996 and was a study with implants of valves that were half coated with Silzone and half uncoated. Five of the sheep had valves with Dacron cuffs and two of the sheep had valves with Teflon cuffs. The Long Term or 10 week sheep study commenced in November 1996 and was completed in April 1997. There were six sheep implanted with Silzone-coated valves and three sheep implanted with conventional valves as controls.

[130] Dr. Tweden was responsible for the design and oversight of both sheep studies. The examination of gross pathology and histopathology was carried out by Dr. Douglas Cameron, a board-certified pathologist and Adjunct Professor at the University of Minnesota who had some training with Dr. Jack Titus, a pre-eminent cardiovascular pathologist. Dr. Tweden had previously worked with Dr. Cameron in regard to another heart valve research project and was satisfied with the quality of his work. She participated with Dr. Cameron in the gross and microscopic pathology on the explanted specimens. Mr. Holmberg was also present at times. Dr. Cameron did not testify but his pathology reports were admitted as business records.

[131] The plaintiffs criticize the sheep studies for being conducted with too few animals and for too short a period of time. They contend that these studies showed that of the 13 sheep implanted with partially or wholly-coated Silzone cuffs, two developed such abnormal healing that one died (KTMV-2) and the other (SJII-8) would not have survived to 20 weeks. They allege that an early death from an unknown cause (KTMV-2), an excessive pannus formation obstructing a valve leaflet (SJII-8), discoloured tissue, spalled silver fragments and discernable tissue healing differences all pointed to Silzone adversely affecting critical tissue healing. I will review the expert evidence from Dr. Factor and Dr. Wilson in Common Issue 2 in considering the effect, if any, that Silzone has on tissue healing. The issues to be considered here are whether the Silzone sheep studies were conducted in a reasonable manner and whether they raised serious safety concerns, as the plaintiffs allege, or provided a reliable basis for St. Jude to conclude that the Silzone-coated Dacron cuff was safe and effective.

Short Term or 4 to 5 Week Study

[132] The Short Term Sheep Study was conducted partly at the University of Minnesota and partly at Loma Linda University in California. Its purpose was to assess tissue ingrowth into a Silzone-coated Dacron sewing cuff at an intermediate stage of healing (30 days) to see if there was any difference compared to uncoated polyester. A valve with a half coated and half uncoated sewing cuff was implanted in each sheep. The sheep implanted at the University of Minnesota were identified as KTMV and were sacrificed at different times during the study. They were given sequential numbers at the time of implantation. KTMV-1 was the first sheep to be implanted. When KTMV-2 died at 10 or 11 days post implantation, it was replaced by KTMV-3. The sheep implanted at Loma Linda with half-coated Dacron sewing cuffs were LL-1 and LL-3. There were two sheep implanted with half-coated Teflon sewing cuffs known as LL-2 and LL-4.

[133] Dr. Tweden had used the ‘half and half’ model in another project and the weight of the evidence establishes that this method provides the advantage of having a control within the same animal. This minimizes variability from animal to animal as well as variation in surgical procedures. St. Jude considered this study to be a feasibility study that was not intended for regulatory submission, but it was described in summary form in the narrative portion of the submission to Health Canada and Dr. Cameron’s pathology reports were included as an

attachment to the SNOC submission. In them, he described findings of particulate material and discolouration in several sheep, but he reported good healing and comparable tissue growth on both coated and uncoated portions of the six sheep that survived to planned sacrifice.

[134] The most contentious issue in the 4 to 5 week study is the early death of KTMV-2 whose valve dehisced or ruptured and developed a paravalvular leak. The cause of the dehiscence was not determined.[36] The plaintiffs submit that the defendants failed to adequately investigate the cause of the animal's death.

[135] Dr. Tweden testified that she and Mr. Holmberg examined the explanted valve and observed the PVL/dehiscence on both the coated and uncoated sides of the sewing cuff of KTMV-2 and that they also observed missing sutures where the PVL/dehiscence appeared. The plaintiffs submit that Dr. Tweden's evidence is not credible or reliable since Dr. Tweden acknowledged that Dr. Cameron made no notes about the missing sutures, came to no conclusion about the cause of death of KTMV-2, and there are no records documenting these observations. While initially, I thought it unlikely that either Dr. Tweden or Mr. Holmberg would recall their observations of the explanted valve from one sheep, I have since changed my mind.

[136] The early death of an animal in an animal study is not uncommon, but the death of this animal was a significant event in the context of this study. The 4 to 5 week study was the first opportunity to evaluate the Silzone coating *in vivo*. KTMV-2 was the second animal to be implanted, but the first to have its valve explanted and examined. Dr. Tweden was the senior scientist on the project and the individual who had developed and proposed the 'half and half' method for this study. She had prior experience with this and it was important for her to determine where the dehiscence was located in order to understand if the Silzone coating was implicated. I have concluded that these are circumstances that make it likely she would remember whether the dehiscence was on the Silzone side of the cuff or on both sides. Mr. Holmberg would have been equally concerned. He regarded this study as an opportunity to make

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[36] Dr. Cameron's pathology report records that "KTMV-2 was an early death, cause of death unknown".

a “go/no go” decision on the project. If the death of KTMV-2 was device-related, this could have terminated the project. As they were both looking for an explanation for the early death of this sheep, I find that their recollections are credible.

[137] By the time of the Design Review meeting on October 24, 1996, all of the sheep had been sacrificed. Dr. Tweden testified that “part of the design review is you are starting to put together your failure modes and effect analysis, and it is a group of not only the team but outside people who are brainstorming on all the possible failure modes. So it is important to bring up any possibility”. The meeting was attended by eighteen St. Jude employees including Dr. Flory, Darin Bergman, Director of Mechanical Valve Research and Development, and Bill Mirsch, Director of Tissue Valve Research and Development. Many of those in attendance would have been knowledgeable about sheep studies as this is a common animal model used for testing prosthetic heart valves. At the meeting, Dr. Tweden discussed the results of the 4 to 5 week study, including the early death of KTMV-2. Dr. Tweden did not recall anyone expressing concern or suggesting that further work be done to evaluate the death of this sheep.

[138] A cross-functional group was also brought together in December 1996 for the FMECA process to brainstorm failure modes and participants there were also made aware of KTMV-2. The possibility of dehiscence and paravalvular leak was addressed as an effect of the potential failure mode, “Silver coating results in inadequate tissue ingrowth”. Thus, there were numerous experienced individuals at the company who knew about KTMV-2, who were familiar with sheep studies and who had the opportunity to suggest that further investigation was necessary.

[139] Dr. Cameron’s pathology report for KTMV-2 did not mention anything about missing sutures, but he reported on the tissue development and found it to be comparable on both sides. His pathology reports for the six other animals described good healing on both sides of the cuff with a similar degree of tissue growth. After reviewing the pathology with Dr. Cameron for KTMV-2 and for all the other animals in the study, Dr. Tweden concluded that the death of KTMV-2 was not device-related. In my view, this was a reasonable conclusion to reach.

[140] I also find it significant that the Short Term study results were described in a peer-reviewed article (the ASAIO article) co-authored by Dr. Tweden, Dr. Cameron, Mr. Bianco, Dr. Razzouk, Mr. Holmberg, John Barry, Ray Bricault and Eric Tobin.[37] All were aware of the study results, including the death of KTMV-2. It is reasonable to think that if any of the authors believed the PVL/dehiscence to be related to the Silzone coating, they would have suggested further investigation before publishing the article. Neither KTMV-2 nor the two sheep implanted with Teflon valves were described in this article, as the focus of the article was the evaluation of the Silzone coating on Dacron. In the case of KTMV-2, it died too soon after implantation to give meaningful information one way or the other on tissue healing.

[141] The ASAIO article described comparable tissue ingrowth of coated and uncoated fabric with "a more organized thinner pannus formed on silver coated fabric." A more organized pannus indicates better or more advanced healing. Dr. Tweden considered the thinner pannus to be a more ideal pannus because a thinner cuff is compatible with a milder thrombotic response to the cuff. The histopathology also described signs of immature or less organized pannus only on the uncoated sides of the cuff and a "lamellar pattern" of cell organization in tissue in the coated halves, indicating advanced maturity in the pannus. Dr. Cherian, the plaintiffs' toxicologist, testified that he would not expect to see more organized pannus if the thinner pannus was under toxic stress.

[142] Finally, the study analyzed blood samples taken from the sheep during the course of the study. They revealed an increase of silver levels after implantation with a slight peak after two weeks, never exceeding 50 ppb and then declining to below quantitation levels at the time of sacrifice. This data suggests that there was only a small amount of released silver from the cuff that declined over time.

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[37] Tweden et al (1997), "Silver Modification...".

Long Term or 10 Week Study

[143] The recommendation of the Heart Valve Guidance for conducting preclinical animal studies on new heart valves is that a minimum of six animals must survive an implantation period of 20 weeks with at least two additional animals to serve as controls. Mr. Runquist wrote to the FDA on August 30, 1996 to propose that St. Jude shorten its animal study from 20 weeks to 10 weeks based on previous studies (including the Short Term study then underway) that showed that healing in the sheep model was complete by six weeks. There was no evidence from the Short Term study to support this statement, but Dr. Tweden had been involved in other projects where she had studied the time course of healing in sheep. She informed Mr. Runquist that based on her experience, sheep would be completely healed in terms of tissue ingrowth by six weeks. While the plaintiffs criticize the length of the study (and the "misleading" letter to the FDA), none of the plaintiffs' expert witnesses challenged Dr. Tweden's conclusion that tissue healing in sheep is complete by six weeks.

[144] Dr. Williams testified that if healing is complete by six weeks, differences in healing response would be observed by that time and that extending the study to 20 weeks would not provide any additional information on the healing response, which was the purpose of the study. Both the FDA and Health Canada were aware of the rationale for shortening the study to 10 weeks and neither took issue with its length. Dr. Hilbert of the FDA was a pathologist who reviewed all of the animal studies for prosthetic heart valves and it can be inferred that he was capable of assessing the length of the study. I find that the study was of sufficient length to assess the tissue healing response of the Silzone valve.

[145] The six test animals and three controls that St. Jude used in the Long Term Sheep Study met what was recommended by the Heart Valve Guidance for a new valve and was consistent with ISO standards, including the principle in ISO 10993-2 to minimize, where possible, the number of animals used for testing. Dr. Olson's opinion that industry standards required the use of power calculations to determine the number of animals in the study, and that this required 25 Silzone animals and 25 controls, is contradicted by the written standards and by the experience of all other witnesses familiar with pre-market testing of prosthetic heart valves.

[146] I do not find it necessary to review Dr. Olson's evidence on deficiencies in the design and conduct of the Long Term Sheep Study at Loma Linda University, such as lack of GLP compliance. There is no evidence that any of his criticisms, assuming they are valid, compromised the reliability of the data or the study objectives of assessing the healing of the Silzone-coated valve and quantifying the release of silver from the cuff into the bloodstream over time. At the time, it was consistent with both industry and regulatory standards to conduct large animal studies without full GLP compliance.

[147] The Silzone sheep in this study were SJII-1, SJII-2, SJII-3, SJII-4, SJII-5 and SJII-8. The sheep with uncoated valves were SJII-6, SJII-7 and SJII-9. The surgical staff at Loma Linda performed necropsy and gross examination of the animals at the time of sacrifice. They reported that all animals "seemed to be in healthy condition at the time of sacrifice". With the exception of SJII-8, the surgical notes indicate that the sewing rings for both control and coated valves were epithelialized, with no thrombus or vegetation.

[148] Dr. Cameron evaluated the gross and microscopic pathology and recorded that none of the sheep had unhealed areas. He wrote, "[a]ll cardiac specimens appeared to exhibit a similar degree of epicardial reaction to the surgical procedure which had occurred 10 weeks earlier". There was no evidence of thrombus formation. There were variable differences in areas of thin and thick pannus, but the degree of variability was similar in Silzone cuffs to controls and Dr. Tweden testified that the variability was similar to what she had observed in valves in other projects. Dr. Tweden agreed with Dr. Cameron's assessment and concluded, based on the gross pathology, that the healing was comparable.

[149] Dr. Cameron also conducted a microscopic evaluation to evaluate tissue healing and potential toxicity, including pannus measurements, foreign body response and macrophage incorporation of the coating material.[38] He recorded his results on a chart. Using an evaluation system for pannus formation developed by Dr. Schoen, the Silzone valves showed equal or greater tissue growth into the sewing cuff than controls. There was comparable foreign body

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[38] Foreign body response is an inflammatory reaction to the presence of a foreign material.

response, indicating that Silzone permits healing without causing an undue inflammatory response. The macrophage assessment showed that the accumulation of silver in the macrophages was not having an adverse effect on tissue formation and growth. This is an indication that the material is biocompatible and is not having a toxic effect.

[150] Dr. Cameron concluded: "There was no apparent differences [sic] in the parameters of granulomatous inflammatory infiltrate (giant cell formation) or degree of fibrous tissue integration into the sewing cuff fibres of the coated and uncoated specimens. There appeared to be a greater degree of pannus formation in the sections available in the uncoated specimens relative to the coated specimens although the number of observations is small." His summary comment was: "The tissue reaction to coated and uncoated synthetic materials appears to be similar by the parameters available for study."

[151] The pannus measurements were the basis for Dr. Tweden and Dr. Cameron's conclusions in the JHVD article that there was "a suggestion" that the pannus formed on the coated cuff was thinner. Dr. Tweden said that word was deliberately chosen as they were unable to show a statistically significant difference. The plaintiffs allege that testing should have been performed to determine the effect of thinner pannus on tissue ingrowth. Dr. Tweden was not aware of a test to assess this and there is no expert evidence regarding a testing method or whether such a test was possible. Neither is there evidence that the thickness of pannus affects tissue ingrowth into the cuff.

[152] Two valves in this study – SJII-8, a coated valve and SJII-9, an uncoated valve – exhibited excess pannus. As I mentioned earlier, Dr. Tweden forwarded them to Dr. Schoen for gross evaluation. Dr. Schoen did not think the excess pannus on SJII-9 was unusual. In Common Issue 2, I discuss the conflicting expert evidence from Dr. Factor and Dr. Wilson on this valve. It is sufficient to note here that Dr. Schoen informed Dr. Tweden that there were two prominent suture knots adjacent to the pivot guards and while their relationship to the excess pannus was uncertain, he could find no other apparent cause for the excessive pannus. Dr. Cameron's gross and microscopic pathological examination of SJII-8 did not indicate any underlying problem.

[153] Dr. Tweden and Dr. Cameron both came to the reasonable conclusion that the 10 week study showed that Silzone did not inhibit, delay or impair tissue healing. It confirmed the pattern of good healing seen in the 4 to 5 week study. Dr. Tweden wrote in the JHVD article: "The ten-week study showed that both the uncoated standard cuff and the silver-coated cuff reached the same endpoint of fully healed, functional pannus." The paper was co-authored by Drs. Cameron and Razouk and Mr. Bianco. While the paper is not admissible as proof of the truth of the opinions in it, it is admissible as corroboration of Dr. Factor's opinion, and to contradict Dr. Wilson's opinion where they differ as discussed in Common Issue 2. It is also corroboration of Dr. Williams' opinion, which I accept, that the Short and Long Term Studies provided a reasonable assurance of the safety of the Silzone valve.

Was a clinical trial required?

[154] The plaintiffs submit that the failure to conduct a clinical trial to assess the safety of the Silzone valve fell below the standard of care. At times, their submissions suggest that the standard of care required the defendants to delay the introduction of the Silzone valve and conduct a pre-market clinical trial such as AVERT in order to show that Silzone was effective in patients and posed no additional risk. At other times, they refer to clinical data, but they do not describe the kind of clinical data that was necessary to meet the standard of care. In their submissions, they refer to a paper by Dr. Grunkemeier as evidence that "a much smaller OPC (Objective Performance Criteria) study, with 800 patient-years, would have been sufficient to identify the increased risk of major leak."[39]

[155] I agree with the defendants that the OPC paper is not admissible as evidence of its contents or for the truth of the authors' opinions. Not only did the plaintiffs fail to call any of the authors at trial, they failed to put the paper to any witness or attempt to establish through their own witnesses or cross-examination of the defendants' witnesses that the Silzone valve would not have met the OPC criteria in the Heart Valve Guidance. I therefore place no weight on this

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[39] Grunkemeier et al. (2006); Objective Performance Criteria or OPCs are performance criteria based on data from historical databases that are generally accepted as acceptable values. Exhibit 258, the U.S. Department of Health and Human Services' 1994 Draft Replacement Heart Valve Guidance, establishes OPCs for heart valves for 8 specific complications reported from heart valve trials over the prior 20 years.

paper. This leaves a RCT such as AVERT or the LIMRA (discussed below) as there is no other evidence on the kind of clinical study or clinical data that might be required to meet the standard of care.

[156] In the context of determining the appropriate requirements for studies generating human clinical data for a new mechanical heart valve, the FDA, with input from many industry participants, rejected a requirement that data be derived from RCTs for valve related morbid events that occurred at very low rates. As the Heart Valve Guidance states, there was a concern that "... requiring such a study would essentially eliminate the possibility of introducing an improvement in technology to the market before the improvement itself was obsolete".[40] It recognized the need to strike a compromise "... between knowing before the product is marketed whether it was safe and effective for the intended use and keeping these new, innovative valves out of the hands of the surgeons and preventing treatment of patients". Thus, the document that reflects industry standards strikes a balance between innovation and risk and did not require a RCT such as AVERT before introducing a new prosthetic heart valve to the market, much less a modification. Instead, event rates could be compared against pre-established acceptance criteria for clinical performance called objective performance criteria, even though RCTs provide the most scientifically valid information.

[157] In the FDA's initial communication to St. Jude in February 1996, it stated that it wished to have some pre-market clinical data and suggested several options for providing this, including "a clinical study via IDE or other available means, European clinical data and/or clinical data in the Spire Master File." St. Jude responded in two ways. The Limited Initial Market Release Authorization or LIMRA was a limited release of the Silzone valve to two European centres before the Silzone product was released to a more general market. It provided clinical data on silver serum levels in a small number of patients implanted with Silzone valves and monitored short-term complications. As well, part of the Spire Master file discussing Dr. Bambauer's clinical work and his related papers were included as part of the regulatory submissions.

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[40] Exhibit 258/6, the U.S. Department of Health and Human Services' Draft Replacement Heart Valve Guidance (1994).

[158] Although the plaintiffs criticize the LIMRA as being too small to assess the safety of the valve and the tissue healing response to Silzone, Health Canada and the FDA approved the Silzone valve without a clinical trial beyond the LIMRA study. At the time of the submission to Health Canada in May 1997, there was limited data on the LIMRA patients. This was updated for Health Canada in July and December while the FDA review process was ongoing. The FDA requested an additional summary report of the 38 patients in the study, but at no time did it require clinical data beyond the LIMRA, let alone a more comprehensive clinical trial.

[159] The Heart Valve Guidance provides that modifications to the sewing ring material require clinical data. The plaintiffs ask me to find "on the totality of the evidence" that Silzone is "chemically fundamentally different" from Dacron or Teflon, to reject Ms. Johnson's evidence that the addition of Silzone to the sewing cuff was not considered to be a change of fabric, and to find that industry standards required clinical data beyond the LIMRA. The plaintiffs do not point to any expert evidence that Silzone-coated Dacron is chemically different from uncoated Dacron or to any evidence of the kind of clinical data that industry standards would require if the provision applied. The only evidence on this point comes from Ms. Johnson who testified that the provision does not apply.

[160] The FDA reviewers of the Silzone modification included, as I have mentioned, Dr. Hilbert, a pathologist experienced in valve implant studies in sheep, as well as several engineers, a cardiac surgeon and a biomaterials expert. All had input into the drafting of the Heart Valve Guidance. The internal FDA documents show that they considered many of the issues raised at trial in their review of the PMA Supplement, but the record contains no evidence that any FDA reviewer (or Dr. Butler) thought that the addition of Silzone was a change of fabric, implicitly corroborating Ms. Johnson's opinion that it was not.

[161] The FDA and Health Canada were clearly aware that no clinical trial beyond the LIMRA had been conducted. Dr. Williams and Ms. Johnson opined that industry standards did not require this. The plaintiffs' position is not supported by the expectations of the regulators or by industry standards. All of the evidence supports the conclusion that the industry and regulatory standards for evaluating the safety of the Silzone modification did not require a clinical trial or

clinical data beyond the LIMRA. The plaintiffs' assertion that a pre-market clinical trial was necessary in this case to meet the standard of care is not supported by any of the evidence led at trial.

Regulatory Approval

[162] The PMA Supplement was submitted to the FDA on May 14, 1997 and the SNOC was submitted to Health Canada on May 23, 1997. They were not identical, but they were substantially similar. Health Canada completed its review and issued the SNOC in less than sixty days on July 16, 1997, but the FDA did not approve the valve until March 1998, and only after St. Jude submitted two Amendments to the PMA Supplement that addressed the FDA's queries. This included: (i) providing complete pathology reports and microphotographs from the sheep studies; (ii) justifying why biocompatibility testing relied on Spire data rather than testing on the finished sterilized product; (iii) addressing issues related to corrosion testing; (iv) substantiating the hypothesis that endocarditis is attributable to colonization of bacteria on the sewing cuff; (v) revising the labelling and promotional material; and, (vi) revising the proposed efficacy study.

[163] The FDA and Health Canada both concluded, based on the materials they each reviewed, that there was sufficient evidence of safety and effectiveness to warrant approval of the valve. The defendants submit that Health Canada's approval of the submission and issuance of the SNOC indicates that it agreed that the testing that St. Jude described in the submission was adequate and met Heart Valve Guidance and ISO standards as required, and that the results included in the submission showed that the Masters series valve with Silzone would continue to be as safe and effective as the conventional valve. The defendants do not contend that regulatory approval displaces the common law standard of care, but rather that it is corroborative evidence of the defendants' experts' opinions that St. Jude conducted adequate testing in accordance with industry standards and interpreted the results of the testing in a reasonable manner.

[164] Health Canada's mandate requires it to strike a balance between innovation and patient safety, but Health Canada is largely dependent on manufacturers of medical devices for information regarding the safety of their products.[41] As regulatory approval is based on the information provided by the manufacturer, the plaintiffs argue that it cannot be seen as strong evidence that the defendants met the standard of care. They suggest that Dr. Butler lacked the appropriate qualifications and specialized knowledge relevant to a review of the SNOC submission and that he performed only a cursory review as he was under pressure to complete his review within the 60 day timeline set out in Part V of the *Medical Devices Regulations* promulgated under the *Food and Drugs Act* (the legislation that was the statutory framework for the regulation of medical devices in Canada at the time).[42] While the plaintiffs acknowledge that compliance with industry standards and the fact of regulatory approval can be useful evidence of reasonable conduct and the standard of care, they deny that it is of value in this case because St. Jude's regulatory applications, contained "a series of contradictory statements, material misrepresentations, misstatements and omissions concerning the company's pre-market efficacy and safety testing".

[165] Neither regulator was in a position to conduct any independent testing of the Silzone valve and St. Jude possessed vastly greater resources than either did, but the FDA process shows a group of experienced technical experts in biomaterials, engineering, corrosion, cardiac surgery and experimental pathology reviewing the PMA Supplement and Amendments for compliance with industry standards and FDA expectations before granting approval. It is clear that Health Canada did a much lesser review than the FDA and less weight attaches to its analysis, but the same test data was used to show safety and effectiveness for both the Health Canada and FDA submission. As well, although Health Canada conducted an independent review of medical devices, Dr. Butler testified that Health Canada placed considerable importance on the FDA's approval or rejection of a device because of their greater experience with medical devices. To the

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[41] *Attis v. Canada* (*Minister of Health*), 2008 ONCA 660, [2008] O.J. No. 3766 at para. 78, leave to appeal to S.C.C. refused, [2008] S.C.C.A. No. 491.
[42] C.R.C., c. 871, s. 38(a).

extent that the FDA reviewed additional material and still approved the valve, this is some evidence that Health Canada would have also approved the valve if it had reviewed the additional information provided to the FDA.

[166] This is also borne out by Dr. Butler's responses to questions posed by plaintiffs' counsel during direct examination about whether he would have wanted to know or whether he would have expected St. Jude to disclose specific types of information. At no time did Dr. Butler testify that he would have refused to recommend approval of the SNOC if he had known any of the additional information that plaintiffs' counsel put to him. As well, while Dr. Butler testified that "we accept the word of the company", both he and Dr. Freeland gave evidence that a reviewer could request additional information, or clarification, including that a manufacturer conduct a clinical trial. The conclusion to be drawn from their evidence is that unless a submission was hopeless, before rejecting an application, a manufacturer was given every opportunity to provide the information that was necessary to satisfy the reviewer of the safety and efficacy of the product. Thus, if Health Canada had raised the same queries as the FDA, it is likely that St. Jude would have responded in a similar fashion and approval of the valve would have followed as it did in the United States.

[167] Dr. Butler's background was in physiology. His Ph.D. from Duke University related to cell membrane biology and transport processes, which involves the study of the structure of cellular membranes and the transport of ions across membranes. He also had training in statistics and had been involved in the design of animal studies and *in vitro* studies. While he was at Health Canada, and before that at the National Research Council, there were frequent seminars led by outside experts on a wide variety of topics. Also, he attended annual meetings of the American Heart Society and the Canadian Cardiovascular Society.

[168] Dr. Freeland testified that the Health Protection Bureau had many sources of scientific information available to it, including access to experts in the fields of cardiac surgery, toxicology, biomaterials, microbiology and statistics and a large scientific body of information. Dr. Butler testified that he spoke with physicians in the department about silver toxicity and discussed the submission with the reviewer of the Masters series valve application and reviewed the submission report coming out of that review. He contacted Mr. Runquist in July 1997

seeking further information on biocompatibility. While Dr. Butler could not recall conducting an independent literature review, his report shows that he obtained a copy of the US Public Health Service's Toxicological Profile for Silver. He was therefore alive to the issue of silver toxicity. In my opinion, Dr. Butler had sufficient expertise and resources to evaluate the SNOC.

[169] Dr. Freeland testified that while every attempt was made to process applications for a SNOC within 60 days, there were procedures in place to extend the period if it was necessary. Dr. Butler testified that he felt pressure in general to meet this deadline if possible, but it is clear from his evidence that whether or not the deadline was in fact met was largely due to chance:

> Well, it's one of these things like, the line in the grocery store. I mean, if you happen to get in the line right behind somebody with two carts full, you're going to be a while. If you happen to get ahead of them, you grease through. So sometimes there was a big load, sometimes there wasn't. It was irregular.

[170] The evidence is insufficient to conclude that Dr. Butler rushed his review of the St. Jude submission as there is no evidence one way or the other as to the line in which the application for the SNOC ended up. However, it is apparent that it received far less scrutiny than the comparable application submitted to the FDA, and that Health Canada was far more reliant on the veracity of the assertions contained in the submission and the data that was provided to support the claims that were made.

[171] I am satisfied by the evidence that the submissions did not misrepresent, misstate or fail to disclose the results of the pre-market efficacy and safety testing in any material way. The only serious omission was the failure to mention the early death of KTMV-2 (discussed below). Otherwise, I attach little weight to the plaintiffs' submissions. In some cases, they are simply wrong as St. Jude did disclose the tissue discolouration observed in the sheep studies and accurately described the parallel streak test results. I have found that the disclosure of the *in vitro* test results was fair and accurate. Further, as I have said, it was apparent from the submission that no clinical trial had been conducted and Dr. Butler gave evidence that, at the time he reviewed the SNOC submission, he knew that St. Jude had not been able to prove that Silzone prevented infection. There was no need for St. Jude to disclose that it was aware that it would be unable to establish Silzone's efficacy in humans without conducting a clinical trial as this was evident from the submission.

[172] The plaintiffs criticize Dr. Tweden's literature summary on silver toxicity. I attach no weight to Dr. Healy's opinion that it was inadequate as he admitted that he looked at "only 50 to 60 percent" of the articles she referenced. Dr. Williams testified that the summary was not comprehensive and did not contain the totality of the literature that existed, but he concluded that she had done a good job and presented a balanced review of the matters in issue. All witnesses agreed that the most significant characteristic of a literature summary for regulatory submission is that it be balanced.

[173] I am also satisfied that St. Jude made no misleading statements in describing the results of the washout studies, corrosion testing, blood silver studies and tissue silver studies. They consistently showed that the coating was minimally leaching. No confusion would have been created by the reference in one part of the submissions to "non-leaching" and in other parts to "minimally leaching". Both Health Canada and the FDA were aware that some silver ions would be released from the Silzone coating once the valve was implanted. It was apparent from the submission that some silver would be present in annular tissue.

[174] The plaintiffs allege that St. Jude "grossly exaggerated" reported PVE rates "for the purpose of justifying the approval of its unproven Silzone valve". The PVE rates given in the submission ("less than 5%") and in Dr. Tweden's Literature Review on Infective Endocarditis ("reported to range from 1 to 4%/patient-year") are quite a bit higher than those referred to by the plaintiffs in the two published articles they rely on, although the article by Grunkemeier et al. was not published until after the valve was approved.[43]

[175] Dr. Sexton testified that there were a number of reasons for the range in rates and that "there are all kinds of numbers in the literature", including those provided by the defendants in their submissions. Even if the plaintiffs are correct that the rates are exaggerated, they were not exaggerated to a degree that it would likely have affected Health Canada's decision to approve the valve. The submission makes clear that the disease affects only a small number of patients, but with serious consequences.

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[43] Avrom et al. (1996); Grunkemeier et al. (1997).

[176] The defendants acknowledge that it would have been preferable for the early death of KTMV-2 to have been mentioned in the Health Canada submission as it was later mentioned in the FDA review process. The FDA approved the Silzone valve with knowledge only of the early death of KTMV-2 and that the cause of death was unknown. The FDA did not have Dr. Cameron's pathology report or Dr. Tweden's report on the 4 to 5 week study which the plaintiffs allege should have been disclosed to Health Canada. The FDA did not request further information about the early death of KTMV-2. This is some evidence that this was not of concern to them.

[177] In direct examination, Dr. Butler was asked about his expectations in the circumstances of the early death of an animal in a study. He testified that he expected the company to "come clean and say: We had this one sheep who died early. We did the pathology. This is why it died. This is why we don't think it is relevant to our study. We did replace it with another". Dr. Butler was aware that it was not uncommon for animals to die early in a cardiovascular implant study and he agreed that if the early death of a sheep was disclosed and he was satisfied that it didn't reflect any toxicity with respect to Silzone, he would still have approved the SNOC for the Silzone valve. As St. Jude had concluded that the death of this animal was not device-related and Dr. Cameron's pathology report described comparable tissue healing on both coated and uncoated sides of the cuff, I believe that Health Canada would have approved the Silzone valve if St. Jude had provided this information.

[178] The plaintiffs argue that the submission to Health Canada should have proceeded as a NOC rather than as a SNOC. Whether a SNOC or a NOC was required was ultimately Health Canada's decision. Dr. Butler testified that it would have been appropriate for a manufacturer to proceed by way of SNOC instead of NOC "[w]henever most of the characteristics of the device are unchanged". However, he also explained that whether a device was submitted for approval as a NOC or a SNOC made no difference to the regulatory approval process:

> This was a perpetual issue, but really, it doesn't make a major different [*sic*] because the reviewer has the flexibility of reviewing what is necessary. The company has to convince the reviewer, and hence the rest of the Bureau, that the device continues – that the device is safe and effective. And it really doesn't matter whether it's a SNOC or NOC that comes in, as long as there is sufficient evidence from previously notified devices and testing on the new device that it is safe and effective.

[179] The plaintiffs' Health Canada witnesses each agreed that no implanted device is without risk and neither the regulations nor Health Canada require that an implantable device be 100% safe prior to approval. As the Court of Appeal explained in *Attis* in considering whether to impose a duty of care on Health Canada:

> … In making decisions about whether medical devices should be available in Canada, Health Canada must weigh the need of some individuals to obtain relief from suffering (and sometimes death), despite the risks of a particular device, with the desire of others to avoid all risk, no matter the consequences. In doing so, Health Canada is obliged to consider the needs of the public at large in determining whether a device meets the minimum requirements for sale and/or distribution in Canada. … [44]

[180] A device known to have significant risks, even greater risks than similar devices of the same type, may still be found to be "safe and effective" for the purposes of approval under the regulations, depending on the benefits associated with that device. In response to a series of questions from plaintiffs' counsel relating to whether he would approve the SNOC if the device under consideration was worse than the predicate device, Dr. Butler testified that, "if there was a device that was -- hypothetically a device that was worse in several aspects but was life-saving for a small group of people, we would almost definitely approve it".

[181] The disclosure issues that the plaintiffs raise are not significant, but even if they were, the FDA's more thorough review and approval of the valve shows that it is unlikely that the lack of disclosure would have affected Health Canada's approval of the Silzone valve. The plaintiffs presented no evidence that the information the plaintiffs allege should have been disclosed would have changed Health Canada's decision to approve the valve. I find that regulatory approval corroborates the opinions of Drs. Hancock, Williams and Rodricks that St. Jude conducted appropriate and sufficient testing that met industry and regulatory standards.

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[44] *Attis* at para. 75.

Conclusion on Common Issue 1a

[182] The evidence satisfies me that St. Jude's pre-market testing to develop Silzone was reasonable and in accordance with the standard of care. St. Jude identified the appropriate issues for testing and performed standardized approved tests which showed that Silzone had a low potential for causing a toxic reaction, especially *in vivo*. *In vitro* efficacy testing demonstrated that Silzone was effective against infectious agents that cause endocarditis. The sheep studies showed that the Silzone valve was comparable to the conventional valve from a safety and healing perspective. The pattern of release of silver was also evaluated in the LIMRA study with results that showed values to be well below toxic levels.

[183] The testing results were reviewed by a broader group within the company. St. Jude reasonably interpreted the results and reasonably concluded that the testing was consistent with the scientific literature, which showed silver had low toxicity to human cells but was effective against bacteria. Products on the market at the time also demonstrated this. There was no indication that Silzone inhibited tissue growth, caused an abnormal inflammatory response or toxic effect, or that the inflammatory reaction seen with Silzone was any different than uncoated Dacron. The FDA and Health Canada reviewed and approved the distribution of the Silzone valve, implicitly concluding that the design and testing met industry and regulatory standards. Although there are serious risks associated with the implantation of a mechanical heart valve, the likelihood of risk for both conventional and Silzone valves was low. It is only with the benefit of hindsight that it can be argued that Silzone patients were put at greater risk. In weighing the potential benefits and likely risks, St. Jude conducted an appropriate assessment and reasonably concluded that the benefits to health for heart valve patients outweighed the risks of the Silzone valve. Accordingly, this portion of Common Issue 1a is answered in the negative.

Common Issue 1b – Post-Market Surveillance, Warning and Recall

[184] In *Hollis v. Dow Corning Corp.*,[45] La Forest J., for the majority, provided a thorough overview of tort law in the context of the duties imposed on medical device manufacturers:

> 20 It is well established in Canadian law that a manufacturer of a product has a duty in tort to warn consumers of dangers inherent in the use of its product of which it has knowledge or ought to have knowledge. This principle was enunciated by Laskin J. (as he then was), for the Court, in *Lambert v. Lastoplex Chemicals Co.*, [1972] S.C.R. 569, at p. 574, where he stated:
>
> > Manufacturers owe a duty to consumers of their products to see that there are no defects in manufacture which are likely to give rise to injury in the ordinary course of use. Their duty does not, however, end if the product, although suitable for the purpose for which it is manufactured and marketed, is at the same time dangerous to use; and if they are aware of its dangerous character they cannot, without more, pass the risk of injury to the consumer.
> >
> > The duty to warn 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; see *Rivtow Marine Ltd. v. Washington Iron Works*, [1974] S.C.R. 1189, at p. 1200, per Ritchie J. All warnings must be reasonably communicated, and must clearly describe any specific dangers that arise from the ordinary use of the product; see, for example, *Setrakov Construction Ltd. v. Winder's Storage & Distributors Ltd.* (1981), 11 Sask. R. 286 (C.A.); *Meilleur v. U.N.I.-Crete Canada Ltd.* (1985), 32 C.C.L.T. 126 (Ont. H.C.); *Skelhorn v. Remington Arms Co.* (1989), 69 Alta. L.R. (2d) 298 (C.A.); *McCain Foods Ltd. v. Grand Falls Industries Ltd.* (1991), 116 N.B.R. (2d) 22 (C.A.).
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> 21 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

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[45] [1995] 4 S.C.R. 634 [*Hollis*].

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.

22 The nature and scope of the manufacturer's duty to warn varies with the level of danger entailed by the ordinary use of the product. Where significant dangers are entailed by the ordinary use of the product, it will rarely be sufficient for manufacturers to give general warnings concerning those dangers; the warnings must be sufficiently detailed to give the consumer a full indication of each of the specific dangers arising from the use of the product. This was made clear by Laskin J. in Lambert, supra, where this Court imposed liability on the manufacturer of a fast-drying lacquer sealer who failed to warn of the danger of using the highly explosive product in the vicinity of a furnace pilot light. The manufacturer in Lambert had placed three different labels on its containers warning of the danger of inflammability. The plaintiff, an engineer, had read the warnings before he began to lacquer his basement floor and, in accordance with the warnings, had turned down the thermostat to prevent the furnace from turning on. However, he did not turn off the pilot light, which caused the resulting fire and explosion. Laskin J. found the manufacturer liable for failing to provide an adequate warning, deciding that none of the three warnings was sufficient in that none of them warned specifically against leaving pilot lights on near the working area. At pages 574-75, he stated:

> Where manufactured products are put on the market for ultimate purchase and use by the general public and carry danger (in this case, by reason of high inflammability), although put to the use for which they are intended, the manufacturer, knowing of their hazardous nature, has a duty to specify the attendant dangers, which it must be taken to appreciate in a detail not known to the ordinary consumer or user. A general warning, as for example, that the product is inflammable, will not suffice where the likelihood of fire may be increased according to the surroundings in which it may reasonably be expected that the product will be used. The required explicitness of the warning will, of course, vary with the danger likely to be encountered in the ordinary use of the product.

23 In the case of medical products such as the breast implants at issue in this appeal, the standard of care to be met by manufacturers in ensuring that consumers are properly warned is necessarily high. Medical products are often designed for bodily ingestion or implantation, and the risks created by their improper use are obviously substantial. The courts in this country have long recognized that manufacturers of products that are ingested, consumed or otherwise placed in the body, and thereby have a great capacity to cause injury to consumers, are subject to a correspondingly high standard of care under the law of negligence; see *Shandloff v. City Dairy*, [1936] 4 D.L.R. 712 (Ont. C.A.), at p. 719; *Arendale v. Canada Bread Co.*, [1941] 2 D.L.R. 41 (Ont. C.A.), at pp. 41-42; *Zeppa v. Coca-Cola Ltd.*, [1955] 5 D.L.R. 187 (Ont. C.A.), at pp. 191-93; *Rae*

> *and Rae v. T. Eaton Co. (Maritimes) Ltd.* (1961), 28 D.L.R. (2d) 522 (N.S.S.C.), at p. 535; *Heimler v. Calvert Caterers Ltd.* (1975), 8 O.R. (2d) 1 (C.A.), at p. 2. Given the intimate relationship between medical products and the consumer's body, and the resulting risk created to the consumer, there will almost always be a heavy onus on manufacturers of medical products to provide clear, complete and current information concerning the dangers inherent in the ordinary use of their product.

[185] While the above excerpt is lengthy, the standard is really quite simple. The underlying question is always "what was reasonable under the circumstances?" As a manufacturer occupies the position of an expert in the field, it is under a continuing duty to inform physicians when additional dangerous side-effects are discovered.[46] It must therefore assess the information that it receives regarding the performance of its product to determine whether or not it reasonably indicates an additional risk that requires an updated warning or other action. In *Hollis*, Dow Corning had received between 48 and 61 field experience reports (FERs) prior to the implant rupture that the plaintiff experienced. These were categorized as "unexplained". The court concluded that as these were not attributable to any known cause for which a warning had been provided, the manufacturer had notice of an additional or new risk that was not disclosed in its warnings for the product.

[186] In the present case, all of the adverse events that were observed and the FERs that were received between the time that the Silzone valve went to market and its recall, were of a type that St. Jude had already warned about in the labelling and in the physicians' manual. The question under Common Issue 1b, then, must be whether at any point during that period, sufficient evidence of an increased risk of one or more of the complications already warned of arose, such that a reasonable manufacturer of heart valves in the position of St. Jude would have either (a) issued an additional warning, or (b) recalled the Silzone valve. Since St. Jude did eventually recall the Silzone valve, this question can be reframed as: did the timing of St. Jude's recall of the Silzone valve fall within the timeframe that could be considered reasonable in the circumstances?

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[46] *Buchan* (C.A.) at para. 54.

[187] With respect to these two questions, I propose to discuss the most persuasive evidence and arguments adduced by the plaintiffs as well as the defendants' response. Broadly speaking, I believe the strongest evidence for the plaintiffs relates to the concerns raised by Mr. Butchart and Dr. Butany prior to recall, the MDA Advice Notice, and the Australia/New Zealand regulatory action. Strictly speaking, I do not need to consider the evidence of Mr. Butchart as I have found that the Silzone valve did not materially increase the risk of thromboembolism (discussed in Common Issue 3). Thus, the failure to warn of an increase in risk of this complication cannot result in liability. However, for completeness, I will review this evidence.

Mr. Butchart

[188] Mr. Butchart contacted St. Jude in the fall of 1998 about high rates of thromboembolism in Silzone patients at his hospital in Cardiff, Wales. On November 11, 1998, he met with key personnel from St. Jude and with Dr. Schoen who attended by videoconference to present his findings. An action plan was developed at the meeting and the evidence shows that St. Jude followed up on each of the items. This included a survey of three of its earliest implanting centres, a review of explanted Silzone cuffs returned to the company to that point in time, and pathological reviews of two of Mr. Butchart's explants. Efforts were also made to conduct a comparative valve review of explanted Silzone and conventional valves and this was discussed with Mr. Butchart in a conference call on December 15, 1998.

[189] The plaintiffs are critical because Mr. Butchart was told that he was the only surgeon who had reported a *pattern of thromboembolic events*, but this in fact was true. He was reporting five or six TE events in a fairly small group of patients and no other centres had reported a similar experience at that time. The plaintiffs also allege that St. Jude discouraged Mr. Butchart from reporting his findings to regulators, but this is not so. Mr. Butchart was simply asked not to *publish* his findings until the company had an opportunity to gather further information. Mr. Butchart, in fact, agreed to this request: "[w]ell, at that stage, I was, I suppose, prepared to give them the benefit of the doubt because they told me that they were going to provide me with further information based on their own investigations and based on obtaining data from other centres. And I agreed to wait to see what that would show before reporting our own results". Dr.

Flory testified directly that St. Jude never asked Mr. Butchart not to report his findings to the MDA, and indeed, there is no evidence that the company did make such a request. In any event, Mr. Butchart did, in fact, report his findings to the MDA, and St. Jude did not object.

[190] It is also noteworthy that the CERFS abstract, which was prepared in mid-1999 by Mr. Butchart and his colleagues, stated that "[t]hese findings need to be investigated in other studies". It did not, for example, make any recommendation that surgeons cease implanting the Silzone valve in patients. Further, as recommended, "other studies" were already being conducted by St. Jude, including AVERT.

[191] The AVERT DSMB was provided with details of the concerns of Mr. Butchart, and following an April 1, 1999 meeting unanimously recommended that AVERT proceed as planned, stating that presently they had "no reservations concerning thromboembolic rates" in AVERT. Dr. Schaff also continued to implant the Silzone valve at the Mayo Clinic in the summer of 1999, despite his knowledge of Mr. Butchart's concerns. He testified that "we didn't see increased rates of thromboembolism or reoperation" in AVERT.

[192] In July 1999, Dr. Flory gave a presentation to St. Jude's Scientific Advisory Board (SAB), a group of cardiologists and surgeons who provided direction to St. Jude on product development efforts and scientific issues. In the presentation, Dr. Flory presented details of Mr. Butchart's thromboembolic events and Dr. Butany's Toronto cases along with the recommendations from the April meeting of the DSMB that the AVERT trial continue. He also described the company's ongoing investigations. The minutes to the "SAB Meeting Recap", which was an open discussion at the end of the meeting, note that "it was apparent to the SAB members who commented, that the findings did not represent evidence of problems with Silzone. The follow up being conducted by SJM was well-received. SAB members seemed confident in the technology, and in the manner in which issues have been addressed by SJM".

[193] St. Jude advised both Health Canada and the FDA of Mr. Butchart's events and kept both regulators updated on their investigations. At no time did either regulator request that St. Jude undertake additional or other investigation activities. Therefore, the feedback that St. Jude was receiving at the time from advisors and experts strongly supported the company's view that Mr. Butchart's cases were not sufficient data on their own from which to draw conclusions. As Mr.

Butchart's experience was not being seen elsewhere and investigation revealed no unusual pathology findings, this did not reasonably indicate an additional risk that required an updated warning.

[194] Dr. Flory believed that an independent review of Mr. Butchart's data was appropriate and contacted Mr. Jules Dussek, President of the Cardiothoracic Surgeons of Great Britain and Ireland. On September 13, 1999, Mr. Dussek requested an external review of data gathered and reported by Mr. Butchart and colleagues at the University Hospital of Wales in Cardiff. The reviewers released their full report in late November 1999, a week after the MDA Advice Notice was issued. Under "recommendations for further data analysis", they stated that "the ability to draw general conclusions from these results will continue to be limited due to the small number of events observed and the fact that all results are based on data from one hospital". This is consistent with St. Jude's assessment. Notably, the reviewers had released an Executive Summary earlier in the month, on November 8th. It was this one-page Executive Summary that precipitated Ms. Randall's decision to issue the MDA Advice Notice on November 15th. Hazel Randall was Senior Product Specialist – Cardiovascular Implants, Device Technology and Safety at the MDA.

[195] Finally, two internal FDA documents are noteworthy. In an internal email dated December 7, 1999, Mathematical Statistician Gary Kamer wrote that the Cardiff data was not sufficient on its own to justify action, that the methodology used "greatly overstated the problem" and that the AVERT data was "by far" the best source for evaluating the risks of excess thromboembolism. He indicated that the data was a "red flag", in that it demonstrated a need to review more scientifically valid data. Of course, St. Jude was already doing this with its ongoing analysis of AVERT. In a December 10, 1999 internal email, cardiac surgeon Dr. Sapirstein, commenting on a proposed "Dear Doctor" letter that the FDA had requested St. Jude prepare, wrote: "[d]on't want to kill a possibly useful device with the message at this stage."

[196] In my view, the defendants thoroughly investigated Mr. Butchart's concerns in spite of their reasonable belief that AVERT provided far more reliable data regarding the safety of the Silzone valve. As Dr. Frater testified, it was "always better to get data from a randomized control study being independently monitored than it is from any single isolated institution. That didn't

mean that [Mr.] Butchart was not appropriately commenting on this experience, but in terms of deciding what its importance was in the big picture, the trial was far more important than a single report from a single institution". St. Jude received consistent feedback from other experts at the time that it was reasonable to rely on AVERT as the most reliable indicator of the performance of the valve and adverse events.

Dr. Butany

[197] With respect to the concerns raised by Dr. Butany of TGH, the evidence demonstrates that St. Jude investigated these thoroughly as well. In January 1999, Dr. Butany travelled to St. Jude's headquarters at the company's invitation. High-ranking St. Jude scientists and executives were present at the meeting and a "wet lab" review of explanted valves was performed. There is extensive evidence regarding St. Jude's review and follow up with respect to Dr. Butany's concerns, including the efforts that were made to find matched controls in order to conduct a comparative valve review. Also noteworthy is Dr. Butany's own admission that his observations were consistent with those seen in explanted valves of all types: "[a]s I said repeatedly, every one of these modes of failure or every one of these pathology findings can be, were, and are seen with every valve". St. Jude arranged a meeting between Dr. Butany and Dr. Titus to do a pathological review of Dr. Butany's explants on May 19, 1999. Dr. Butany's cases were discussed at the Silzone Summit meeting convened by St. Jude in Toronto on May 20, 1999, which was also attended by several Canadian surgeons. Dr. Butany was also invited to attend a later meeting on Silzone issues in Quebec City in October 1999.

[198] Health Canada, the FDA, and St. Jude's SAB were all informed of Dr. Butany's concerns but none recommended that St. Jude alter its course of action in any manner. All of Dr. Butany's evidence was derived from a single centre (TGH), and, as Dr. Schoen testified, was at best a series of anecdotal case reports. Dr. Butany acknowledged that as of the summer of 1999, he had concerns about whether his data could be generalized to all users of the Silzone valve. Dr. Flory testified that there was a bias in the selection of patients implanted with Silzone valves at TGH: "two layers of bias: One, a bias towards using St. Jude valves in double valve and mitral cases; and two, toward using Silzone valves in patients that had a history of endocarditis. The overall concern is it appears there is selection bias and it is difficult to assess how significant that

selection bias is. But it seems to be there". This concern was echoed by Dr. Joan Ivanov, the TGH's statistician in a slide presentation at the Silzone Review Meeting in Quebec City in October 1999.

[199] Additionally, with respect to the concerns of both Mr. Butchart and Dr. Butany, none of the clinical data that St. Jude received and reviewed from other clinical studies was consistent with the findings of those doctors. This was the evidence of Dr. Flory, who testified as follows with respect to the concerns of Dr. Butany: "[y]es, the fact that a site was coming to us expressing concern about the valve always causes us concern. However, we weren't seeing the same phenomenon at that point at other centres or in the major clinical work that we had done. So, we wanted to find out more about it. We did take it seriously, but at this point it was a single centre reporting the events".

The DSMB

[200] As noted above, the Data Safety Monitoring Board, or DSMB, met on April 1, 1999 and recommended that the AVERT trial continue. As discussed elsewhere, the DSMB members comprised a panel of experts who were not AVERT investigators, had no direct affiliation with St. Jude, and whose role it was (as the name suggests) to monitor the safety of patients enrolled in AVERT. The DSMB met again on November 1, 1999, and made the same recommendation, largely on the basis of there being no statistically significant evidence from AVERT of a difference in performance between the two valves at that time. Following the meeting, St. Jude received a letter from Dr. Holubkov, who at that time was AVERT's Principal Investigator at the Data Co-ordinating Centre at the University of Pittsburgh, stating that "the DSMB unanimously recommended that AVERT continue enrollment as planned. While the DSMB requested that all event rates in AVERT be kept confidential, they noted that AVERT is 'safe to continue' and that there are at present 'no differences' in event rates between the two AVERT treatment arms".

The MDA Advice Notice

[201] As noted above, the reviewers for the Society of Cardiothoracic Surgeons of Great Britain and Ireland had released an Executive Summary on November 8, 1999, which was followed later in the month with their full report. It was this one page Executive Summary that precipitated Ms. Randall's decision to issue the MDA Advice Notice on November 15th.

[202] The Executive Summary stated that a preliminary statistical analysis showed a statistically significant difference in thromboembolism rates between Silzone and conventional valves in the CERFS study. However, the reviewers also noted that "in view of small numbers and incomplete follow up in the two groups, the p-value and confidence intervals should be interpreted with caution".

[203] Before releasing the Advice Notice on November 15th, Ms. Randall sent a copy to St. Jude on November 11th and gave the company one day to comment. Dr. Flory and Dr. Frater both responded that they "continued to believe that the Advice Notice is inappropriate and unwarranted". The Advice Notice did not have any regulatory implications in the United Kingdom or anywhere else. St. Jude advised the FDA and Health Canada about the Advice Notice the day it was issued.

[204] Dr. Flory testified that St. Jude did not consider stopping the sale of the Silzone valve after the Advice Notice was issued because:

> Again, at this time we had just had the Data and Safety Monitoring Board review meeting, which saw no safety issues with the valve. We continued to collect clinical data and review it with the other regulatory agencies, who accepted that. And we continued to believe that the product was safe for sale. Safe for use.

[205] Following the Advice Notice, St. Jude sent a "Dear Doctor letter" to Canadian surgeons on November 26, 1999. The letter included a letter from Dr. Frater, the MDA Advice Notice, a summary of the clinical data that St. Jude had regarding the performance of the Silzone valve, a copy of the letter from the University of Pittsburgh of the recommendations of the November 1 DSMB meeting, and copies of Mr. Butchart's abstracts. Dr. Frater's letter stated that "[t]he data from this single centre [Cardiff] is in direct contrast to the data we have received from multiple other studies on the valve with Silzone coating involving a much larger patient population. The intent of this letter is to update you as to the clinical experience with the St. Jude Medical Mechanical heart valve with Silzone coating". The covering letter, signed by Dave Stronach, a Canadian sales representative, advised doctors that "based on the sum of the evidence collected to-date, St. Jude Medical Canada, Inc. continues to be confident in the Silzone technology". Dr. Flory testified that he agreed with this statement:

> [b]ecause at this point, again, as we've discussed before, the Company had done a number of reviews of the data, with independent agencies and government agencies, like the Data and Safety Monitoring Board, and we continued to feel that the valve was safe.

[206] The FDA's response to the MDA Advice Notice demonstrates the FDA's belief that there was little reason for concern. St. Jude met with FDA officials on December 2, 1999 regarding the issuance of a "Dear Doctor" letter to surgeons in the United States. The FDA was concerned that the MDA Notice did not contain balanced information as it was based on "limited observational information". After a telephone conversation with Dr. Flory on December 10, 1999, discussing the Dear Doctor letter, an internal FDA memorandum notes that the letter should contain "[t]he message that there is limited observational information of a possible incidence of early thromboembolic (TE) events – and that this is being studied further". Internal FDA documentation reveals that the FDA disagreed with the MDA's decision to issue the Advice Notice and still saw potential in the Silzone valve. St. Jude provided a draft of the "Dear Doctor" letter to the FDA on December 17, 1999, but did not hear back until January. Among the FDA's comments was a suggestion that the letter not even refer to the MDA Advice Notice. An earlier internal draft of the FDA's comments sheds light on the reason for this suggestion. It states:

> Consider whether the specific reference to the MDA's Advice Notice is necessary. US physicians are not likely to be aware that the MDA seems to send out notifications more frequently, and with less supporting data, than we do. Also, our experts have stated that the results of the Cardiff study, the major basis for the MDA notification, need to be interpreted with caution. In lieu of direct reference to the MDA's advisory the letter's discussion of the clinical information provides the reader with the information available for making an informed decision.

Australia/New Zealand Regulatory Action

[207] Shortly after the MDA Advice Notice, on November 26, 1999, the Australian health products regulator, the Therapeutic Goods Administration (TGA), cancelled the registration of Silzone products in that country due to concerns about thromboembolic events. The evidence is that the TGA action was based largely on the MDA Advice Notice. Following that Notice, the TGA requested more information from St. Jude. St. Jude sent the TGA a package including information that there had been 244 Silzone valves implanted in Australia and no reported adverse events. St. Jude also provided some details of AVERT and invited the TGA to speak

directly with Dr. Holubkov to discuss the study further. New Zealand elected to remove Silzone products at the same time as Australia did and the evidence shows the regulators worked together and New Zealand did not undertake a separate review and decision-making process.

[208] The TGA did not take St. Jude up on its offer to speak with Dr. Holubkov and made its decision to cancel the registration of the Silzone valve without reviewing the AVERT data. The TGA stated that its decision was made by a panel of experts who were given the materials forwarded by St. Jude, the Cardiff data, and the TGH survey. However, Dr. Flory testified that he never came to know the names of the individuals on the panel or their backgrounds or expertise. It is of interest that the TGA consulted with Health Canada and the FDA before making its decision. On December 7, 1999, Health Canada held an internal meeting to discuss the TGA action and determined that "there is no indication that the valve is not safe or ineffective at this point".

[209] I am satisfied by the evidence that the defendants took seriously all reports of adverse events prior to their recall of the Silzone valve. They reasonably considered AVERT to be the most reliable evidence of the risks associated with the Silzone valve, reinforced through the feedback they received from Dr. Schaff and Dr. Frater as well as the regulators. However, they did not, for this reason, ignore evidence from other sources. When Mr. Butchart and Dr. Butany came to the company with their reports, this was carefully investigated in order to assess whether their reports were isolated to Mr. Butchart and Dr. Butany's respective centres or whether they indicated an additional risk associated with the valve more generally. The results of those investigations reasonably indicated to St. Jude's employees that these events were isolated as they did not show any unusual pathology and were inconsistent with the clinical data that the company had collected from various Silzone surveys and studies, including and in particular from AVERT.

[210] Further, throughout 1999, St. Jude was in frequent contact with regulators from several jurisdictions, including Health Canada, the FDA, and the MDA in the UK. Despite conducting AVERT on an ongoing basis, St. Jude nonetheless collected and reviewed clinical data from a number of other sources, including the Japanese Cohort Survey, the London Survey, the Vancouver Survey, LIMRA, and Top Accounts. Each of these studies was of lesser

epidemiological value than AVERT, but provided sources of information that showed nothing unusual. There is no evidence that St. Jude attempted to "cover-up" any reports of adverse events. Contrary to the plaintiffs' assertion, the fact that St. Jude did not inform Dr. Butany and Mr. Butchart of one another's concerns does not demonstrate impropriety on the part of the defendants. Dr. Butany's concerns related to explants, pannus overgrowth, valve dehiscence, paravalvular leak and suspected cases of endocarditis. Mr. Butchart's concerns related to thrombus and thromboembolism. As such, I agree with the defendants that the concerns of these physicians were reasonably treated as distinct and unrelated.

[211] The MDA Advice Notice and the Australia/New Zealand regulatory action are not separate evidence of a risk as they were driven by Mr. Butchart's concerns. St. Jude reasonably concluded based on a thorough investigation and reliable expert advice that the increased TE events at Cardiff Hospital did not indicate an additional risk that required a warning. Assuming the MDA Advice Notice and Australian/New Zealand regulatory action should be viewed as evidence that St. Jude ought to have issued a warning or recalled the Silzone valve in November 1999, this is countered by the actions and statements of the FDA, Health Canada, the DSMB and the SAB who were all aware of these reports, but did not express any concerns or recommend any action be taken other than the preparation of a "Dear Doctor" letter requested by the FDA on December 10, 1999.

The Recall

[212] On January 5, 2000, St. Jude received a report from the University of Pittsburgh that indicated a higher number of explants in the Silzone arm of the study. Peter Perduzzi, a statistician from Yale and member of the DSMB, performed a statistical analysis of the data and Dr. Chesebro, DSMB chair, determined that a DSMB meeting should be held. It was scheduled for January 21, 2000. Dr. Flory recognized that one of the possible outcomes of that meeting was that after reviewing the data, the DSMB would recommend that enrolment in AVERT be terminated. As a result, St. Jude began to plan for this scenario. Before this, the information available to St. Jude did not indicate an additional risk that would have reasonably required an updated warning or some other action.

[213] On January 21, 2000, the DSMB unanimously recommended that AVERT patient enrolment be immediately suspended when the AVERT data showed a statistically significant increase in the rate of explants due to paravalvular leak in the Silzone arm of that study. At that time, the company acted swiftly to voluntarily recall all Silzone products worldwide. In Canada, all Silzone valves, Regent valves (which were all Silzone-coated at that point in time) and Sequin Annuloplasty Rings with Silzone were recalled.

Conclusion on Common Issue 1b

[214] The evidence shows that St. Jude effectively monitored the clinical performance of the Silzone valve, thoroughly investigated the concerns that were reported to them, and appropriately assessed the information gained through those investigations. Until the decision was made to recall the valves, the information that St. Jude had and the advice it received supported a reasonably held belief that there were no additional risks that had not already been communicated or required an additional warning or other action. The plaintiffs have not established that St. Jude fell below the standard of care with respect to its post-market surveillance and duty to warn of a reasonable and prudent heart valve manufacturer in similar circumstances. Accordingly, this portion of Common Issue 1 is answered in the negative.

COMMON ISSUE 2

What effect, if any, does such Silzone coating have on tissue healing?

[215] Common Issue 2 is a question of general causation. This common issue requires the court to determine whether there is evidence of a difference in healing response between Silzone and non-Silzone valves, whether there is a plausible scientific explanation for the difference, if any, and whether the difference, if it exists, is adverse, in that it makes Silzone more likely to cause or contribute to a medical complication than uncoated Dacron. The plaintiffs contend that Silzone is toxic and that it not only impairs or delays tissue healing, but that it also damages existing annular tissue in the heart, which is a very strong biological response. The evidence that bears on this issue arises in three principal areas: (i) the scientific literature on silver; (ii) healing in the sheep studies; and, (iii) clinical evidence of toxicity derived from Dr. Wilson's clinico-pathological correlation of 18 Silzone valves in 14 patients.

[216] The plaintiffs adduced evidence from Dr. Healy as well as from Drs. McLean and Cherian who are both experienced and qualified toxicologists. Dr. Cherian is a Professor Emeritus at the University of Western Ontario, a metals toxicologist and an expert on metallothionein. Professor McLean is a Professor Emeritus at University College, London. Dr. Healy is a Professor of Bioengineering and Materials Science at the University of California at Berkeley. They testified about the toxicity of silver on cells involved in the healing process. Neither Dr. McLean nor Dr. Cherian expressed a clear opinion that Silzone was toxic, but Dr. Healy concluded that the release of silver ions from the Silzone coating places patients at risk and that silver's cytotoxic properties impairs pannus formation.

[217] The defendants' experts were Dr. Williams and Dr. Rodricks. Dr. Williams is a Professor Emeritus at the University of Liverpool. He is one of the world's leading biomaterial experts with over 40 years of experience in conducting research in the field, including extensive work in the use of silver as a biomaterial. Dr. Rodricks has more than 45 years of experience in evaluating the toxicological safety of products, including almost 20 years with the FDA where he directed the FDA task force responsible for assessing the toxicological risks from metals in medical devices and developed the FDA Guidelines for the preclinical toxicity testing of medical devices.

[218] Dr. Wilson and Dr. Factor are cardiac pathologists. Their evidence addressed healing in the sheep studies. As well, Dr. Wilson reviewed the findings from his 14 patient study. Dr. Schoen was the defendants' expert. I will describe their qualifications later. Mr. Butchart, for the plaintiffs and Drs. Hirsh, Mizgala, Snyder, Sexton and Factor, for the defendants, also provided opinions on selected patients in the 14 patient study.

Tissue Healing Process

[219] The tissue healing process of a prosthetic heart valve implant is complex at both the cellular and molecular level, but it is similar to the manner in which the body's reparative processes heal any injury, modified by the presence of a foreign body. Inflammation takes place, blood clots, tissue forms and the wound closes, sealing the injured site.

[220] The first stage of healing commences immediately on the implant of a prosthetic valve. The Dacron of the sewing cuff is filled with biological material from the bloodstream. Due to the presence of a foreign material, an inflammatory response occurs. At a cellular level, tissue proteins from the blood are deposited or adsorbed to the surface of the fibres of the sewing cuff, both within the cuff's material and on its surface. As the proteins are adsorbed to the surface of the cuff's fibres, they activate platelets in the blood that adhere to the proteins' surface and, in turn, attract more platelets from the passing blood. As the platelets aggregate to the protein covered surface of the cuff fibres, they release their contents and thrombin is generated, which together with fibrin, creates thrombus.

[221] The second stage of the healing process involves a series of cellular events, during which polymorphonuclear (PMN) cells, lymphocytes and monocytes enter the wound site. As the monocyte cells leave the bloodstream and enter the connective tissue of the thrombus they are converted into macrophage cells to remove foreign debris, kill invading bacteria and counteract viruses. Macrophages can join together to create foreign multi-nucleated giant cells and perform a similar function. The presence of a large number of foreign body giant cells may indicate an attempt to deal with particulate debris or be a response to the presence of Dacron.

[222] The final stage of healing involves remodelling or the formation of pannus. As the macrophages engulf dead tissue or bacteria, substances are emitted and fibroblast cells form and stimulate the production of collagen, which is composed of approximately 20 different proteins. At the same time, leukocytes from the passing blood are deposited and lyse the thrombus that was originally deposited on the fibres of the sewing cuff. Eventually, as the macrophages clear the lysed thrombus and the body walls off the biomaterial, the collagen replaces the thrombus with pannus, which is composed of strong fibroconnective tissue. Ideally, the blood contacting surface of the pannus is covered with a layer of endothelial cells that work to inhibit the growth of further thrombus, creating a non-thrombogenic surface.

The Mechanism of Action of Silver

[223] Toxicity means an adverse effect on some part or system in the body. The experts are in general agreement concerning the factors which establish the potential of silver to be toxic to human tissue. Any potential toxic effect related to silver will arise from silver ions (Ag+) as

metallic silver is inert. Because the silver ion is the potential toxic agent, the amount and rate of release of such ions determine whether there can be any toxic reaction to tissue in a given circumstance. Toxicity is, in turn, influenced by other factors including the form of silver, adsorption, excretion and cell type. When the silver ion (Ag+) is bound up with another entity, it is biologically inactive. Thus, the potential for toxicity is related to bioavailability, or the amount of material that is available to interact with cells as well as the body's protective mechanisms that reduce potential toxic effects. Silver salts such as silver nitrate release more silver ions more quickly than silver metal and as such, salts have a greater potential to affect cell toxicity than silver metal.

[224] Protein adsorption is an important factor in the bioavailability of all biomaterials. Silver ions will bind to a number of things in the human body including chloride ions, sulfur compounds, and proteins like albumin, metallothionein, and glutathione. Dr. Cherian testified that there are lower levels of metallothionein and antioxidants in heart tissue, but he did not provide a clear opinion that the diminished protective effect of these substances can cause toxicity to annular tissue. Albumin is the most abundant of the plasma proteins and Dr. Cherian agreed with Dr. Williams that silver ions have an affinity for albumin. Although albumin may increase the rate of silver ions released initially, the ions remain tightly bound to the molecules of albumin, limiting the number of available free silver ions. Silver ions may be released from the compounds that bind them, but released silver ions may again be bound by new proteins and rendered inert. The experts agree that silver ions will be excreted by normal processes in urine and feces.

[225] While silver ions do not discriminate between mammalian and bacterial cells, mammalian cells are more protected from silver ions than bacterial cells. While Dr. Healy and Dr. Cherian testified that silver ions will affect mammalian and bacterial cells in a similar manner, neither produced any convincing evidence to support this and both acknowledged that they had limited personal experience studying bacterial cells. Dr. Hancock, an expert in microbiology, and Dr. Williams were the most qualified on this issue. They explained why silver is selectively more active against bacteria than human cells arising from differences in the structure and function of mammalian and bacterial cell types. As a result of these differences, silver ions can demonstrate effective killing of bacterial cells without being toxic to host cells. If

differences of this nature did not exist, there would be no antibiotic medication of any kind since bacteria must always be killed in the presence of other cells. Moreover, a reason that silver has been used for centuries in medical applications is because it offers high differential toxicity between bacterial and human cells.[47]

The Scientific Literature on Toxicity of Silver

[226] Dr. Williams indicated that you need to look at the whole of the literature on silver biocompatibility and toxicity in order to get an idea of toxic potential. Silver ions can be toxic at some dose. The question with silver and other metals is at what level you might see toxicity from the metal in the context of the normal exposure of individuals for the use in question. He testified that while all data should be looked at, the animal studies are far more predictive of what might happen in humans than *in vitro* studies. Dr. Rodricks cautioned that all studies are not equal. The more helpful studies involve similar chemical entities to the one being investigated – in this case, metallic silver.

[227] Dr. Healy testified that he reviewed more than 500 studies concerning silver or silver compounds, including studies that were positive about the use of silver in medical devices, but in providing his opinions to the court, he selected only 12 papers to include in his report, all describing the toxic effects of silver. The focus of his testimony was on these studies, although he acknowledged there were other studies that showed no or minimal toxicity to silver. He also relied on silver concentration measurements taken by Matthew Ogle, a company scientist, using samples from the 10 week sheep study. I will later explain why his reliance on this data is misplaced.

[228] Dr. Healy concluded that there was no well established toxicity level for silver and that toxicity was dose and time dependent. In forming his opinions, he largely relied on *in vitro* studies that demonstrate that at relatively low concentrations, silver ions can and do injure mammalian cells. There are studies that show that silver causes disordered collagen biosynthesis and interferes with the assembly of connective tissue components; that silver ions affect cell

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[47] Bambauer et al. (2004).

DNA synthesis leading to the inability of cells to advance through division and replication; that silver ions can penetrate the mitochondria where the cell's energy is produced and thereby affect the cell's ability to reproduce and carry out its functions; that the heart has very low levels of antioxidants compared to the liver to counteract the toxic effects of free radicals that damage tissue; and that at relatively low concentrations, silver ions will impair and kill cells involved in the healing process including fibroblasts, monocytes, leukocytes and lymphocytes.

[229] Drs. Rodricks and Williams discussed the limitations and proper uses of the studies that Dr. Healy and the plaintiffs' witnesses have emphasized in their testimony, including papers by McCauley, Hemmerlein, Hollinger, Wataha, Steffensen, Garcés-Ortiz, Ellender and Ham, Hidalgo and Dominguez, and Sudmann.[48] They identified two major problems. First, the results of *in vitro* laboratory studies, while useful, cannot be extrapolated to predict how a material will react with tissue *in vivo* in the body. Second, most of the studies relied upon by the plaintiffs are not terribly relevant as they investigate forms of silver (i.e. silver salts) in which the bioavailability of silver ions is much greater and is released more quickly than the slower release of the metallic silver on the Silzone fabric. As well, some studies are merely individual case reports, the lowest level of epidemiological evidence.[49]

[230] Drs. Rodricks and Williams also discussed other studies that are more relevant to an evaluation of silver toxicity and its application to Silzone. Dr. Hancock testified that based on his review of the literature, the vast majority of studies indicated that silver was effective against bacteria, confirming Dr. Rodricks's testimony that silver's low toxicity is one of the reasons it has a long and successful history in medicine. The defendants' experts supported their opinions with sounder analysis based upon a more comprehensive and balanced view of the scientific literature. I therefore have greater confidence in relying on their opinions.

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[48] Hemmerlein et al. (1997); Ellender and Ham (1989), "Connective tissue responses to some heavy metals..."; Ellender and Ham (1989), "Silver wire implant..."; Hidalgo and Dominguez (1998); Jansson and Harms-Ringdahl (1993); Chen et al. (1994); Kraft et al. (1999); Wataha et al. (1991); McCauley et al. (1989); McCauley et al. (1994); Hollinger (1996); Trerotola et al. (1998); Steffensen et al. (1994).
[49] See e.g. Ellender and Ham (1989), "Silver wire implant...".

In Vitro Studies

[231] Despite their use of the *in vitro* data related to silver to support an argument that Silzone is toxic, the plaintiffs' experts also seemed to agree that such extrapolation is problematic. For example, Dr. Cherian testified that *in vitro* tests can give various types of useful information: "[b]ut I agree that you cannot extrapolate *in vitro* studies into *in vivo*." Dr. McLean viewed *in vitro* testing as part of a "step-wise" process which, along with animal testing, can be used to assess materials. In going up the ladder of evidence, Dr. McLean said that *in vitro* tests can shed light on possible mechanisms of action and provide warnings of possible safety concerns, but then "[t]here's a limit to what you can do with *in vitro* tests", and you need to go to animal tests. Dr. Healy agreed that it is difficult to extrapolate because of the challenge in making the *in vitro* test mimic the particular environment in which you are going to implant the device. Thus, the plaintiffs' experts agreed with Drs. Rodricks and Williams that *in vitro* testing has limitations that must be considered in drawing conclusions about the toxicity of a material in the body.

[232] Dr. Healy relied on the Steffensen and Wataha papers in forming his opinions and suggested that the levels of silver exhibiting cytotoxicity in these *in vitro* studies might also cause problems in tissue *in vivo*. These studies used silver nitrate and silver sulfate solutions which were applied to human cell cultures. Thus, unlike in the body where the silver ions are bound up with other compounds, all of the silver ions would have been available to contact the cells surrounded by the solutions of silver salts. Moreover, metals such as the Silzone coating release small amounts of silver slowly over time as opposed to a silver salt which has greater solubility and releases quickly.

[233] The *in vitro* studies conducted in the laboratories of Dr. McCauley dealt with potential cytotoxic effects of silver sulfadiazine, which is used in the treatment of burn patients. Dr. Healy used the McCauley studies to compare silver levels in those *in vitro* studies to the levels in the Silzone valve. Dr. Williams explained why such a comparison was inappropriate and not relevant to heart valves. Subsequent studies on silver sulfadiazine, for example by Lansdown,[50]

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[50] Lansdown et al. (2004).

have confirmed that silver sulfadiazine does not impair healing in the burn wound environment with grams of silver sulfadiazine much greater than the amount of metallic silver released from Silzone in the sewing cuff.

[234] Dr. Williams disputed Dr. Healy's opinion that a silver ion in contact with a cell will cause damage over time. Dr. Williams testified that he had performed many studies on the time-dependence of metal levels in tissue, and although they varied, there is no evidence to support Dr. Healy's opinion. As the *in vivo* environment is dynamic rather than static, silver ions that are released from the Silzone coating will be distributed; they will be removed by macrophages and largely excreted. Ninety per cent of absorbed silver is excreted, typically in feces. Moreover, Dr. Healy agreed that the tissue healing process is dynamic, that cells have a natural life expectancy and that the same cells will not be exposed to silver ions in the annulus of the heart for the duration of the implant.

[235] In discussing the Hemmerlein study, Dr. Williams explained that it is not possible to extrapolate from an *in vitro* study using fast release silver salts to the effects of Silzone. Moreover, Dr. Bambauer's studies directly contradict the speculation of the authors in Hemmerlein. The question of whether silver on catheter cuffs could lead to tissue problems and loosening was examined in the Dr. Bambauer investigations. In those studies, which impregnated the substrate using the Spi-Argent process, the catheters were effective and not loose. This is a more relevant comparator than an *in vitro* study with a salt that ionizes quickly. Thus the Bambauer Studies, which more directly addressed the question, contradict the suggestion that loosening of the cuffs would occur if a slowly releasing silver compound was applied.[51]

The Kraft Studies[52]

[236] Dr. Healy and Dr. Wilson both relied on a study by Kraft et al. to suggest that silver would have an effect on the microvasculature of a wound and inhibit healing. This was an *in vivo* study where the investigators made a chamber on the back of a hamster and enclosed it in a titanium frame. They saw that silver had an effect on the microvasculature of the tissue within

[51] Bambauer et al. (1995); Bambauer et al. (1996); Bambauer et al. (2004) [Together, "the Bambauer Studies"].
[52] Kraft et al. (1999); Kraft et al. (2001).

the chamber. Dr. Schoen criticized the study because it did not evaluate healing beyond three days and the inflammatory reaction observed may have related to the surgery. Dr. Williams thought that there was a problem with the experimental approach. He testified that he searched the literature for other papers using the same experimental technique and found only one, raising questions about the reliability of this technique. Moreover, the Kraft group performed a second study using a similar technique in which they found that stainless steel also affected the microvasculature of the wound. However, stainless steel is used commonly as a biomaterial without any obvious clinical problems. Dr. Williams concluded that the test technique in both studies showed results contrary to clinical performance.

[237] The suggestion that silver or Silzone could impact healing through an adverse effect on the microvasculature is also contradicted by the work of the plaintiffs' own expert witness, Dr. Olson, in a co-authored study that examined the effects of metallic nanoparticles of silver on wounds.[53] Although Dr. Olson testified that there are a number of distinct differences between the wound dressing tested in that study and the Silzone valve, the study evaluated the potential for healing facilitated by silver ions released by metallic silver compounds in a wound dressing and concluded that the silver-coated dressings promoted rapid wound healing and enhanced the formation of vascular tissue.

[238] Dr. Rodricks reviewed the study that was co-authored by Dr. Olson. He testified that it exhibited even better healing than was seen in a study by Lansdown et al.[54] In that study, two silver salts that release silver ions were introduced into deep wounds in rats. The silver compounds were introduced in concentrations much greater than in Silzone (500 mg in the study as compared to between 17 to 50 mg on the cuff). This did not cause a toxic effect and it appeared to improve healing. The study also showed that silver has the capacity to induce the production of metallothionein.

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[53] Wright et al. (2002).
[54] Lansdown et al. (1997).

The Goodman Studies[55]

[239] The plaintiffs rely on studies by Dr. Steven Goodman who examined and compared platelet adhesion and aggregation on exposure to the Silzone-coated fabric and non-coated fabric. Dr. Goodman observed greater platelet disruption and reduced platelet aggregation on the Silzone-coated fabric and suggested that this could explain the thinner pannus observed in the sheep studies. The plaintiffs argue, relying on the evidence of Mr. Butchart, that Dr. Goodman's studies support a finding that the Silzone coating had a biological effect on healing into the sewing cuff by adversely affecting the organization of thrombus into stable pannus.

[240] Dr. Tweden, Dr. Williams and Dr. Hirsh each discussed the Goodman studies in their testimony.

[241] Dr. Tweden described studies she had conducted with Dr. Goodman before her work on the Silzone project. One of these studies examined the behaviour of platelets to pyrolitic carbon, a material that is considered to be blood-compatible with a low potential for thrombogenecity. In that study, they observed extensive platelet spreading and disruption, a response similar to that observed with the Silzone fabric.

[242] Dr. Williams was familiar with Dr. Goodman's work and regards him as a "good scientist", but characterized Dr. Goodman's studies as relatively simple *in vitro* studies that are difficult to extrapolate to *in vivo* performance regarding wound healing or thrombogenicity. Dr. Hirsh did not think that Dr. Goodman's findings provided a reliable foundation for Mr. Butchart's opinion that Silzone affects platelets and red blood cells to increase the risk of thromboembolism.[56] He testified that the role of platelets in wound healing was controversial and abnormal wound healing had not been described in chronic conditions that result in a very low platelet count. Like Dr. Williams, he also pointed out that Dr. Goodman performed his experiments in a static system in which platelets were suspended in a buffer and that this is very different from *in vivo* where there is a constant flow of platelets that are suspended in plasma which contains modulating proteins.

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[55] Goodman et al. (1998).
[56] Dr. Hirsh is Professor Emeritus, Department of Medicine (Haematology), McMaster University.

[243] The plaintiffs also overlook Dr. Goodman's suggestion in the 1998 paper (and referred to again in his later paper) that the rapid disruption and coverage of the silver coated fabric by the platelets may more rapidly initiate later stages of healing:

> The observation of greater surface coverage increased platelet spreading and extensive disruption of platelets on the silver treated fabric may provide an explanation for the reduced pannus formation observed *in vivo*. Since platelet spreading and disruption are a normal part of wound healing processes it is possible that the rapid disruption and coverage of the silver coated fabric by the platelets may more rapidly initiate later stages of healing. That is the flat spread platelet cytoskeletons may provide a matrix for the adhesion and ingrowth of cells necessary for healing. *Hence silver coating may not only reduce bacterial infection by virtue of its bacterial toxicity but may also reduce infection by initiating a more rapid healing of the sewing ring. This would then reduce the fabric surface area available for bacterial adhesion and colonization. Of course more rapid healing may also have benefits with respect to device thrombogenicity.* (Emphasis added)

[244] For these reasons, I do not think that the Goodman studies are terribly helpful to the plaintiffs' toxicity theory. If anything, the study appears to show a potentially beneficial effect from Silzone on healing.

[245] Finally, in a study by Trerotola and others,[57] the authors reported that two patients experienced rash and discolouration, but no tissue damage. This study also used a catheter that had been subsequently removed from the market. Trerotola can be contrasted with a study by Kathuria et al.,[58] which also involved an IBAD coated catheter. Dr. Rodricks described the results as showing a "very compatible response" in rats, with no loosening of the coated catheter cuff and good tissue morphology.

[246] In their written submissions, the plaintiffs did not reference studies by Sudmann or Garcés-Ortiz,[59] although both were relied on by Dr. Healy in his testimony. The Sudmann study involved the Christiansen hip prosthesis, a replacement device that had massive failures. The

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[57] Trerotola et al. (1998).
[58] Kathuria et al. (1996).
[59] Sudmann et al. (1994); Garcés-Ortiz (1997).

Garcés-Ortiz study involved Ketac silver dental cement, which also contained lead and aluminum fluoride, later determined to cause the cytotoxic effects of the cement.

[247] In summary, the plaintiffs have focused on *in vitro* studies, investigations involving silver salts which release ions very quickly, and/or case reports that involve unusual sets of facts or unreliable experimental techniques that are of limited value in assessing the *in vivo* toxicity of Silzone.

Other Scientific Literature on Silver

[248] The collection of scientific articles considered by the defendants' experts to form their opinions was far more comprehensive and far more relevant than the largely *in vitro* studies referred to by the plaintiffs. It constitutes a more reliable body of scientific opinion.

[249] For example, Dr. Rodricks evaluated 200 to 250 studies, including the literature cited by Drs. Cherian, McLean, Healy and Mr. Butchart. As well, he conducted an independent exploration of the pertinent silver literature from 1950 to 2010. He provided an analysis of a subset of 114 *in vivo* studies that addressed the effects of silver and silver compounds in implantable medical devices including vascular grafts, orthopaedic prostheses, grafts and pins, surgical meshes and rings, catheters, and urological stents. Among the studies were a significant number of RCTs as well as non-randomized clinical trials and cohort studies. Dr. Rodricks found that there was no data in these studies indicating that silver or silver compounds used in the implantable devices were toxic.

[250] Dr. Rodricks selected a number of these *in vivo* studies to discuss in more detail in his testimony.[60] In their Reply submissions, the plaintiffs point out limitations in some of the studies referred to by Dr. Rodricks, for example, the studies by Collinge et al. on fixation pins; Lansdown et al., on the use of silver sulfadiazine and silver nitrate in rats; and Batt et al., on silver-coated polyester grafts. However, they do not reference any testimony about these studies.

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[60] Clark et al. (1974); Collinge et al. (1994); Lansdown et al. (1997); Wright et al. (2002); the Bambauer Studies; Batt et al. (2003); Hardes et al. (2007).

Similarly, the plaintiffs reference one paragraph from a review article by Dr. Lansdown. In cross-examination, Dr. Rodricks accepted that the article was authoritative because of Dr. Lansdown's research in this area, although he did not think the article was published in a peer-reviewed journal.[61] However, Dr. Rodricks was never referred to this paragraph in the article and asked to comment on it. As the plaintiffs failed to adduce any testimony on the alleged limitations in the studies, these submissions lack an evidentiary foundation.

[251] Although I have carefully reviewed each of the studies discussed by Dr. Rodricks, I will only provide a few examples that I consider particularly relevant.

The Bambauer Studies

[252] These studies were conducted by Dr. Rolf Bambauer, of the University of Saarland, Homburg/Saar, Germany. It will be recalled that Dr. Tweden spoke with him about his work early in the development of the Silzone project. The devices under study were hemolysis catheters that were treated with silver using either ion implantation (Spi-Argent II) or the IBAD process (Spi-Argent I). Hemolysis catheters are susceptible to infection because they need to pass through the skin and into veins. For these reasons, the Bambauer Studies have direct relevance to the Silzone product. Patients were studied up to 300 days. Drs. Rodricks and Williams evaluated different studies, but both concluded that they supported the safe use of silver, reduced infection and demonstrated no adverse effects in patients. Silver levels in the blood were found to be very small and the IBAD coating did not cause thrombogenicity.

[253] The plaintiffs point out that the Bambauer Studies showed that the Spi-Argent coating inhibited attachment of proteins and cells compared to an uncoated surface. They submit that the lack of fibrin, blood cells and thrombogenicity seen on the IBAD coated surfaces in the Bambauer Studies as compared to an uncoated surface was an indication that a silver coated surface will reduce tissue formation (contrary to Mr. Butchart's hypothesis that the Silzone coating increases thrombogenicity because unhealed clotting material forms on the sewing cuff).

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[61] Lansdown (2004).

They assert that the defendants try to dismiss the inhibitory effects of the coating by suggesting that a similar result will not play out in the interstices of a sewing cuff because it is not in a blood flowing environment and that this ignores the fundamental reality of Dr. Bambauer's observation that the presence of Spi-Argent caused delayed and diminished protein attachment as compared to controls.

[254] Dr. Williams was cross-examined about these observations in the Bambauer studies and satisfactorily explained why it is inappropriate on this issue to draw analogies between the surface of catheters, which are designed to have a surface free of blood and other debris, and the interstices of Dacron cuffs. It is the physical differences in the design of the devices that control whether there will be formation of a clot and subsequent tissue formation. Dr. Williams also pointed out that tissue did actually grow into the outside portion of the cuff that was on some of the catheters used in the studies, and which was coated with Spi-Argent I or II. It is true that Dr. Bambauer did not attempt to evaluate or study comparative ingrowth between the coated and uncoated catheters, but his paper records and Dr. Williams noted that the tissue infiltration into the Spi-Argent cuff was "intensive without any inflammatory signs" and needed to be removed with a knife. This is some evidence that, notwithstanding the lack of protein attachment, tissue ingrowth did occur on the coated cuffs. Thus, the Bambauer Studies also show that a Silzone-coated device can be thromboresistant in free flowing blood, but permit tissue ingrowth.

Vascular Graft Studies

[255] Vascular grafts are often used to replace portions of femoral (leg) arteries in patients 50 to 60 years old, and are expected to last for their lifetimes, or 20 to 25 years. They are typically made of Dacron or Gortex, so the fabrics are similar to the sewing cuff in the heart valve. The grafts are attached to the remaining artery by an anastomosis, and blood will flow into the interstices in this area and clot in the same manner as blood clotting in the interstices of the heart valve sewing cuff. The clot is then reorganized with new tissue. Some parts of the vascular graft, such as the lumen through which blood flows, are different than a heart valve, but other parts, such as the anastomosis, are similar to the sewing cuff. Dr. Williams testified that the clotting and tissue reorganization in the anastomosis of the vascular graft "is a very, very similar mechanism" to the tissue growth that occurs in the sewing cuff. Dr. Schoen also said that healing into a prosthetic valve sewing cuff is well represented by healing of a vascular graft.

[256] The B. Braun Vascular Systems Silver Graft is coated with silver by the same IBAD process used to coat the Dacron fabric of the Silzone valve. While the vascular graft is coated with silver from the outside of the fabric, and may have a thin coating, experts agreed they would still expect to see some effect in the anastomosis if silver was toxic, such as (i) leakage at the anastomosis where the graft attaches to the artery, (ii) an adverse effect on endotheliazation of the vessel causing it to block very quickly, and (iii) inflammation of the tissue surrounding the graft.

[257] In a study of the graft's performance, the B. Braun Vascular Graft was implanted into the aorta of pigs and compared to uncoated grafts.[62] Gelatin was added to the grafts, but as Dr. Williams explained, this has no effect on the contact between silver and tissue. Microscopic evaluation after explant revealed similar healing between the silver-coated grafts and control grafts. There was no significant difference in either neo-intimal thickness or in the immunohistochemical investigations between the coated and uncoated groups. Consistent with the authors' conclusions, Dr. Williams found that there was no disadvantage of the silver coating in terms of healing, and that the aortas remained patent or open. None of the signs of a toxic reaction were present.

[258] The plaintiffs rely on this study and the evidence of Dr. Rodricks in cross-examination, but their submissions do not fairly describe his evidence. Dr. Rodricks testified correctly that Dr. Ueberrueck's study concluded that the measurement of neo-intimal thickness after *six* months (as opposed to three months) revealed no significant differences between coated and uncoated grafts.[63] Vascular grafts coated with silver were also implanted into rabbits by Dr. Ueberrueck's group. The study was published in the prominent *Journal of Biomedical Materials Research*.[64] The animals were challenged with bacterial infections, and after 52 weeks the devices were explanted. Dr. Williams explained that this study confirmed the antibacterial effect of silver in

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[62] Ueberrueck et al. (2003), "Healing Characteristics...".
[63] The plaintiffs rely on Dr. Rodricks' testimony in cross-examination at paragraphs 573 to 575 of their Reply submissions, but they do not fairly describe his evidence. I agree with the defendants that the plaintiffs mischaracterize his testimony or provide incomplete references to the transcript. See defendants' further written submissions at paragraphs 35-36.
[64] Ueberrueck et al. (2005) "Vascular Graft Infections...".

these silver-coated devices with no adverse effects on healing. Blood silver levels were taken and confirmed what was seen in the animal studies and in the LIMRA. After the initial release, silver levels decreased to a constant low level.

[259] Finally, the B. Braun Vascular Graft was studied over 18 months in 50 patients supervised by the Committee on Infections in Vascular Surgery of the German Society of Vascular Surgery.[65] While this was a non-randomized cohort study, the investigators found that the study supported the safe use of the coated devices. The results show no adverse effect on the healing process, including no reports of bleeding in the anastomosis. Dr. Williams concluded that there was good healing in the grafts and this would be comparable to healing associated with the Silzone valve.

Silver-coated Prostheses

[260] The investigators in a study by Hardes et al. studied 20 patients who received very large silver-coated megaprostheses that replaced parts of the bones in their arms or legs.[66] The megaprostheses were coated with silver metal, but by a different process than IBAD, and are marketed in Europe. The amounts of silver used in the prostheses were many times greater than that used in the Silzone valve. The amount of silver ranged from 0.33 grams (330 mgs) to 2.89 grams (2890 mgs). In comparison, the amounts of silver used in the Silzone valve varied depending on size. The largest possible amount of silver in a Silzone valve was 0.050 grams (50 mgs), with the average being around 0.017 grams (17 mgs). The amount of silver in the larger prostheses of 2.89 grams was therefore 170 times the amount in the average Silzone valve, but as Dr. Rodricks explained, the investigators found no evidence of toxicity even with this relatively large amount of silver.

Dr. Williams' Research

[261] By the 1980s, there was widespread recognition of the antimicrobial properties of silver compounds and an increasing interest in incorporating the materials into medical devices. In

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[65] Zegelman et al. (2009).
[66] Hardes et al. (2007).

1989, Dr. Williams, along with colleagues at the University of Liverpool and the Biomedical Department of the Johnson Matthey Technology Centre, undertook a comprehensive review of the safety and efficacy of silver and silver compounds in medicine. He and colleagues published a review article that focused on the physiological events at the interface of the materials and tissue, corrosion and degradation effects, the development of local tissue responses, systemic effects following implantation of silver devices, and included an assessment of the antimicrobial effects of silver.[67]

[262] In this paper, the authors evaluated the potential toxicity of silver compounds to cells and discussed both their own findings and the literature in the section entitled "Cytotoxicity". When Dr. Williams' laboratory used an *in vitro* method to evaluate various silver alloys and silver samples, they found that the extent of the toxic response was determined by the form of silver. Metallic silver sheet (the form of silver used in Silzone) produced a very tiny response as measured by an observable cytotoxic zone around the sample while other mixtures of silver such as "sintered" silver produced a larger cytotoxic zone. In providing his opinion that Silzone lysed fibroblast cells, Dr. McLean mistakenly believed that Silzone used sintered rather than metallic silver.

[263] The paper also described studies in the literature reflecting the effects of silver on mouse peritoneal macrophages. The investigators in those studies found that high levels of silver may have an effect on cell functions but there was no impairment of phagocytic, migratory or interferon-producing capabilities in the cells unless there was also an acute (i.e. immediate) cytotoxic effect. Phagocytosis is the process of ingestion and digestion by cells of solid substances such as other cells, bacteria, bits of dead tissue and foreign particles. This is important because macrophages play an important role in tissue healing and the observations in these studies showed that in the presence of low levels of silver, macrophages could digest or absorb silver particles and still function.

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[67] R. Williams et al. (1989).

[264] This was also demonstrated by research Dr. Williams conducted in his own laboratories to assess the local host tissue response to silver by using an intramuscular implantation method in rats. Some particles from the silver were seen and were demonstrated in fibroblasts and macrophages. However, these materials did not have an adverse impact on the cells, indicating that the material was not toxic to the tissue. The study continued for ten months and Dr. Williams concluded, consistent with other studies referred to in the paper, that silver produced a very mild tissue response. The deposition of silver particles, mainly in macrophages, was also described in a catheter study using silver-coated Dacron without any adverse cellular response.[68]

[265] The plaintiffs do not appear to take issue with the conclusions reached by Dr. Williams in the review paper, except to point out that "science is ever-evolving and that peer-reviewed articles published after 1989 and before July 23, 1997 demonstrate the ongoing study and evaluation of the toxicity of silver". I am satisfied that the conclusions reached by Dr. Williams and colleagues in this paper fairly represented the state of knowledge on silver in 1997 and indicated that silver could be safely used in a permanently implantable device.

Regulatory Filings

[266] Dr. Rodricks undertook a review of the regulatory filings in the United States and Canada from February 1992 to January 2010. He compiled a list of the "FDA Approvals for Silver-Containing Medical Devices: Feb. '92 to Jan. '10".[69] Since 1992, over 100 silver-containing medical devices have been approved for use in patients in the United States. A similar compilation was created for approvals by Health Canada, at "Health Canada Approvals for Silver-Containing Medical Devices: Feb. '92 to Jan. '10".[70] From February 1992 to January 2010 Health Canada also approved over 100 medical devices which contained silver for use in patients in Canada. The types of medical devices included wound dressings, catheters, tracheotomy tubes, surgical patches, laryngectomy tubes, and endotracheal tubes.

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[68] Oloffs et al. (1994).
[69] Exhibit 1844/2.
[70] Exhibit 1844/3.

[267] The plaintiffs point out and the defendants do not dispute that the vast majority of approved medical devices containing silver post-date the Silzone valve. This evidence cannot be used to evaluate the defendants' decision to market the Silzone valve and to continue to market it up to the recall in January 2000, but it can be used to evaluate whether or not silver is a safe biomaterial. Regulatory agencies, such as the FDA and Health Canada, have the responsibility to ensure that the benefits or potential benefits of the devices they approve outweigh any potential risks. The risk benefit analysis that Health Canada is required to undertake was discussed in *Glaxo Canada Inc. v. Canada*, in the context of a competitor's challenge to the Minister of Health's decision to grant a Notice of Compliance for a new drug:

> … In exercising his discretion, the Minister weighs the benefit of the drug against the foreseeable risk of adverse reaction to it. … [it] is a decision made on the basis of public health considerations. The Minister in exercising his discretion weighs the predicted benefit of the drug in relation to the foreseeable risk of adverse reaction to it. The Minister's determination is one made in contemplation of public health and represents the implementation of social and economic policy.[71]

[268] Health Canada's subsequent approval of numerous implantable medical devices containing silver is corroborating evidence of the opinions of the defendants' experts that silver is a safe biomaterial to use in an implantable device.

Conclusion on Scientific Literature

[269] The scientific literature overwhelmingly supports the conclusions of Drs. Williams and Rodricks that silver exerts little to no toxic effect in animals and humans, that it can be tolerated by cells involved in the healing process, and that it can be used safely in medical devices. While there is evidence that silver salts can exert a cytotoxic effect on cells *in vitro*, metallic silver, like the outer layer of Silzone, has only mild toxicity to cells *in vitro* and these effects are not generally seen *in vivo* through an adverse host response even where very large amounts are used and continuously released into tissue. The small amounts of silver used on the sewing cuff, and its metallic character, make it highly unlikely it causes a toxic effect. The current use of hundreds

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[71] *Glaxo Canada Inc. v. Canada (Minister of National Health & Welfare)*, [1988] 1 F.C. 422, [1987] F.C.J. No. 838, aff'd [1990] F.C.J. No. 275 (F.C.A.).

of silver coated products, including studies on implantable products coated with silver by the same IBAD process used in the Silzone cuff, is compelling evidence that Silzone is not toxic when used on the sewing cuff of a heart valve.

Sheep Studies

[270] *In vivo* studies provide the best evidence to evaluate biocompatibility. The sheep studies are therefore quite significant in understanding if Silzone is toxic. The competing expert evidence on these studies comes from Dr. Factor, a New York based cardiac pathologist certified in anatomic and clinical pathology, and from Dr. Wilson, a staff pathologist in the Department of Laboratory Medicine at the Hospital for Sick Children. Dr. Wilson is certified in anatomic pathology and has a sub-specialty in cardiovascular pathology. In the 1970s and 1980s, he trained and worked with Dr. Malcolm Silver, an extremely distinguished cardiovascular pathologist. However, over the last two decades, his work and experience has been in a pediatric setting where he sees very few cases of PVL, dehiscence and thrombosis in valves explanted from children. In fact, since his work with Dr. Silver through the time he was retained in this litigation, he has not evaluated any mechanical heart valve explanted from an adult. Since completing his residency, he has done histopathological sections on fewer than five valves involving endocarditis and he acknowledged that endocarditis was not one of his research interests. This is pertinent not only to the sheep studies, but also to the 14 patient study that I will discuss later.

[271] While Dr. Wilson is an eminently qualified pathologist with an impressive array of publications in peer-reviewed journals, Dr. Factor has considerably more experience in the areas that are relevant to evaluating the healing in the sheep studies. Like Dr. Wilson, he has taught medical students, conducted research and published, but unlike Dr. Wilson, Dr. Factor's pathology experience has included assessments of many more explanted prosthetic heart valves, almost exclusively from adults. He has far greater experience with infective endocarditis in humans and animals. He has conducted animal research involving prosthetic heart valves in both small and large animals, including sheep, and he has evaluated healing in tissue and mechanical heart valve sewing cuffs implanted in sheep. Apart from this litigation, Dr. Wilson has never been involved in an animal study in which heart valves were implanted in sheep, nor has he evaluated the healing of a sewing cuff in sheep. As both experts base their opinions on

observations from photographs and micrographs of the explanted sheep valves, their relative knowledge and experience becomes a much more important consideration than it might otherwise be. Where their evidence conflicts, Dr. Factor's opinion carries more weight.

[272] Dr. Wilson's opinion that Silzone is toxic and impairs tissue healing is based on his gross observations of healing differences in the 4 to 5 week and 10 week studies as he saw tissue ingrowth between both Silzone-coated and non-Silzone coated fibres in the histopathological analysis of the valves explanted from the sheep that survived to planned sacrifice. He admitted there was no evidence of toxicity in the microscopic histopathology of the sheep that survived to planned sacrifice, making it implausible that Silzone damages annular tissues. Dr. Wilson was critical of the histology analysis in these studies (as well as in other studies) because the tissue samples did not focus on "areas of concern in terms of healing, particularly areas where the pannus was too thin or did not exist." I accept Dr. Factor's opinion that Dr. Cameron's sectioning of tissue samples was neither inappropriate nor incomplete.

[273] Dr. Factor concluded that there was comparable healing between the Silzone and non-Silzone portions of the sewing cuffs in the Short Term study. Dr. Olson agreed that from his review of the pathology reports, the valves in the Short Term study, including from KTMV-2, all showed comparable healing into the Silzone and uncoated sides of the cuff and there was no information to suggest that the healing was different between the two sides.

[274] Although Dr. Wilson testified at trial that the most likely cause of death of KTMV-2 was a PVL or dehiscence due to silver toxicity, in the reports he prepared for litigation he acknowledged that surgical technique or infection could not be excluded. In sheep implants of prosthetic heart valves, it is generally known that early death that is not device-related may occur and surgical technique or infection can be factors. There is evidence that KTMV-2 had fewer stitches than KTMV-1 or KTMV-3 and it is possible that surgical technique contributed to the dehiscence as Dr. Tweden and Mr. Holmberg believed.[72]

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[72] The animal care records show that KTMV-2 had 14 stitches as compared with KTMV-1 (16 stitches) and KTMV-3 (15 stitches).

[275] It is not necessary for me to delve into the detail of the Clostridium organism that Dr. Factor explained and Dr. Wilson disputed was the source of the infection that Dr. Factor said led to the dehiscence and PVL. The important issue is whether the evidence persuades me that silver toxicity is the likely explanation for the death of KTMV-2. In my view, it is called into question by the striking fact that no other animal in either study demonstrated a toxic response to Silzone. All of the other animals in both studies survived to their planned sacrifice dates. Dr. Williams and Dr. Rodricks both found it very hard to understand how this could occur in one animal with no evidence of this in the others. As Dr. Rodricks testified:

> … as a toxicologist looking at all the data from both studies, in fact, the 5 week study and the 10 week study, given the performance in all of the other animals, it's impossible to imagine that that's -- that that early death is related to a toxic event. In other words, toxicity doesn't work that way. It wouldn't be just having a very, very serious effect on one animal and having no effect on the others. That's not a toxic phenomenon. So whatever happened there, I don't know the answer to, but it isn't silver toxicity, I'm quite confident.

[276] I find that Silzone toxicity is an unlikely explanation for the dehiscence and PVL in KTMV-2.

[277] Dr. Factor also concluded that in the 10 week study the tissue response to the Silzone-coated cuff was equivalent to the controls. He disagreed with Dr. Wilson that there was marked variability in healing with the Silzone valve and found Dr. Wilson's areas of concern of pannus growth (sometimes too thick; other times, too thin) to be arbitrary. The tissue reaction to Silzone in the microscopic pathology was no different than uncoated Dacron, notwithstanding the presence of silver particulate. Dr. Factor's overall view with respect to the tissue reaction to Silzone as compared to uncoated Dacron was that there was no difference and that there was no adverse response to silver whether it was attached to fibres of the cuff material or was free in tissue. The inflammatory multinucleated giant cell response was comparable.

[278] In the 10 week study, there was one animal, SJII-8, that developed excess pannus. Although the animal survived to planned sacrifice at 10 weeks, the pannus was restricting the movement of one of the valve's leaflets. On receipt of this sheep's explanted valve and surgical records, Dr. Tweden concluded the pannus formation was unusual and as I have said, she contacted Dr. Schoen and asked him to examine SJII-8 and SJII-9's valves. Dr. Schoen found

two prominent green suture knots on SJII-8's valve and while he concluded that the relationship between the sutures and the pannus was uncertain, he could find no other apparent cause for the excess pannus. Dr. Cameron conducted a gross and microscopic pathological examination of SJII-8 that revealed nothing unusual.

[279] It was Dr. Wilson's opinion that silver toxicity caused the excess pannus. Matthew Ogle, a company scientist, measured the silver concentrations in the annular tissue of the sheep in this study and found that SJII-8 had silver levels that were higher than the other sheep in the study. However, as discussed below, these values are unreliable. Dr. Wilson suggested that the higher silver levels might account for the excess pannus, but this is inconsistent with his Silzone toxicity theory as it assumes an increase in cell activity to cause excess tissue growth at the same time as silver is interfering with cellular functions to impair or delay tissue healing. Dr. Schoen testified that this is biologically implausible.

[280] Dr. Schoen and Dr. Errett testified that they had seen numerous cases in non-Silzone valves where excess suture material contributed to excess pannus. It seems to me that excess suture material is a more likely explanation for the excess pannus in this animal than silver toxicity, although, like thrombus, the cause of excess pannus in animals or humans is not always known.

[281] I accept the evidence of Dr. Factor and conclude that these sheep studies do not show healing differences at all, and certainly none that can be attributed to Silzone.

Sheep Silver Concentrations and Silver Loss

[282] Dr. Tweden's literature review included references to studies that reported on the measurement of silver toxicity in burn patients treated with silver sulfadiazine cream.[73] From her review of these studies, she concluded, as her April 1, 1997 memorandum states: "The most conservative level reported for silver toxicity is 300 ppb". Both Dr. Williams and Dr. Rodricks said that 300 ppb was a reasonable interpretation of the data reported in the studies. Dr. Williams acknowledged that some studies reported higher values and other studies reported lower values,

[73] Deitch et al. (1989); Boosalis et al. (1986).

but that 300 ppb was not an unreasonable figure to use as a reference for blood serum concentrations in the animal studies and in the LIMRA in order to assess the risk of systemic toxicity. Although the plaintiffs argue that Dr. Tweden thought 300 ppb was a measurement of silver toxicity at a cellular level, I am satisfied that Dr. Tweden understood that 300 ppb was a blood serum level. She did not rely on 300 ppb as the concentration level at which silver starts interfering with cells involved in tissue healing.

[283] Blood serum concentrations, while of interest, are not directly relevant to an assessment of the toxic effects of silver on tissue. In the study of megaprostheses by Hardes et al. that I referred to earlier, the investigators used 300 ppb of silver as one of the guidelines for assessing toxicity. However, they recognized the limitations of this measurement for reasons I have discussed:

> However, the therapeutic and toxic effects can be only exhibited by the free silver ions (Ag+). If the silver ion is bound it has no function any more. Therefore, the reported threshold values since when [sic] silver can exhibit toxic side-effect can be interpreted with caution only, because the measured silver concentration includes bounded and not bounded silver. Therefore there can be no correlation between the silver concentration and toxic side-effects.

[284] The original protocol for the 10 week study as sent to the FDA for comment on August 30, 1996, did not propose to measure silver concentrations in the tissues. However, in the FDA's September 26, 1996 reply, they commented that "It may be useful to consider preserving … an aliquot of the sewing ring, ingrowth tissue and valve annulus for *in vitro* quantification of silver content" suggesting that "Tissue quantification of silver concentration may prove to be a more sensitive measure, compared to serum levels, of the presence of silver-ion protein complexes in the near vicinity of the sewing ring." Mr. Ogle developed a method for measurement of the silver concentrations using samples from KTMV-2 in October 1996, and after the FDA's request, he proceeded to do an analysis in March 1997 of samples from the 10 week study. Tissue surrounding the valve was examined and tested for silver concentrations. The results were reported, but no conclusions were drawn from them.

[285] As the plaintiffs place so much reliance on Mr. Ogle's data, I think it is important to reproduce the following transcript excerpt from Dr. Williams' direct examination. The assumptions he was asked to make accurately describe Mr. Ogle's evidence about the difficulties he encountered in sectioning the tissues for analysis:

> Q. And what I would like to do is ask you to make some assumptions with respect to this work and then I will ask you a couple of questions at the end. What I would like you to assume, first of all, is that in order to make these calculations, Mr. Ogle was provided with a block -- let's deal with the annular tissue concentrations in particular. That Mr. Ogle was provided with a block of annular tissue and sewing cuff from the sheep in question, and in these cases it is each of the sheep in the long-term study. Secondly, I would like you to assume that the sewing cuff had tissue ingrowth into the interstices of the fabric of the cuff. Third, I would like you to assume that Mr. Ogle separated the annular tissue from the sewing cuff in order to make his measurements using a scalpel blade. And finally, I would like you to assume for the moment that Mr. Ogle probably caught a bit of the silver-coated cuff material in the annular tissue section. Given those assumptions, what conclusions would you draw from Mr. Ogle's measurements of the silver concentration in the annular tissue that we have just looked at?
>
> A. Thank you, I understand those assumptions. In my opinion, it was always going to be very difficult to be able to analyze the silver levels in tissue adjacent in contact with the cuff without the possibility of including some of the fibers. I see technically that as being very, very difficult. With that possibility, in my opinion, just a small amount of the coated fiber being included in the tissue for analysis makes interpretation of that silver level very, very difficult. Could I just add to that that the technology for measuring silver is very similar to that which we used in my paper which we discussed yesterday. It involves digestion of the sample, typically in nitric acid, and then analyzing total silver content; that is the way in which it is done. That gives a total silver content, irrespective of whether that is silver ions in tissue or silver particles. So if you have one bit of fiber with a bit of silver attached to that which is now digested in the sample, clearly, that is going to distort and in my opinion distort in a very significant way the total silver level there. I should also add that even without that assumption, since we know we have seen from pathology slides that there is the occasional particle of silver in tissue anyway, that will also get taken up in that digestion process. So in no way, in no way at all does this figure for silver content reflect total available silver. If it was one small fragment of silver which we have seen has no effect on the inflammatory response, one small fragment of silver would totally distort these figures, and they haven't any implication whatsoever on the relevance to safety.

> Q. And so is your opinion then with respect to these measurements the same whether or not Mr. Ogle caught some of the fabric in the diesection (sic) process?
>
> A. I think it is most likely he did, but even if he did not, I do believe that it is very difficult to have any confidence in these figures to give us the level of available silver. In my opinion, both those factors could contribute.

[286] In cross-examination, Dr. Healy was asked to make the same assumptions, but refused to do this because Mr. Ogle did not record in his notebook the problems that he described in his evidence and Dr. Healy did not think this was "scientifically valid". As a result, I do not have Dr. Healy's evidence on a point that the plaintiffs emphasize in their submissions. Assuming Dr. Healy is correct and I should have no regard to Mr. Ogle's evidence, I am left to resolve conflicting evidence from Dr. Healy and Dr. Williams about what the data showed.

[287] Dr. Healy testified that the silver concentration levels are higher than those that would be toxic to cells involved in the wound healing process, but his opinions are based on toxicity levels seen *in vitro* or on blood serum levels, which have no direct application to the evaluation of toxicity in tissue. It is not possible to extrapolate from a concentration of silver that is toxic *in vitro* to the *in vivo* situation as the study by Hardes et al. explains. Dr. Rodricks and Dr. McLean agreed that there are no *in vivo* studies describing a threshold value for silver concentration leading to damage to fibroblasts. Dr. Williams' evidence confirms that Mr. Ogle's data tells us very little about toxicity because it does not measure available silver ions in the tissues. Dr. McLean agreed that measuring quantities of silver in tissue does not tell you the dose of free silver ions, which is the only reliable measure of the potential for toxicity.

[288] It is also telling that notwithstanding the importance the plaintiffs place on the sheep silver concentration data, Dr. Wilson has had in his possession for more than a decade between five and ten human hearts with Silzone valves in them, but he has never attempted to measure the silver concentration levels in tissue adjacent to the sewing cuff. I think it is fair to infer that if Dr. Wilson believed such measurements to be of scientific value in his analysis of the effect of Silzone on tissue healing, he would have done this. This lends further support to the defendants' position that such measurements are not meaningful even if they could have been reliably obtained.

[289] It is also of interest that the sheep silver concentration data from the 10 week study was reported to both regulators. The plaintiffs submit that the data would have been difficult to interpret without a description of the methods Mr. Ogle used to derive the values that are depicted on the chart that was included in the regulatory submissions. Dr. Healy testified that the relevant and important value is that which is provided for silver concentration in the column labelled "Wet (µg/g)". However, Mr. Ogle's memorandum, which was included in the submissions to Health Canada and the FDA, does provide a description of how the tissue was prepared for analysis, how the ppb of silver was determined, how the ppb value was converted to weight of silver, how it was compared to the dry and wet weight of tissue, and how a value for weight of silver per weight of tissue was reported. Dr. Wilson acknowledged that Dr. Hilbert is an experienced pathologist. As it was the FDA that requested that silver concentration be measured in the area adjacent to the cuff, I would expect it to pay attention to the results, and it is apparent from Dr. Hilbert's memorandum that he reviewed the results obtained. There is no indication that he had any difficulty interpreting the data or, more importantly, that he had any concerns about it.

[290] It is also of significance that the gross photographs and representative microphotographs, as well as the animal care records, pathology reports of Dr. Cameron, and silver concentration results obtained by Mr. Ogle for the 10 week study were all reviewed by Dr. Hilbert who concluded:

> The data provided are satisfactory and adequately demonstrate the short-term safety of the silver coated sewing cuff, based on explant pathology findings and the establishment of blood and selected organ silver levels.
>
> …
>
> The sponsor has adequately demonstrated the short-term preclinical safety of the silver coated sewing cuff based on handling and implantation characteristics tissue response and silver levels in blood and selected organs (kidney, liver, heart valve annulus). The individual surgical notes/progress and pathology reports, gross photographs and representative micrographs included in this submission provide satisfactory documentation of the study findings.

[291] The plaintiffs are critical of St. Jude's failure to investigate the toxicity level for silver for cells exposed to the silver ions immediately adjacent to the cuff. The evidence shows and I find that no investigations were possible that would have yielded meaningful information. I also find

that even if Mr. Ogle's measurements can be considered reliable, the concentrations of silver in the annular tissue of the sheep in the 10 week study are not significant. This is confirmed by Dr. Williams' evidence. He repeatedly disagreed with counsel's attempts to characterize the concentrations of silver in the annular tissue of 6300 ppb, 8330 ppb and 17330 ppb as significant and instead was of the opinion that the amounts were not only extremely small, but represented the total level of silver "wherever it came from" and not available silver ions. Finally, regardless of what the silver concentrations in the annular tissue were, there were no adverse effects seen on the tissue in the pathological analysis.

[292] The FDA had also suggested that St. Jude measure the amount of silver in samples of the cuffs themselves and compare these to the amount of silver before implantation in order to assess the release of silver from the cuff. St. Jude attempted to do this. The evidence of Mr. Ogle, Mr. Holmberg and Dr. Williams explains why the evaluation was difficult and no conclusions could be drawn from it. St. Jude provided this information to Health Canada and the FDA, but neither sought further information or expressed any concerns.

Regent Study

[293] Unlike the 4 to 5 week and 10 week studies, the Regent study focused on an evaluation of the valve's function and safety rather than the effect of the Silzone coating on tissue healing. The study was conducted at the University of Minnesota under the direction of Mr. Bianco. The study pathologist was Dr. Kirchhof. The study evaluated nine sheep implanted with Regent valves and four controls implanted with non-Silzone valves. The animals were sacrificed at time periods between 20 and 22 weeks, with one early death, SHP-8, at 21 days.

[294] The study protocol required St. Jude to arrange for histopathological examination of suspected thrombus formation in the hinge area and samples for two valves, SHP-8 and SHP-15, were sent for evaluation.

[295] With respect to the early death of SHP-8 at 21 days, Dr. Factor testified that the gross photograph depicted an infected vegetation that was similar to those he had seen numerous times in infected valves explanted from both animals and humans. He attributed its early death to endocarditis caused by a thrombus infected with Pasteurella. Relying on Dr. Kirchhof's

pathology report which found no infection in the section of thrombus analyzed, and on his own observations of the gross photographs and review of the pathology reports, Dr. Wilson attributed this death to a PVL and thrombus caused by Silzone.

[296] As with the early death of KTMV-2, it does not make sense that only one animal in the study would experience a toxic injury. Thrombus is a well-known complication in all animal studies as well as in humans with mechanical valves and there may be multiple possible causes that cannot always be explained. The pathology report attributed the animal's death to Pasteurella sepsis. Dr. Wilson disputed that there was evidence that the Pasturella infection in the blood had affected the thrombus due to the absence of organisms. While there were no organisms found in the section sampled, that does not lead to the conclusion that there were no organisms. Dr. Wilson has seen very few cases of endocarditis and none in sheep. Dr. Factor is clearly more experienced on this issue and I accept his opinion that this was an infected thrombus.

[297] With respect to the other study animals, Dr. Factor reviewed all photographs and records from the Regent study and concluded that there was no evidence that Silzone had any toxic effect on heart tissue or impaired healing. Dr. Factor noted excess pannus on some Silzone valves, but this was also present on some control valves. He found comparable variable healing between Silzone sheep and controls, whereas Dr. Wilson found abnormalities in all nine valves, including a number of sheep with PVLs and thrombus.

[298] The study concluded that the valve demonstrated preclinical safety. This conclusion was reached notwithstanding the early death of SHP-8, and in reliance on the necropsy reports of Dr. Kirchhof, whose work Dr. Wilson admired. Although the focus of the study was on valve performance rather than tissue healing, Mr. Bianco was a co-author of the ASAIO article reporting on the results of the 4 to 5 week study, and very much aware of the Silzone project. It is therefore reasonable to think that if the Silzone sewing cuff was implicated in the leaks that were identified or that Silzone played a role in the formation of thrombus, this would have been raised.

[299] The final report from the Regent sheep study, including all of the necropsy reports that Dr. Wilson relied on for his opinions, was included in the submission filed with Health Canada prior to its approval. The plaintiffs place some reliance on the fact the report was unaudited. Mr. Bianco noted this in his letter submitting the report, but also noted that the GLP audit "rarely if ever" results in altering conclusions or recommendations on preclinical safety of the device under investigation. That this was an unaudited report is of no significance.

Epic Study

[300] The Epic sheep study with six Silzone valves and six controls and explants at 20 weeks was conducted at BioSurg, Inc. a facility in Winters, California. Dr. Cameron served as study pathologist. Four more Silzone sheep and four controls were explanted at 52 weeks. The plaintiffs point out that this was the largest and longest sheep study conducted by St. Jude on a Silzone valve. However, the Epic valve was a new tissue valve, used a different fabric on the sewing cuff and differed from both Regent and Silzone valves in several other respects. In view of this, the study results are not directly applicable to conclusions about the Silzone valve. Nonetheless, the results from the Epic study were positive and did not raise concerns about the Silzone coating. The Study Director, Ross Lirtzman, DVM, concluded in his report of the 20 week study that: "The Epic valves showed no interference with the local inflammatory tissue response: in fact fibrous reaction to the coated cuff is well organized and *pannus formation on the valve surface is thin and smooth*" [Emphasis added]. Dr. Lirtzman's description of well organized (i.e. healed) pannus is some corroborative evidence of Dr. Tweden's view that thinner pannus is more ideal pannus.

[301] In contrast, Dr. Wilson found focally poor healing in the Silzone valves in this study overall. He identified leaks in four of the animals. While Dr. Factor agreed with Dr. Wilson that two of the animals demonstrated PVLs, his opinion was that in one animal it was caused by infection and in the other the leaks were similar to leaks frequently seen in valves without Silzone. He found comparable healing variability between the Silzone sheep and controls. Based on his review of the records, explanted valves and histology slides, he found no evidence in any of the sheep in the study that Silzone had any adverse effect on the heart tissues, or that it was toxic or impaired healing.

[302] The plaintiffs suggest that the amount of silver remaining on the Silzone-coated valve in the Epic sheep study (81.9% at 52 weeks) as reported in Mr. Ogle's poster be compared with the amount of silver remaining on the B. Braun Vascular Graft (97.8% at 52 weeks) in Dr. Ueberrueck's study.[74] They argue that these results indicate that the silver coating leached off more rapidly from the Silzone cuff than from the vascular graft. This comparison cannot be made as the B. Braun results are derived from an *in vitro* washout study whereas the Epic results are derived from an *in vivo* analysis of silver concentration in tissue. Dr. McLean testified that silver released in an *in vitro* study cannot be used to draw conclusions about the quantity of silver that will be released in a blood environment. Also, Mr. Ogle's evidence was that his sectioning techniques were not uniform ("I guarantee that I clipped some silver fabric. So from that standpoint, I believe it was the worst case amount of loss of silver seen"). The B. Braun results, if they are at all relevant, tend to demonstrate that only small amounts of silver are released from an IBAD coated surface after an extended time.

Tailor Ring and TSPV Studies

[303] For completeness, I will briefly mention the Tailor Annuloplasty Ring and the Toronto Stentless Porcine Valve Series (TSPV) sheep studies. Dr. Wilson examined explanted rings from the Tailor study and took some histological sections from them, but did not discuss his findings in his reports or testimony. I infer that he accepted Dr. Factor's conclusions that there were no healing differences between coated and uncoated rings in the study, which used the same fabric as the Silzone valve. Dr. Wilson had the opportunity to review the explanted valves from the TSPV study, but expressed no opinion about the study. The TSPV reports are business records and reach positive conclusions about the healing response of the Silzone-coated valves.

Conclusion on Sheep Studies

[304] The sheep studies showed comparable healing into Silzone-coated sewing cuffs and no evidence of toxicity in the gross and microscopic evaluations. These studies are not perfect predictors of what will happen in humans, but as they show the response of a whole organism to

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[74] Ueberrueck et al. (2005), "Vascular Graft Infections...".

a potentially toxic agent with all of the protective mechanisms intact, they are better indicators of biocompatibility than *in vitro* studies. Silzone did not inhibit tissue growth or cause an abnormal inflammatory response that was unusual for an implanted device. The early death of KTMV-2 in the 4 to 5 week study and the pannus overgrowth of the valve leaflet in SJII-8 in the 10 week study was not caused by Silzone toxicity.

Spoliation

[305] Common Issue 6 asks: Is the burden of proof of causation or negligence affected by spoliation of evidence by the defendants? It is convenient to address this here as there is no dispute that the organs, explanted heart valves, and histology blocks from the 4 to 5 week and the 10 week studies (the "Masters series sheep study materials") and explanted heart valves from the Regent sheep study (collectively, the "missing materials") were either inadvertently destroyed prior to the litigation or could not be located during the course of the litigation. Although the plaintiffs originally submitted that findings be made in their favour in respect of each of the common issues, they revised their position in their Reply with respect to this common issue. They now submit:

> The answer to Common Issue 6 is:
>
> The burden of proof in causation or negligence is not affected by the spoliation of evidence by the defendants. However, the defendants' spoliation of evidence leads this Court to presume that explanted Silzone valves and tissue samples from the Sheep Studies would have been unhelpful to the defendants' case and helpful to the plaintiffs.

<u>The Legal Test for Spoliation</u>

[306] In *McDougall v. Black & Decker Canada Inc.*, the Court referred to *St. Louis v. R.*, for the following statement on the law of spoliation: "[spoliation] occurs where a party has intentionally destroyed evidence relevant to ongoing or contemplated litigation in circumstances

where a reasonable inference can be drawn that the evidence was destroyed to affect the litigation".[75] Spoliation can thus be divided into four elements:

1. the missing evidence must be relevant,
2. the missing evidence must have been destroyed intentionally,
3. litigation must have been ongoing or contemplated at the time the evidence was destroyed, and
4. it must be reasonable to infer that the evidence was destroyed in order to affect the outcome of the litigation.

[307] This interpretation of the law regarding spoliation has been followed by courts in Ontario.[76]

[308] The plaintiffs have not referred to any evidence regarding the relevance of the missing materials. Rather, they invite the court to infer that those materials would have been relevant, apparently based on the circumstances in which the materials went missing. However, they have not referred to any evidence about those circumstances. The plaintiffs also have not referred to any evidence regarding the question of whether the missing materials were destroyed intentionally. Rather, they invite the court to infer such an intention since they assert that the destruction of the materials would have been contrary to federal regulations and St. Jude's internal policies. However, the plaintiffs have not referred to any regulations or evidence of St. Jude's internal policies.

[309] The only evidence regarding the circumstances in which the Masters series sheep study materials went missing came from the defendants' answers to undertakings that were read in by the plaintiffs at trial. The evidence of Mr. Holmberg was that the materials were discarded in a lab cleanup despite his instructions to save them. Mr. Holmberg recalled speaking to someone who said that "she did not think the specimens needed to be saved since all the approvals had been received and that slides for all the specimens were available".

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[75] *McDougall v. Black & Decker Canada Inc.* (2008), 440 A.R. 253 (C.A.), at para. 18; *St. Louis v. R.* (1896), 25 S.C.R. 649.
[76] *Blais v. Toronto Area Transit Operating Authority* (2011), 105 O.R. (3d) 575 (Ont. S.C.), at para. 82; *Gutbir v. University Health Network*, 2010 ONSC 6752, at para. 18.

[310] At the time the materials were destroyed, litigation had not commenced. The plaintiffs have not referred to any evidence as a basis for finding that the materials were destroyed in contemplation of litigation. While they assert that the materials were lost "shortly after St. Jude officials met with the MDA for the second time," the defendants dispute this claim, and the plaintiffs have not referred to any evidence to support it. The defendants also point out that Mr. Holmberg was the source of information regarding the destruction of the Masters series sheep study materials. At trial, the plaintiffs had the opportunity to cross-examine Mr. Holmberg regarding the time during 1999 that the materials were destroyed and whether this was before or after discussions with the MDA in June 1999. The plaintiffs did not do this, nor did they attempt to elicit any further evidence at trial on how the Masters series sheep studies materials were destroyed from any of the other company witnesses who testified at trial.

[311] Given that the evidence of Mr. Holmberg is the only evidence regarding the circumstances under which the Masters series sheep study materials went missing, it would not be reasonable to infer that the evidence was destroyed in order to affect the outcome of pending litigation. Indeed, the only available evidence indicates that whoever discarded the material did so because they were under the impression that it was no longer needed for any purpose.

[312] In the case of the missing materials from the Regent sheep study (originally in the possession of the University of Minnesota), the defendants' answers to undertakings read in by the plaintiffs at trial detail that St. Jude initially had "some second hand information" that the explanted valves and organs were "inadvertently destroyed in 2000" but then subsequently, the organs were located. There is a document showing their delivery to St. Jude but it was "unable to confirm with any degree of confidence that the explanted valves were ever in St. Jude's possession, or when or how they went missing". The read-in evidence shows that it is uncertain that St. Jude ever received the explanted valves from the University of Minnesota.

[313] In substance, the plaintiffs are asking the court to infer all of the elements of spoliation, dressed up as a presumption from the mere fact that the Masters series and Regent sheep study materials are missing. In failing to refer to any evidence in their submissions on spoliation, the plaintiffs have failed to establish any of the four elements listed above. Thus, the plaintiffs have

failed to establish spoliation on a balance of probabilities. It is therefore not necessary to consider whether the defendants have rebutted any adverse inference that would arise from a finding of spoliation, nor is it necessary to consider whether a presumption should be made.

Clinical Evidence of Silzone Toxicity

[314] A very large part of the plaintiffs' causation case is based on Dr. Wilson's clinico-pathological correlation of 18 Silzone valves from 14 patients. A clinico-pathological analysis involves reviewing the medical records and analyzing the gross and microscopic pathology for a patient and then correlating the findings. While Dr. Wilson's study is only one part of the plaintiffs' causation picture, it is a very important part. It is the causal lynchpin that attempts to connect the plaintiffs' theory of Silzone toxicity with clinical evidence of abnormal healing and resulting medical complications in patients. Although a number of expert witnesses provided testimony about this, the primary opinions come from Mr. Butchart, Dr. Wilson and Dr. Schoen.

Independence of Dr. Schoen and Neutrality of Dr. Wilson

[315] The plaintiffs made a considerable effort to exclude or neutralize the evidence of Dr. Schoen on the basis that he lacks independence. Their attack is focused on Dr. Schoen's consulting work with the medical device industry in general, and with St. Jude, in particular, although less than 1% of his time has been spent consulting for St. Jude and Dr. Schoen consults to several of St. Jude's competitors as well as the FDA. I did not agree to exclude his evidence as inadmissible when this was raised during the trial and my ruling explains why.[77] The plaintiffs reprised this at some length in their written submissions and also during oral argument. Having heard Dr. Schoen's evidence, I have not changed my mind.

[316] The plaintiffs do not dispute that Dr. Schoen is a highly qualified cardiac pathologist, but they resist a finding that his evidence is to be preferred solely on the basis of his qualifications. I accept that a trial judge must tread the path of relative experience cautiously as even highly qualified experts can be wrong. Nonetheless, as I said when I was discussing the sheep studies,

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[77] *Anderson v. St. Jude Medical*, 2010 ONSC 5768.

relative expertise takes on greater significance when the expert opinions are based on the observations that each made from the appearance of the valves. Knowledge about how valves heal comes from experience.

[317] While it is true that in their respective roles as litigation experts Dr. Wilson and Dr. Schoen have equivalent experience with Silzone valves, it is not credible for the plaintiffs to argue that Dr. Wilson's experience matches the depth of experience of Dr. Schoen who, like Dr. Butany, is acknowledged to be among a very small group of six or eight internationally recognized specialists in the pathology of prosthetic heart valves. Dr. Schoen is a professor of pathology at the Harvard Medical School and Director of the Cardiac Pathology Department at one of the four principal teaching hospitals of the Harvard Medical School.

[318] Dr. Schoen also holds a Ph.D. degree in materials science and, as well as teaching medical students at Harvard, he also teaches students at MIT working toward PhDs in biomedical engineering. Dr. Schoen's practice has focused on the pathology of prosthetic heart valves and he has examined at least a thousand prosthetic heart valves over the course of a thirty year career. Apart from his early work with Dr. Silver, Dr. Wilson's professional career has taken him in other directions. It is undeniable that Dr. Schoen has far more experience with prosthetic heart valves than Dr. Wilson and that he is far more qualified to discuss the range of healing that can be seen in them. While the concerns that the plaintiffs raise could in some circumstances affect the independence of an expert, I found Dr. Schoen's evidence to be fair and impartial. In my view, he fulfilled the duties of an expert witness who is providing opinion evidence to the court.

[319] In contrast, it was Dr. Wilson who lacked neutrality and testified as an advocate in support of the theory of Silzone toxicity. He was selective in his choice of the valves from the sheep studies, choosing not to discuss the explanted Tailor annuloplasty rings or review the TSPV sheep studies and he was also selective in his choice of patients for his clinical study. He testified that he needed "complete medical records" in order to do a clinico-pathological correlation, but, he included three long-term patients despite very incomplete records. There were other long-term patients, the so called "lettered patients", that he did not include, although there is evidence that at least some of them died of non-valve related causes and showed good

healing of their Silzone valves. Dr. Wilson confirmed this to be the case with Patient "S", who died with an apparently well healed valve that had been functioning for at least nine years. He gave no adequate explanation for this and I was left with the impression that the patients in his study were not chosen in an unbiased, scientific manner.

[320] Dr. Wilson made clinical diagnoses on individual patients that went well beyond his own experience as a pathologist. He had a tendency to be dismissive of the opinions of treating physicians and other experts where their conclusions undermined his theory, although he clearly lacked their expertise. As well, his evidence was not presented in a neutral manner. He was often argumentative, repetitive and unresponsive to questions posed in cross-examination. While the record will speak for itself, I try not to interrupt the testimony of a witness except to seek clarification. There were a number of occasions when I found it necessary to do this and direct him to answer the questions. I do not accept the plaintiffs' suggestion that this is explained by Dr. Wilson's inexperience as an expert witness. Dr. Wilson has previously given expert testimony and he testified in this trial over the course of ten days. Regrettably, Dr. Wilson's commitment to his own theory of causation impaired his objectivity and reliability as an expert witness. I find he lacked neutrality. Given this concern and his limited experience with prosthetic heart valves, I attach little weight to his opinions where they differ from those of Dr. Schoen and the defendants' clinical experts.

Mr. Butchart

[321] Mr. Butchart is an eminently qualified cardiac surgeon, with particular expertise in valve related thromboembolism. Although he is in quite a different category than Dr. Wilson, they have in common that each formed their opinion early on, with little scientific analysis, that Silzone was the culprit. Neither has wavered from that opinion. Understandably, Mr. Butchart was offended and upset by St. Jude's actions when, without informing him (as Dr. Flory now acknowledges he should have), the company contacted Mr. Jules Dussek, the President of the Society of Cardiothoracic Surgeons of Great Britain and Ireland to request a review of his CERFS data. After this, the relationship between Mr. Butchart and St. Jude quickly deteriorated. Mr. Butchart's response to St. Jude's actions was a normal human response, but his

predetermined opinion that patients had suffered because of the Silzone valve and his negative views about St. Jude affected his ability to look at the evidence dispassionately in providing his opinions to the court.

The Timing and Manner of Tissue Healing in Prosthetic Heart Valves

[322] Mr. Butchart and Dr. Schoen described different biological processes that result in the formation of pannus, but they agree that an implanted heart valve sewing cuff is capable of healing and, if fully healed, that it will become encapsulated in connective tissue or pannus. Obviously, valves that have been safely implanted in human patients and that continue to function well cannot be removed for study. Dr. Schoen testified that valves that have been explanted for medical complications after different lengths of time demonstrate variable healing characteristics from patient to patient, from mitral to aortic, from inflow to outflow surface on the same valve and around the circumference, largely due to anatomic factors. Dr. Schoen disagreed with Mr. Butchart and Dr. Wilson that tissue formation and ingrowth normally occurs by three months and is necessary for the clinical performance of a valve.

[323] Dr. Wilson testified that he observed a grossly abnormal healing process in the heart valves in the 14 patients in the study, involving too little pannus, too much pannus or a combination of both, and sometimes, thrombus with pannus. He attributed these abnormalities and the resulting medical complications in each of the patients to Silzone toxicity. His conclusions are, to a significant extent, based on the assumption that a sewing cuff on a mechanical heart valve will normally be healed by three months and that thrombus will not form on a well healed valve. Mr. Butchart also testified that the literature confirms that healing is complete within the first two to three months, but he did not testify about what he has seen in his own clinical practice.

[324] Dr. Schoen demonstrated from comparative gross photographs of selected valves that there is tissue lost in the surgical removal a valve or its removal at autopsy. He explained that assessment by a pathologist of the reasons for poor healing can be constrained by the inability to understand the anatomic context into which the valve was implanted. Understandably, the surgeon’s primary concern is addressing the problem at hand and typically, the surgeon is not paying attention to preserving tissue or endothelium on the valve and the endothelial layer

abrades easily. As a result, the specimen the pathologist receives may be and is often different with less tissue on the valve than was there at the time of removal. Dr. Butany's evidence confirms this.

[325] This was also demonstrated in a 1981 paper by Marbarger and Clark, where the authors studied the degree of tissue overgrowth and the strength of tissue adhesion in 118 explanted bioprosetheses. Sufficient tissue for evaluation was present in only 66 of the 118 valves.[78] This suggested to Dr. Schoen either that the tissue was not there at the time of explant or had been removed inadvertently in handling the valves. The authors in this study also reported, although on limited data, that many months may be required before tissue ingrowth is complete. As Dr. Wilson's 14 patient study had no valve handling protocol, he cannot account for changes in appearance and quantity of tissue that occurred after the valve was removed from the patient or at autopsy.

The Three Month Guideline

[326] All patients with mechanical valves require anticoagulation therapy to reduce the risk of clotting on the valve and are usually prescribed Coumadin (*Warfarin*) with the goal of maintaining the patient's anticoagulation within a target range, measured using the International Normalized Ratio (INR). The therapeutic INR range for a patient is usually set by his or her treating physician, but with reference to general recommendations set out in generally accepted guideline documents such as in the Canadian Cardiovascular Society's Guidelines for the Surgical Management of Valvular Heart Disease. These guidelines recommend, and it is the practice of many physicians, to anticoagulate bioprosthetic or tissue valve recipients for only the first three months following implant. Dr. Wilson's theories that a sewing cuff should be normally healed by three months so as to protect against the formation of thrombus is based largely on his extrapolation from the guidelines and his understanding of this practice of physicians.

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[78] Marbarger and Clark (1981).

[327] While there is consensus in the medical community that the anticoagulation guideline is a sound treatment guideline based on clinical studies of the effectiveness of anticoagulation, there is no clinical or animal data to establish that a sewing cuff will be endothelialized within three months. As well, there is no evidence of any practice that the target INR for mechanical valve recipients is lowered after three months, although one would expect this could happen if the sewing cuff on all mechanical valves is completely healed by three months.

[328] Dr. Wilson's reliance on animal studies to support his opinion that normal healing in valve patients occurs at three months fails to account for differences in the rate of healing between humans and animals. The Bull and Braunwald studies, on which he and Mr. Butchart relied, demonstrated these differences as the authors found that the rate of tissue organization in human prosthetic valves is "markedly slower" than that seen in experimental animals.[79] There are very few clinical studies that document the time course of healing in mechanical valves. The studies are small, making it difficult to understand what should be expected in the majority of patients over time. The studies that have been done support Dr. Schoen's evidence that the timing and manner of healing in mechanical valve patients is extremely variable and it is not possible to say with any confidence that healing is complete by three months in the vast majority of patients.[80]

[329] This was graphically demonstrated by photographs of the Starr Edwards valve that Dr. Schaff explanted for PVL after 15 years with intact sutures and absolutely no endotheliazation or tissue ingrowth on the sewing cuff. Dr. Schaff has explanted more than 300 valves over a 30 year career. He testified that this valve was at one extreme, but that he had seen many other valves, from different manufacturers, with a wide range of healing characteristics, most explanted after five years.

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[79] Bull and Braunwald (1971).
[80] Vitale et al. (1997).

[330] The evidence of Dr. Errett is consistent with this. He testified:

> I think the natural history of healing following valve--mechanical valve or any valve implantation in humans is not entirely understood, and I think that's understandable because valves we place in patients that function normally and last the patient's life are never really studied along the line. So we don't know in thousands of patients what is happening at certain times during the course of that valve's life…we make conjectures on how well they're healed and when they're healed but that is conjecture.

[331] Like Dr. Schaff, Dr. Errett had observed non-Silzone valves with the same patterns of healing that Dr. Wilson described, including little to no healing of valves explanted months or sometimes years after implantation, intact pledgetted sutures pulling through the tissue around valves, excess pannus on valves, and valves explanted with little or no endotheliazation. Dr. Butany testified that the pathological findings and modes of failure he observed in his study of 19 Silzone valves are seen in every kind of valve.[81] To the extent that Dr. Wilson's opinions are based on the assumption that a valve will be fully healed and endothelialized by three months, the assumption is unproven.

The Scientific Value of a Clinico-Pathological Correlation

[332] The very nature of a class action requires the bifurcation of the causation analysis between general causation and specific causation. The question at this stage is not whether Silzone *did* cause impaired healing in any class member, but rather, whether it *can* cause this adverse effect. The plaintiffs submit that the evaluation of Dr. Wilson's evidence is a question of sufficiency and weight, which combined with other evidence regarding Silzone's effect on tissue and cells, will allow me to determine whether the plaintiffs have discharged their onus with respect to Common Issue 2. The issue that I find difficult is how to assess the sufficiency and weight of a study of 14 patients in answering a question on general causation in a class action.

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[81] Butany et al. (2006).

How should the evidence on individual patients be approached and how does it assist the court in reaching conclusions about the effects of Silzone in the broader group of class members who have Silzone valves? During oral submissions, I repeatedly pressed counsel for assistance with this.

[333] Counsel for the plaintiffs proposed that I should, in effect, go through each of the patients in the study in order to determine whether or not, on balance, this supports Dr. Wilson's opinions about the effects of Silzone on tissue healing. In other words, are Dr. Wilson's opinions with respect to each patient mostly correct? I do not see how a scorecard on 14 individual patients will assist me in answering a general causation question and the plaintiffs provided no meaningful guidance on this. Assuming that the court agreed with Dr. Wilson that Silzone is the likely explanation for a particular medical complication in eight of the 14 patients, but not in the other six patients, what conclusion could I draw other than this outcome occurred more frequently in patients with Silzone valves? This cannot establish on its own that the Silzone valve is causal of the complication since there is no control group or corresponding group of patients who suffered the complication and is exactly the same except for the Silzone valve.

[334] The plaintiffs' approach would be useful if the question to be answered was whether Dr. Wilson correctly concluded that Silzone toxicity is the more probable explanation than other probable explanations for the medical complication in each of the 14 patients. But, this is a question that will only arise in individual hearings. The question at this stage is one of general causation – does Silzone have a different and adverse effect on healing than uncoated Dacron? In other words, is there a causal relationship between Silzone and the harm the plaintiffs allege?

[335] The approach I propose to follow is to determine in what circumstances a clinico-pathological correlation of 14 patients can provide evidence of causation. I will then explain why I reject Dr. Wilson's analysis. My conclusion is that this kind of evidence cannot establish a causal link between Silzone and the medical complications that occurred in these patients.

[336] As I touched on in the Introduction to these reasons and as I discuss further under Common Issue 3, there is a generally accepted hierarchy within the scientific community as to the kinds of studies that may be helpful in investigating cause and effect relationships. It is generally accepted in the scientific community that a case series such as Dr. Wilson's 14 patient

study, provides, at best, weak evidence of whether a treatment, in this case a Silzone valve, causes a condition, for example, PVL. A case series can address the question: what is the frequency of the occurrence of an outcome in patients with a particular characteristic? It can suggest that there might be a problem that should be studied, but a case series cannot answer the question: was the occurrence of PVL more likely in patients with a Silzone valve than in patients without it?

[337] Dr. Schoen acknowledged that proper analysis would be difficult as it would require a study with autopsies of patients whose valves functioned without complication. Dr. Wilson cannot be criticized on this account, but there is inherent bias in a study that only includes patients that have experienced medical complications and excludes other patients whose valves appear to have functioned well. As Dr. Schoen explained, "it is very difficult to take 14 patients or even a larger group of patients who have had their valves removed for some problem and draw conclusion [sic] about the patients who are out there doing fine." The absence of a control group or a standard of comparison limits the use that can be made of the data from a study of this kind. There is simply no information on the patients that are not part of the series and, therefore, one cannot determine if it was the Silzone valve or some other known or unknown factor that caused the condition in issue. This makes it virtually impossible to draw conclusions as to probable causation.

[338] Although a clinico-pathological correlation is a methodology that scientists use, I find that absent an extreme or unique situation, scientists would only rely on a case series without controls to establish a hypothesis and would not rely on this kind of evidence to draw conclusions about cause and effect. In *Rothwell*, Osler J. reached the same conclusion after reviewing very similar evidence on the scientific value of different kinds of epidemiological studies.[82]

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[82] *Rothwell* at para. 59.

An Extreme or Unique Situation

[339] Dr. Sackett, the plaintiffs' epidemiology expert, illustrated an extreme or unique situation where it may be acceptable to draw conclusions about causation by giving the example of a small case series of 12 patients with a relatively mild disease who all died after receiving the same treatment. In this case, the "treatment" is a Silzone valve, common to all patients in the study, but the "disease" is a variety of medical complications, including PVL, thrombosis, endocarditis or stroke. These are risk factors for all mechanical valve recipients.

[340] In analyzing the 14 patients in his study, Dr. Wilson said that he proceeded empirically by a process of exclusion and would only attribute the event to Silzone toxicity where he could exclude other possible causes of the adverse event or the adverse appearance of the valve. The plaintiffs dispute that as a matter of law Dr. Wilson was required to eliminate all other possible causes for medical complications in order to have the court accept his evidence as proof of causation. Causation in law is on a balance of probabilities, but Dr. Wilson approached his task as a scientist. Scientific proof of causation is described in *Rothwell* as follows:

> Proof of causation
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> Causation in scientific and medical matters may be easy to assign or may be extremely difficult. Causation may be taken as proved, for all practical purposes, in many diseases when a specific organism is invariably found in association with a specific physical condition of disease and other possible causal agents can be eliminated. Causation can be assigned when it has been shown that a specific group of symptoms, characteristic only of a specific agent or disease, is present. Causation can be assigned when a specific pathological condition, characteristic only of a specific causal agent, is shown to exist in a patient, in life or at post-mortem examination.[83] [Emphasis added]

[341] Dr. Wilson accepted that this was the degree of proof that was necessary in order for him to draw a causal connection between Silzone and the medical complications experienced by the patients in this study. His evidence was that every single valve he examined had shown abnormal healing to some degree and the consistent themes of too little pannus, too much pannus, thrombus and paravalvular leak were "so clear, striking and really significant" that he was able to

[83] At para. 92.

conclude that "the Silzone coating consistently causes disordered healing and can and does cause a variety of life-threatening complications". While the plaintiffs do not require proof of impaired healing in all class members to establish that Silzone can cause impaired tissue healing, a study of this kind cannot support the conclusion that Silzone is the causal agent, unless other possible causal agents for the complications in issue have been excluded.

The 14 Patient Study

[342] The crux of Dr. Wilson's opinion was that Silzone was the cause of the complications experienced by eleven of the 14 patients in the study. For the remaining three patients, his opinion was that Silzone was the most likely cause. Mr. Butchart provided opinions on eight of the 14 patients in Dr. Wilson's study.[84] I have reviewed the detailed evidence on each of the 14 patients, but I do not find it necessary to discuss this except by way of example to illustrate the weakness of this evidence in establishing that Silzone is the causal agent for the complications.

[343] In virtually all of the cases, Dr. Schoen identified clinical details that indicate alternative causes for the valve problems. The defendants' clinical experts in cardiology, hematology, infectious disease and neurology provided strong evidence of alternate causes or the possibility of alternate causes for the complications in issue.[85] I would expect that the opinions of a patient's treating physician would be significant in a clinico-pathological context and Dr. Wilson agreed that it is the clinician rather than the pathologist who makes the diagnosis. In most cases, Dr. Wilson's opinions are contradicted by evidence from the medical records and the diagnoses of the treating physicians that are found in the records. The evidence of the defendants' clinical experts confirmed those opinions and diagnoses. Several examples will illustrate that there are other medically plausible causes for the complications experienced by these patients that Dr. Wilson and Mr. Butchart have not excluded.

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[84] Patients 2, 3, 5, 6, 9, 10, 13, 14.

[85] The defendants' clinical experts were Dr. Mizgala (Patients 1, 3, 4, 5, 7, 9, 11, 12, 13, 14); Dr. Hirsh (Patients 2, 6, 10); Dr. Sexton (Patient 2); and Dr. Snyder (Patients 6 and 10). Dr. Factor provided evidence on Patient 6. Dr. Schoen testified about each of the patients with the exception of Patient 6.

[344] There was considerable evidence at trial of the ability of surgeons to diagnose endocarditis based on the gross appearance of a prosthetic heart valve at surgery. The consistent evidence from the defendants' experts is that a surgeon's diagnosis of endocarditis based on observation at surgery is highly reliable. Patient 1 - Erik Andersen, and Patient 2 - Sharon Frost are examples. Dr. David and Dr. Cusimano of TGH were involved with Mr. Andersen's second surgery that replaced his first Silzone mitral valve with a second Silzone mitral valve and replaced his native aortic valve with a Silzone aortic valve. Dr. Latter performed Ms. Frost's explant surgery at St. Michael's Hospital. These physicians are regarded as highly experienced and capable surgeons who, in the late 1990s, would have been familiar with the appearance of endocarditis. Despite the inability to identify bacteria, Mr. Andersen's surgeons believed that infection caused poor healing in his first Silzone mitral valve (Dr. Cusimano described the valve as "obviously infected and dehisced") and the treating physicians thought there was sufficient clinical evidence to support a diagnosis of endocarditis.

[345] In Sharon Frost's case, the evidence for endocarditis is stronger. She had a history of culture-negative endocarditis in her native mitral valve and it was explanted and replaced with a Silzone valve. That valve was explanted and replaced with a second Silzone valve that continues to function. The consistent diagnosis from her treating physicians was that her embolic events following implant of her first Silzone valve were caused by embolic material from an infected vegetation on the valve demonstrated by echocardiography. Dr. Latter recorded a diagnosis of definite endocarditis in his operative note and this remained the discharge diagnosis.

[346] All the pathologists agreed that pathology can rule in endocarditis under the Duke Criteria, but cannot rule it out.[86] The pathological criteria, if positive, are sufficient but not necessary to diagnose endocarditis. The Duke Criteria provide clinical factors that allow for a definite diagnosis even where the pathology is negative. While Ms. Frost did not have positive

[86] The Modified Duke Criteria are the most commonly accepted tool for the diagnosis of both native valve and prosthetic valve endocarditis. See, Li et al. (2000).

blood cultures, there was pathological evidence of inflammatory process, a diagnostic criterion under the Duke Criteria that is indicative of endocarditis. Neither Mr. Butchart nor Dr. Wilson convincingly excluded this as the explanation for her embolic events.

[347] Both Mr. Butchart and Dr. Wilson suggested that as surgeons and other treating physicians in the late 1990s were not yet aware of the issue of Silzone toxicity, they were mistaking Silzone toxicity for endocarditis in their observations of necrotic tissue. While Dr. Schoen conceded that it was theoretically plausible for silver toxicity to cause a similar presentation to infective endocarditis, he disputed that there was any evidence to support the hypothesis. Dr. Sexton has worked on the study of infective endocarditis for twenty years at Duke University Medical Center, has participated in an international study collecting data on over 5,000 patients with infective endocarditis and is a co-author of the paper by Li et al. proposing modifications to the Duke Criteria. He testified that he was not aware of any published scientific literature that Silzone toxicity mimics infective endocarditis at surgery, on echocardiogram, on pathology, or even symptomatically. Drs. David, Cusimano and Latter work at downtown Toronto hospitals and are physicians of class members. If the plaintiffs wanted to establish that in the late 1990s surgeons were mistaking Silzone toxicity for endocarditis, it would have been a relatively simple matter to adduce this evidence. I attach little weight to Mr. Butchart's evidence that he mistook annular necrosis caused by Silzone as infection.

[348] It is known that all mechanical-valve recipients are at risk of medical complications and there is an accepted background rate for each complication. For example, the Heart Valve Guidance sets out a background rate of 1.2% per valve-year for the incidence of clinically diagnosed PVL in mechanical heart valve recipients and this is based on studies of patients who have had valves for thousands of patient years. It seems reasonable to think that at least some Silzone patients must have had complications regardless of Silzone, but Dr. Wilson's conclusions ignore or dismiss the background rate. He blamed all of the outcomes in the 14 patients on Silzone, even Patient 7 where he agreed with the treating physicians and experts that the patient had prosthetic valve endocarditis, but said that Silzone was the underlying cause of the poor healing. He did not exclude the possibility that the endocarditis developed through an infection contracted during dental work several months before the final hospital admission or that the poor healing would have occurred regardless of Silzone.

[349] Similarly, for Patient 9, Dr. Wilson's opinion was that Silzone toxicity caused substantially more paravalvular leakage and necessitated the replacement of both Silzone valves, even though this patient had several well-known risk factors for PVL, including multiple valve surgeries, a history of rheumatic valve disease, the explant of a previous non-Silzone valve due to PVL, and a technically complicated surgery in which her Silzone valve was implanted. Patient 11's Silzone valve was explanted after more than 6 years due to PVL. Like Patient 9, he had many of the same risk factors as she did, but none of these were properly excluded, notably a previous PVL.

[350] The same is true of Patient 13. Dr. Christakis performed the explant surgery at Sunnybrook Hospital in Toronto. He described the unusual appearance of pannus on the valve, but gave no evidence that Silzone caused the PVL. He also did not comment on the opinions of this patient's treating physicians that annular damage from disease and previous surgeries were the most likely cause of the PVL. These opinions were supported by the defendants' clinical experts.

[351] Dr. Christakis also performed the explant surgery for Patient 12. This patient had two Silzone valves implanted in 1997. Nearly eight years later, only the aortic valve was explanted due to a build-up of pannus. Dr. Christakis was not asked any questions about this surgery. He gave no evidence that the appearance of the aortic valve in this patient was unusual or that he observed any abnormalities in the healing of the patient's mitral valve. It can reasonably be inferred there were none. Importantly, Dr. Wilson's theory does not explain how Silzone toxicity would cause an exuberant build-up of pannus in Patient 12 on only the aortic valve while not affecting the mitral valve in the same patient.

[352] Similarly, his theory does not explain the lack of a uniform or universal response to Silzone from patient to patient, from place to place on a given sewing cuff, and from valve to valve in the same patient. If there was a problem with Silzone, one would expect there to be a problem whenever Silzone comes in contact with tissue. That this did not occur is most strikingly demonstrated by Mr. Andersen whose two replacement Silzone valves functioned for more than six years, despite Dr. Wilson's opinion that the PVL in Mr. Andersen's first Silzone mitral valve was caused by Silzone toxicity. The fact that there was no Silzone response to the second two

valves suggests that the problem Mr. Andersen had with his first valve was not a response to Silzone. There is no credible explanation regarding why the alleged toxic destruction of annular tissue would occur only once in the same patient, although on the plaintiffs' theory, Mr. Andersen received a double dose of Silzone between the two valves over a period of six years.

[353] All experts agreed that a toxic material will demonstrate a profound effect on cells, characterized by infiltration of other cells, a sustained inflammatory response and potentially cellular necrosis or cell death. Neither Dr. Schoen nor Dr. Wilson saw evidence of this in the microscopic pathology in any of the patients. Dr. Wilson testified that the passage of time prevented a diagnosis of cell death, but he found material consistent with previous cell death where silver particulate was present.

[354] Dr. Williams' research and the Oloffs study that I referred to earlier, demonstrate that silver particulate can be tolerated at a cellular level. There are a number of implantable devices that release particulate matter, for example hip replacement devices which contain metals and polymers and release millions of particles into the tissue on a daily basis, usually without any adverse effect. Dr. Williams testified that if particulate in tissue is not having an adverse effect on macrophages, it is extremely likely that it is not having any toxic effect on that tissue. Dr. Schoen saw "very little inflammatory reaction to the black particles and characteristically, as is observed in many other studies, a substantial inflammatory reaction to Dacron".

[355] The plaintiffs rely on case reports by Dr. Butany and Dr. Tozzi to conclude that Silzone is a causal factor in abnormal healing. These reports raise no more than hypotheses and speculation that the tissue appearance observed by these investigators was caused by some toxic injury.[87] Dr. Butany confirmed in his testimony that this was "purely speculative" and that he had "absolutely no proof" that the elemental silver leached from the sewing cuff and killed myocytes that led to tissue necrosis. Similarly, Dr. Schaff testified that the statement in the 2002 AVERT Annals Paper that "it appears that the Silzone coating inhibits normal fibroblast response and

[87] Tozzi et al. (2001); Butany et al. (2002); Butany et al, (2006).

incorporation of the fabric of the sewing ring into host tissue in some patients", was "a poor hypothesis to explain the increased frequency of the finding of poor tissue ingrowth in paravalvular leaks".[88]

[356] Finally, Dr. Wilson's theory does not explain how an allegedly toxic agent can cause both too much healing and too little healing in the same patient. As Dr. Schoen said, it is a contradictory hypothesis and biologically implausible. While the plaintiffs claim that silver may interfere with DNA and collagen synthesis, they also claim that excess tissue growth results from silver exposure. However, they provide no scientific evidence for their theory that damaging cell mechanisms will actually cause more cells to grow. The plaintiffs suggested some possibilities to account for the variability in pannus development seen in the 14 patients and during oral submissions provided me with references to the evidence they rely on. I have carefully considered this evidence, but I do not find it persuasive. I conclude that the most likely explanation for variable pannus formation is the healing variability that can occur in any mechanical heart valve patient, as Dr. Schoen testified.

Conclusion on 14 patient study

[357] The evidence shows that there are other medically plausible, and in some cases, more likely, explanations for the complications the patients experienced that Dr. Wilson did not exclude. The gross and microscopic appearances of poor pannus development and "abnormal" healing that Mr. Butchart and Dr. Wilson described occur with all types of prosthetic heart valves. At best, this study provides anecdotal evidence of less than ideal healing in 14 patients who all had medical complications. This evidence needs to be balanced against other anecdotal evidence from a number of surgeons who testified at trial that the majority of Silzone valves, implanted between 1997 and 2000, are still in place and have performed well over many years.

[358] Dr. Wilson's theories, like those of Drs. Butany and Tozzi, are no more than hypotheses. His methods would not generally be accepted in the scientific community to prove a causal relationship between Silzone and impaired tissue healing, but even if acceptable, his opinions are

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[88] Schaff et al. (2002) ["AVERT Annals Paper"].

convincingly contradicted by Dr. Schoen who saw no different or unique healing reaction with Silzone valves in the patients he reviewed than he has seen in many other valves over a long career. Dr. Wilson's study does not provide reliable evidence that Silzone causes disordered healing and adverse events. It does not establish on a balance of probabilities that Silzone has any different or adverse effect on tissue healing than uncoated Dacron.

Conclusion on Common Issue 2

[359] There is no reliable evidence to support the plaintiffs' theory that silver is toxic and is the mechanism by which the Silzone coating interferes with the proper development of pannus to impair or delay tissue healing or damage existing annular tissue in the heart. St. Jude's *in vitro* testing included standardized toxicity and mouse and human fibroblast tests and confirmed that Silzone exerted little potential to be toxic. The sheep studies established that good tissue ingrowth and comparable healing occurred in the sewing cuff and no toxicity was seen in the LIMRA study.

[360] While any material can be toxic at some dosage, the scientific literature establishes that silver has a low potential for toxicity. The studies on which the plaintiffs rely primarily involve large doses of fast dissolving silver salts rather than a tiny amount of metallic silver slowly releasing ions largely bound to albumin or other proteins/substances and not bioavailable to affect tissue. Neither of the plaintiffs' toxicologists gave a clear opinion that Silzone is toxic and the evidence of the defendants' experts, supported by a wealth of scientific literature, persuades me that it is not.

[361] I have not overlooked the plaintiffs' submissions that additional evidence of the effect of Silzone on tissue healing can be derived from Dr. Wilson's microscopic evaluation of an unimplanted Silzone valve; the AVERT data, (showing a statistical and causal association between Silzone and PVL during the first two years post implant); the FERs; and the Top Accounts survey. None of this evidence persuades me that a Silzone coating on a heart valve has any different or adverse effect on tissue healing than a valve without Silzone.

[362] A Silzone coating on a heart valve sewing cuff has no adverse or different effect on tissue healing than uncoated Dacron.

COMMON ISSUE 3

Does a Silzone coating on heart valves, or annuloplasty rings, materially increase the risk of various medical complications including, but not limited to, paravalvular leakage, thrombosis, thromboembolism, stroke, heart attacks, endocarditis or death?

[363] Common Issue 3 is also a question of general causation. It directs the court to determine whether Silzone materially increases the risk of various medical complications. As there is a risk of medical complications with all mechanical heart valves, Common Issue 3 asks whether these risks are greater for patients with Silzone valves than they are for those with the conventional St. Jude valve. The parties agree that the answer to Common Issue 3 can be found in the epidemiological evidence. They disagree on (1) which epidemiological evidence is the most reliable in respect of each complication, (2) how that evidence should be analyzed, and (3) the standard the court should apply to that evidence in determining whether or not Silzone *materially increases* the risk of a particular complication – in other words, how the word "materially" should be interpreted and applied.

[364] The plaintiffs adduced evidence from Dr. Madigan, a professor and chair of the Department of Statistics at Columbia University, and Dr. Sackett, a Professor Emeritus in clinical epidemiology and biostatistics at McMaster University. They also rely on the evidence of Mr. Butchart, Senior Cardiovascular Surgeon at University Hospital of Wales, and the data derived from two studies he conducted known as the Cardiff Embolic Risk Factor Study (CERFS) and the Cardiff Late Review (CLR). The defendants' main expert witness under this common issue was Dr. Wells, a biostatistician and epidemiologist, and Director of the Cardiovascular Research Methods Centre at the University of Ottawa Heart Institute. The defendants also adduced evidence from Dr. Hirsh, a Professor Emeritus in the Department of Medicine at McMaster University. All of the experts are highly qualified in their respective areas, but in many cases they took different approaches to analyzing the epidemiological evidence.

Overview of Epidemiological Evidence

[365] For the definition of epidemiology, I adopt the language of Justice Osler in *Rothwell*, at para. 51:

> Epidemiology may be described as the study, control and prevention of disease with respect to the population as a whole, or to defined groups thereof, as distinguished from disease in individuals. Clinical epidemiological studies can be carried out for the purpose of investigating the relationship between a particular condition existing in the environment, or population, and a particular disease or condition of health.

[366] As I discussed earlier in these reasons, there is a recognized hierarchy of epidemiological studies in the scientific literature.[89] At the top of this hierarchy is the randomized control trial or RCT. RCTs derive their substantial evidentiary value from the process of randomization whereby patients are randomly assigned to either receive or not receive a given treatment. In AVERT, for example, patients were randomly allocated to receive either a Silzone valve or a conventional valve.

[367] Randomization provides the best means of balancing for known and unknown background factors in each of the groups being compared that may otherwise confound the outcome of a study. Randomization acts to equalize the prevalence of potential causal factors between groups. As such, when patients are randomized, observed differences between the two groups can more reasonably be attributed to the difference in treatment, since that is the only remaining difference, other than in outcomes, between the groups. All experts agreed that RCTs are considered to be the gold standard in comparing one treatment with another treatment in order to draw inferences about causation.

[368] Below the RCT on the hierarchy of epidemiological studies is the cohort study. A cohort study is an observational study in which patients have not been randomized. Results from a cohort study are generally not accepted as evidence of causation because they do not have the benefit of randomization and, as a result, known and unknown potential causes of observed differences between groups cannot be ruled out.

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[89] See *Rothwell*.

[369] Below the cohort study is the case series. A case series is a collection of anecdotal accounts of a particular outcome of interest in a group of patients with a given characteristic (e.g. a Silzone heart valve). A case series can address the question of what the frequency of occurrence of that outcome is in the patients in that group but it cannot on its own provide reliable evidence that the characteristic is causal of the outcome since there is no control group. Unlike a RCT, there is no corresponding group of patients that is exactly the same as the group studied except for the given characteristic.

[370] The court was presented with evidence from each type of epidemiological study. AVERT is a RCT. CERFS was a cohort study. Top Accounts and CLR were case series. I will discuss the AVERT study in detail below. Because CERFS, CLR and Top Accounts only studied thromboembolism, I will discuss them in more detail when I consider that complication later in these reasons.

AVERT

[371] AVERT was designed as an efficacy study to assess whether Silzone was clinically effective at reducing the incidence of prosthetic valve endocarditis, but the AVERT Protocol also made provision for collecting data on adverse events. St. Jude was the sponsor of the study. Key participants in the design of AVERT were Drs. Schaff and Carrel, the study's principal investigators; Dr. Grunkemeier, a consulting statistician; and Dr. Steckelberg, an infectious disease specialist. Drs. Schaff and Carrel were instrumental in proposing and designing AVERT as a randomized, multicentre, international study and participated in drafting the Protocol, aided by input from Drs. Grunkemeier and Steckelberg. In order for AVERT to have sufficient power to detect a 50% reduction in endocarditis in the Silzone arm of the study, Dr. Grunkemeier recommended a randomized sample size of 4400 patients.

[372] Given the sheer size of the study, and as discussed in the Introduction, St. Jude determined that it would require a data coordinating center to receive reports from the various clinical centers and maintain a database for the study. Based on recommendations from Drs. Schaff and Carrel, the University of Pittsburgh Epidemiology Data Coordinating Center (DCC) was selected for this task. The AVERT Protocol was finalized on July 17, 1998. The AVERT study was to have 17 sites – 10 in North America and 7 in Europe. Dr. Schaff was to serve as

Principal Investigator in North America and Dr. Carrel was to serve as Principal Investigator in Europe. The DCC was to perform the monitoring and audit functions in North America, while Medpass International was to fulfill these functions in Europe.

[373] A Data Safety Monitoring Board (DSMB) was established at the start of AVERT. The role of the DSMB was to review the AVERT data and make recommendations as to the conduct of the study having regard to the safety of enrolled patients. It was to operate independently from St. Jude and the DCC. Members of the DSMB were selected by the DCC and they included leading experts in relevant fields.

[374] On January 21, 2000, the DSMB convened by conference call. Given strong evidence of a higher rate of explant in Silzone valve patients than in conventional valve patients, the DSMB recommended that enrolment in AVERT cease immediately. By that time, 807 patients were enrolled in AVERT; 403 with Silzone valves, and 404 with conventional valves. It is these patients who have been followed from the start of AVERT until present. At various points of time, a "data freeze" was conducted whereby the data up to a certain date were compiled for analysis. For example, the October 6, 1999 data freeze simply includes all data from AVERT up until that date.

[375] The plaintiffs acknowledge that AVERT is a well designed efficacy study benefitting from being large, multicentered and randomized. However, they point to limitations in AVERT that, according to the plaintiffs, undermine its reliability, namely, they argue that (i) its design as an efficacy study focusing on the endpoint of endocarditis resulted in the underreporting of adverse events; (ii) inadequate data collection on TE events resulted in the underreporting of TE events; (iii) "improper" adjudication of TE events also resulted in their underreporting; and (iv) "improper" adjudication of the AVERT data on PVLs resulted in the underreporting of PVLs.

[376] With respect to (ii) and (iii), above, the plaintiffs adduce these arguments to support their submission that I should consider data from CERFS and CLR in assessing the risk of thromboembolism (which I will also refer to as TE events) posed by the Silzone valve. I will deal with these arguments when I discuss thromboembolism later in these reasons. Likewise, I will deal with point (iv), above, when I discuss PVL.

[377] With respect to point (i), the plaintiffs note that because AVERT is an efficacy study focused on the endpoint of endocarditis, patients whose valves are explanted are withdrawn from the study and no further events are recorded in respect of those patients. The plaintiffs argue that this is problematic because it fails to account for adverse events that occur post-explant the etiology of which may be associated either with Silzone or the risk created by explant surgeries that would not have been required but for the presence of Silzone.

[378] The plaintiffs did not direct me to any expert evidence indicating that this is a legitimate concern. In fact, as I will discuss below, despite this argument of the plaintiffs, experts for both parties relied almost exclusively on the AVERT data in assessing the risks posed by Silzone, demonstrating that they view it as the most reliable data. Without support from expert testimony I cannot conclude that the plaintiffs' argument in this regard has merit.

The Experts Relied on AVERT

[379] While I will consider the plaintiffs' criticisms of AVERT in more detail when I discuss specific complications later in these reasons, I note that the plaintiffs cite limitations in AVERT to direct me to use other epidemiological evidence (CERFS and CLR) in my assessment of the risk of medical complications posed by the Silzone valve. The key inquiry, then, is whether the limitations they cite sufficiently undermine the reliability of the AVERT data that other epidemiological evidence is more reliable in respect of certain complications.

[380] In that vein, the best evidence before me for comparing the value of the epidemiological studies is the opinions of the expert witnesses in epidemiology and statistics. The fact that those experts, for both the defendants and the plaintiffs, relied on AVERT in assessing the risks posed by the Silzone valve demonstrates their opinion that AVERT is the most reliable data. When Dr. Sackett, the plaintiffs' expert in epidemiology, was asked if he believed AVERT was the best scientific evidence available to assess the risks and benefits of Silzone, he responded unequivocally: "absolutely". The plaintiffs' expert in statistics, Dr. Madigan, also relied only on the AVERT data.

[381] Only Mr. Butchart supported the use of other epidemiological evidence – namely, CERFS and CLR – and only in assessing the risk of thromboembolism. I will discuss his evidence in more detail when I discuss thromboembolism later in these reasons.

[382] Faced with the clear opinion of the expert witnesses for both parties that AVERT constitutes the most reliable data for assessing the risk of medical complications associated with the Silzone valve, I have difficulty understanding how I could come to any other conclusion.

The Nature of Epidemiological Evidence

[383] As I noted above, citing Justice Osler in *Rothwell*, clinical epidemiological studies can be carried out for the purpose of investigating the relationship between a particular condition existing in the environment, or population, and a particular disease or condition of health.[90] Earlier in his reasons, at para. 49, Justice Osler noted that "[t]he design, organization and interpretation of such studies are the province of epidemiology and they involve, to some degree, the discipline or science of statistics".

[384] In the present case, statistical epidemiological evidence has been presented to aid me in determining whether or not Silzone valve patients experience a higher risk of medical complications than conventional valve patients. In other words, the purpose of this evidence is to determine the risk of medical complications posed by the Silzone valve *relative to* the risk posed by the conventional valve. This introduces the concept of *relative risk*. A relative risk (or "risk ratio" or "hazard ratio") is a numerical expression of the risk of medical complications for one class of patients relative to another. In *Rothwell*, at para. 82, Justice Osler used the following example to illustrate the concept of relative risk:

> Suppose 5% of babies born to mothers who do not smoke weigh less than the normal weights for their gestation at the time of birth, but 15% of the babies of mothers who do smoke are underweight. The relative risk of being light weight at birth for the infants of smoking mothers is 15% over 5% or 3. In other words, an infant whose mother smokes has three times the absolute risk of being underweight when born than the infant whose mother does not smoke.

[385] In the present case, the simplest manner of calculating the relative risk for each complication is to divide the number of instances of that complication in the Silzone arm of AVERT by the number in the conventional arm. For example, if there were 150 instances of a

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[90] At para. 51.

complication in the Silzone arm and 100 in the conventional arm, this would yield a risk ratio of 150/100 = 1.5. A risk ratio of 1.0 for a given complication indicates that the risk of that complication is the same for both Silzone and conventional valve patients. A risk ratio of 2.0 indicates that the risk of that complication in Silzone patients is double the risk in conventional patients.

[386] Performing the calculation described above will only yield an *estimate* of the relative risk for that complication. This is referred to as the *point estimate* of the relative risk for that complication. The point estimate is essentially the "best guess" of the true risk ratio. Where, as in the example above, the point estimate is 1.5, this means that the data demonstrate that there is a 50% chance that the true risk ratio is above 1.5, and a 50% chance that it is below 1.5. In other words, the point estimate is the average of the possible values of the true risk ratio.

[387] While the point estimate can be useful in assessing the degree of risk facing Silzone versus conventional valve patients, more information is required to assess the reliability of the point estimate. The mere fact that a relative risk is above 1.0, indicating a higher risk facing Silzone valve patients, is insufficient to determine that Silzone valves actually do present a higher risk than conventional valves. This is because chance can never be ruled out as the causal factor driving a statistical result. In assessing the reliability of statistical results, the most important factor to consider is the likelihood that the result is the product of chance. As Justice Osler noted in *Rothwell*, at para. 66:

> The possibility that two events may coincide by pure chance and without the intervention of any necessarily causal effect can never be entirely eliminated. The effort of those who design statistical and epidemiological studies is always directed to minimizing the probability of chance and the effect that it will have upon the results of the study.

[388] As Dr. Wells testified, in order to determine the likelihood that a statistical result is not simply the product of chance, scientists perform a statistical test on the study results. The test reveals the probability that the observed result is the product of chance. Dr. Wells emphasized the central importance of *statistical significance* as the threshold for determining whether a statistical result is the product of chance. If the probability that a statistical result is the product

of chance is less than 5% the result is considered statistically significant, meaning chance is considered to be an unlikely explanation for the result. The importance of statistical significance was never questioned by any of the experts for either party.

[389] Statistical significance can be expressed in terms of both a *confidence interval* and a *p-value*. The p-value represents the probability that the data are sufficient to reject a given hypothesis. For example, in AVERT, given the hypothesis that the Silzone valve and the conventional valve present the same degree of risk for a certain complication, the p-value represents the probability that this is true. In other words, it represents the probability that there is no difference in the risk faced by Silzone versus conventional valve patients. In order for a p-value to be statistically significant, it must be less than 0.05, meaning there is less than a 5% chance that the hypothesis is correct – that the Silzone and conventional valve present the same degree of risk. In other words, where the p-value is 0.05, we are 95% certain that the Silzone valve presents a greater degree of risk than the conventional valve. In terms of risk ratios, this would mean that we are 95% certain that the true risk ratio is greater than 1.0.

[390] The confidence interval represents the range of values for the risk ratio within which, based on the data, a statistician can be 95% confident the true value for the risk ratio lies. For example, where the point estimate for a risk ratio is 1.5, the range for the confidence interval may span from 0.7 to 2.3. This would mean that, based on the data, one can be 95% certain that the true risk ratio lies somewhere between 0.7 and 2.3. In the present example, the lower end of the confidence interval is 0.7 and the upper end is 2.3. For the data to demonstrate a statistically significant increased risk in Silzone valve patients, the lower end of the confidence interval must be above 1.0. Thus, a statistically significant result is observed where the p-value is less than 0.05 and the lower end of the confidence interval for the risk ratio is at least 1.0.

[391] As I indicated above, the importance of statistical significance in assessing the reliability of statistical results was never seriously questioned by experts for either party. Dr. Wells testified that in determining whether there is evidence of a difference (for example, between the Silzone valve and the conventional valve), “the role of statistical significance is central in this whole process”. Likewise, Drs. Madigan and Sackett agreed that where the difference disclosed in a study is not statistically significant, the convention amongst scientists is to treat this as an

absence of evidence of a real difference. This is consistent with Justice Osler's observation in *Rothwell* at para. 69 that, "[i]t must suffice to say, and I do not believe this assumption was challenged by any witness or by counsel, that medical and biological science has adopted what is called the 5% level of statistical significance as the criterion by which to judge the possible effects of chance".

[392] Likewise, I note that the experts and counsel for both parties in this case frequently referred to statistical significance in discussing statistical results, demonstrating its central importance in assessing the reliability of those results. As I indicated in the Introduction to these reasons, I think the message of *R. v. J.-L.J.*, in which the relevance of the *Daubert* criteria was recognized by the Supreme Court, is that the court ought to assess the weight to be given to individual pieces of scientific evidence using the same methods and principles generally accepted and applied in the relevant scientific communities. It is uncontroversial to note that scientists employ statistical significance in assessing the reliability of epidemiological evidence. As such, I must do so as well.

The Limits of Epidemiological Evidence

[393] Given the importance of epidemiological evidence in this case, I think it is necessary for me to articulate its limitations in determining causation. Epidemiology is the study, control and prevention of disease and other health-related outcomes in *populations*, rather than in *individuals*.

[394] The Ontario Workplace Safety and Insurance Tribunal (WSIAT) has considered epidemiological evidence on many occasions, and I believe its words of caution are apposite here. In *Decision No. 1685/04*,[91] the WSIAT stated some relevant principles with respect to epidemiological evidence (the decision was related to workers who developed cancer after exposure to asbestos):

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[91] 2010 ONWSIAT 2513.

a) "Epidemiology cannot determine which particular factor caused a particular person's disease but only what factors are statistically associated with the occurrence of disease in groups of people".[92]

b) "Since epidemiology studies populations, not individuals, it cannot prove that a particular worker's cancer was caused by the studied exposure".[93]

c) The converse is also true: epidemiology cannot establish that the adverse event was *not* caused in a particular worker. "Epidemiology's usefulness in a claim relates more to issues of risk and the studies cannot prove or disprove causation in an individual case".[94]

[395] As such, epidemiological evidence ought not to be considered determinative in respect of causation in individuals. For example, in the present case, where the epidemiological evidence demonstrates a statistically significant increase in the risk of a complication in Silzone valve patients, this does not mean that all Silzone valve patients who suffer the complication would not have suffered it but for Silzone. Likewise, where the epidemiological evidence does not demonstrate an increased risk of a complication in Silzone valve patients, this does not demonstrate determinatively that Silzone did not cause that complication in any individual patients. In short, epidemiological evidence is not determinative of individual causation.

The Bradford Hill Criteria

[396] The defendants argue that I must determine if there is an *association* between Silzone and a given medical complication before I can determine if that association represents a *causal link*. They argue that epidemiological data, on its own, can only provide evidence of an association between a medical complication and the Silzone valve, and that the Bradford Hill criteria must be considered before a causal link can be inferred. In their submissions in respect of each complication the defendants applied the Bradford Hill criteria and, with the exception of major PVL in the first two years post implant, they argue that the criteria demonstrate that none of the statistical associations between the Silzone valve and medical complications are indicative of causal connections.

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[92] At para. 42.
[93] At para. 47.
[94] At para. 42.

[397] The Bradford Hill criteria are a series of indicia that scientists use to help determine if an association is causal. They help guide scientists in determining whether or not it makes sense to infer causality from an observed association. Dr. Wells testified that epidemiological studies can generally only demonstrate an association between an intervention and a complication, rather than a causal connection. He described the Bradford Hill criteria as a "framework in which to consider causation" that "brings up certain ideas that you should think about if you want to move from the word 'association' to the word 'causation'".

[398] In my view, the defendants' submission that I *must* consider the Bradford Hill criteria before making findings of causation is not supported by the evidence. Nor, for that matter, are their submissions regarding the application of the criteria to specific medical complications.

[399] The architect of the criteria, Sir Austin Bradford Hill, noted that his criteria are not "hard and fast rules of evidence that must be obeyed before we accept cause and effect",[95] and I note that the criteria have not been elevated to the status of a legal test before legal causation can be determined. In a draft policy paper from March 2005, which was referred to by the WSIAT,[96] the Workplace Safety and Insurance Board (WSIB) discussed the Bradford Hill criteria and noted that the absence of any of the criteria does not necessarily rule out a causal relationship.[97]

[400] Similarly, Dr. Wells was far from adamant that I must consider the Bradford Hill criteria in order to make determinations of causation. Rather, he testified that he uses the criteria "just as things to think about". He also said that "[the Bradford Hill criteria] are often used, but as I have indicated, I like to use it more as a framework providing general guidance than as a specific course of action that you must follow".

[401] In the context of interpreting the results of a RCT, Dr. Sackett also did not agree with the defendants' position that it is necessary to consider the Bradford Hill criteria. During an exchange regarding the contents of a text on evidence-based medicine authored by him, Dr.

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[95] Bradford Hill, A. (1965) at page 299.
[96] *Decision No. 646/00R2*, 2006 ONWSIAT 2526.
[97] Medical and Occupational Disease Policy Branch and the Occupational Disease and Survivor Benefits Program, "Taking ODAP into the future: A protocol for occupational disease policy development and claims adjudication," Draft – March 2005 (Toronto: WSIB, 2005) at page 20.

Sackett was asked about whether a section concerning the application of the Bradford Hill criteria indicates that they ought to be applied to RCTs:

> Q: And there's a section on page 155 that starts out: "Are the results of this harm/tiology study valid?[sic]" do you see that?
>
> A: Right.
>
> Q: And this would apply to a variety of types of clinical studies, correct?
>
> A: Again these would almost always be observational studies. That is, they would be the case control or cohort studies, they wouldn't be randomized trials that we'd be talking about here.
>
> Q: Do you agree with me that you don't say, and you can take the time to read it, that you don't say in this section under "Are the results of this… study valid" anywhere that it doesn't apply to a randomized control trial?
>
> A: It's not that it doesn't apply, it's that you wouldn't begin to apply it.
>
> Q: But what it says –
>
> A: I'll take your word that I didn't say it. *But what I'm saying is, if there was a randomized control trial, you wouldn't be concerned about these sorts of issues*.
>
> …
>
> Q: You agree that you need to look at those factors even in assessing the validity of a randomized control trial?
>
> A: *No*. [emphasis added]

[402] What I take from Dr. Sackett's testimony is that he does not agree that the Bradford Hill criteria need to be considered when interpreting a RCT. Rather, in his opinion, the Bradford Hill criteria are useful when interpreting the results of studies that are lower in the hierarchy of epidemiological evidence. I also note that counsel for the defendants' emphasized Dr. Sackett's expertise in the area of epidemiology, stating that he is "probably the most expert on the issue of epidemiological evidence" on the plaintiffs' side. Thus, in my view, the expert evidence does not support the defendants' argument that I must consider the Bradford Hill criteria in assessing the AVERT data.

[403] Further, even if I were to accept that I must apply the Bradford Hill criteria, in my view, I could not do so without the aid of expert testimony. That is, which criteria ought to be considered in interpreting the data for any given complication, as well as the weight that should be given to those criteria, are questions that can only be properly answered by a scientist with the appropriate expertise.

[404] However, no expert testified as to whether and how any of the criteria ought to be applied in respect of any of the complications in question under this common issue. All I have in this regard are the defendants' bald assertions that, having regard to the criteria, none of the statistical associations in AVERT are indicative of a causal connection, except for major PVL in the first two years post implant.

[405] In my view, neither I, nor counsel for the defendants, are properly qualified to assess whether and how the criteria ought to be applied in respect of any particular complication. In fact, even Dr. Wells did not consider himself properly qualified to assess whether and how to consider the criteria. Regarding the data from AVERT for death, Dr. Wells felt he was not qualified to properly consider one of the Bradford Hill criteria: biological plausibility. He stated: "I think it is not in my expertise, but it would be in someone else's expertise to say what is the biological rationale or plausibility [that Silzone causes deaths]". Given Dr. Wells' attestation that he is not qualified to apply this criterion, I do not believe I or counsel for the defendants are so qualified. Thus, in my view, the defendants' assertions for each complication regarding how I ought to apply the Bradford Hill criteria amount to nothing more than argument dressed up as evidence.

[406] For these reasons, I do not believe I am bound to consider the Bradford Hill criteria. Further, even if I were so bound, there is no reliable evidence before me that could support my applying and weighing the criteria in any particular manner.

How the Epidemiological Evidence should be Analyzed

[407] Having determined that AVERT, as a RCT, provides the best available evidence for assessing the relationship between the Silzone valve and medical complications, the next step is to consider the proper method of analyzing that data. While Dr. Madigan and Dr. Sackett for the plaintiffs and Dr. Wells for the defendants have all analyzed the same AVERT data, they applied

different statistical methods and arrived at different findings and conclusions in providing their opinions about whether the AVERT data shows that Silzone increases the risks of particular medical complications and, if so, when those risks are present.

[408] Dr. Wells performed a Kaplan-Meier/life table analysis with a log rank test of significance, using the pre-determined test of statistical significance under the AVERT Protocol, namely a p-value of 0.05 or less. Dr. Madigan used a Cox Proportional Hazards Model, a cohort analysis and a linearized rate analysis in analyzing the AVERT data. Dr. Sackett proposed a two-part test for harm that he applied to the results of Dr. Madigan's cohort analysis ("Dr. Sackett's two-part test"). Each of these methodologies is described below.

Time-to-Event Analysis: Kaplan Meier Curves and the Cox Proportional Hazards Model

[409] Time-to-event analysis refers to a method of analysis in which only the first occurrence of a particular medical complication in a patient is counted – subsequent events in the same patient are not. Once a patient experiences a complication, he or she is "censored", meaning that for the purposes of future calculations relating to that complication, he or she is excluded from the study. Patients are also censored for various other reasons such as death, loss to follow up, or explant of the valve. Two time-to-event curves (one for each treatment arm in a study), referred to as Kaplan-Meier ("KM") curves, are compared to each other in order to determine whether or not a difference exists between two study groups. KM curves, together with life tables (discussed below), are widely used in statistics and show how events/complications are occurring over time.

[410] In a KM analysis, the hazard ratio provides an estimate of the comparison of how the two groups perform with respect to the outcome of interest for the full time period under analysis. Dr. Wells testified that it "expresses the relative probability that an event will occur when the two groups are compared". As an estimate only, the hazard ratio has to be considered in relation to the 95% confidence interval to determine the precision of that estimate. A numerical comparison of two KM curves is performed through a log-rank test by putting the information into a formula to generate a p-value. This is then used to determine if there is a "real", or statistically significant difference between the groups.

[411] The Cox Proportional Hazards Model ("Cox model") is also a very widely used method in biostatistics that considers time-to-event rates, hazard ratios and p-values, similar to the KM approach. The Cox model, however, adjusts for influential variables in the analysis. Dr. Madigan testified that where there is evidence that variables influence the overall analysis, the Cox model is preferable to a KM analysis because it stratifies or adjusts for these variables. The variables said to be in issue in AVERT are study site and valve position – aortic or mitral. In RCTs, randomization is key since it should produce two groups that are comparable – all factors should be well-balanced in the two groups. For this reason, Dr. Wells disputed that a more complex Cox model was appropriate as any differences in patients at different sites would be accounted for by randomization. The AVERT Protocol did not contemplate using the Cox model to stratify by study site suggesting that the study organizers, who are all extremely experienced research scientists, were relying on randomization to perform this function.

[412] Dr. Wells and Dr. Hirsh took issue with Dr. Madigan's analysis of events by valve position as this is a sub-group analysis that may introduce confounders and compromise the integrity of randomization. A more reliable analysis of aortic and mitral valve patients would require that these groups be randomized separately, but in AVERT patients were not randomized by valve position. While some of the differences in the results obtained by Dr. Madigan and Dr. Wells can be explained by their choice of different statistical methods (KM versus Cox), Dr. Wells testified that he also "ran the Cox model" and found no material differences. This would be particularly so where the data did not show significant variation by either study site or valve position. In those cases, the choice of statistical method would make little difference.

[413] However, for some complications the choice of statistical method does make a significant difference. In those cases, there are two main reasons for preferring Dr. Wells' choice of a KM analysis. First, the Cox model was not the *a priori* method of analysis under the AVERT protocol. As such, its use gives rise to concerns about *post hoc* significance bias, that is, bias that arises when methodology is determined after data has been generated. The KM analysis employed by Dr. Wells is consistent with the analysis selected by the AVERT investigators before any data was produced and is the only analysis that does not give rise to this concern.

[414] A related, but arguably more important reason for preferring the KM method to the Cox model is that the KM analysis is the only analysis that does not forfeit the benefits of randomization. All experts agree that AVERT is the most reliable and scientifically valid data for evaluating the risks of complications associated with Silzone valves. This consensus derives from the fact that AVERT is a RCT. In my view, it follows that the most reliable method of determining whether there is an overall difference in the risk of a medical complication is an analysis of the AVERT data that preserves the initial randomization of the AVERT patients into the Silzone and non-Silzone groups.

Linearized Rates Analysis

[415] A linearized rate is an overall measure of the rate of occurrence of an event within a particular group. Unlike a KM analysis or the Cox model, patients are not censored from the study once they experience a complication. It is calculated based on the total number of events occurring in the group divided by the total exposure of the group in terms of person years of follow up multiplied by 100. It is presented in percentage terms per year (i.e. 1%/year). As a result, if there is a high frequency of events in a few patients in a group, this can skew the linearized rate upwards. In other words, patients who have multiple events because of their own particular risk factors may contribute excessively to the calculated event rate. It is therefore necessary to consider the rates to be approximate only and to adjust the rates for valve related events that can occur repeatedly as both the Edmunds and Akins Guidelines recommend. The Edmunds Guidelines are designed "to facilitate the analysis and reporting of results of operations on diseased cardiac valves", while the more recent Akins Guidelines are designed "to facilitate analysis and reporting of clinical results of various therapeutic approaches to diseased heart valves such that meaningful comparisons can be made and inferences drawn from investigations of medical, surgical, and percutaneous interventional treatment of patients with valvular heart disease".[98]

[98] Edmunds et al. (1996) [Edmunds Guidelines]; Akins et al. (2008) [Akins Guidelines].

[416] One of the main reasons for using linearized rates is to compare results to an external standard such as Objective Performance Criteria (OPCs).[99] Although a linearized rates analysis of the AVERT data was a method of analysis that was used by Dr. Schaff et al. in the AVERT Annals Paper, Dr. Schaff testified that this was done because those interested in heart valves are familiar with the OPC rates, but he explained that a linearized rates analysis is not necessary with a RCT such as AVERT. This is because there is already a comparator between Silzone and non-Silzone groups. Dr. Wells performed a linearized rates analysis of the AVERT data based on the September 2008 data freeze but only after the defendants were served with a report from Dr. Madigan that included such an analysis. Dr. Wells testified that this was not in his initial analysis plan. Like Dr. Schaff, he thought such an analysis was unnecessary as AVERT permits a direct comparison between the two groups.

[417] In his first expert report analyzing the AVERT data, Dr. Madigan did not perform a linearized rates analysis. He acknowledged that he performed this analysis at the request of counsel only after he had produced an analysis of the AVERT data in his first report. This gives rise to concerns about *post hoc* significance bias, because the decision to conduct a linearized rates analysis was only made after the results of the initial analysis were already known. Dr. Madigan's use of a linearized rates analysis is puzzling as he admitted that he did not compare his linearized rates with the OPCs. He testified that any comparison between OPC rates and rates in the AVERT study "runs the risk of being hopelessly confounded". The plaintiffs have not compared Dr. Madigan's linearized rates with OPCs or any other external factors or trials. This raises questions about why this analysis was done and the utility, if any, it has in addressing the questions that are before the court.

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[99] See, Footnote 39.

[418] I also have concerns about Dr. Madigan's methodology. Dr. Madigan admitted that he did not conduct his analysis in accordance with standard guidelines as he used a 90-day cut-off for early events rather than the more standard 30-day post implant cut-off that Dr. Wells used.[100] The 30 day cut-off is used in all the AVERT papers that included a linearized rates analysis as well as in the Heart Valve Guidance. It was also used by Mr. Butchart in his CERFS analysis. Dr. Wells' methodology also controls for the potentially misleading impact of multiple events in a few patients, although he presented his data in both ways. For these reasons, it is my view that Dr. Madigan's linearized rates analysis of the AVERT data is unreliable. I accept the defendants' submission that Dr. Wells' linearized rates analysis can be used as a check on his KM analysis, but a linearized rates analysis is unnecessary where there is data from a RCT and should be given much less weight.

Life Tables vs. Cohort Analysis

[419] The cohort analysis as well as the KM and accompanying life tables analysis are both tendered as evidence of *when* risk is present. That is, where there is evidence that the Silzone valve increases the risk of a complication overall over the duration of the AVERT trial, either the KM or the cohort analysis can be used to determine when during the trial the increased risk was present. I will first describe each of these two methods, before discussing which I find more reliable.

[420] Life Tables are presented in Dr. Wells' evidence as tabular versions of the information in the KM curves. They break down the distribution of time-to-event data into yearly intervals and are used to understand what is specifically happening within particular segments of the KM curve. While separate life tables are created for each treatment arm, Dr. Wells' evidence was that these tables are not used to compare or combine the results. Life tables are routinely used by demographers and actuaries not only as a means of determining the chances of an individual experiencing an event over a lifetime (e.g. overall number of car accidents experienced by men

[100] Referring to exhibit 921, the defendants note that despite purporting to use a 90-day cut-off, Dr. Madigan included 17 patients in his study who suffered embolisms within *30* days of implant, casting further doubt on the reliability of Dr. Madigan's linearized rates analysis. The plaintiffs say this was a clerical error that was corrected in the final calculations, but they present no evidence to support this assertion.

vs. women), but also when these events are occurring (e.g. at what age). The defendants submit that the life tables are the most reliable method for answering the questions raised in Common Issue 3 since they identify not only whether there is an increased risk in the Silzone valve group, but also when any such risk is present.

[421] Dr. Madigan used a cohort analysis to analyze and compare the relative risks of complications in the Silzone and standard-valve patients in successive cohorts. A cohort analysis looks forward in time and determines the overall prospective relative risk for a given complication at the beginning of each year. Patients are censored from the study for a given complication if they experience that complication, death, or explant. The year 1 cohort for a complication consists of all patients randomized into AVERT in either the Silzone or the conventional arm of the study. The year 2 cohort for a complication consists of all study patients who did not experience that complication before the start of year 2, or who were not otherwise censored from the study due to death or explant. The events used to calculate the relative risk for the year 2 cohort are those events that occurred *after* the start of year 2. The members of each successive cohort, and the events considered, from year 3 through year 9, are determined in the same manner.

[422] The KM and cohort analyses differ in what they disclose about the timing of risk. The cohort analysis attempts to show whether the relative risk of a particular event increases or abates over time. The KM analysis and accompanying life tables attempt to show when a patient is more at risk of experiencing a particular complication. In both analyses, patients are censored from the study at certain points, such as death or explant. However, as Dr. Wells testified, a KM analysis takes into account all of the AVERT data and analyzes that data as randomized. Where a patient has experienced an event or was censored from the study, data related to that patient continues to be included in the analysis – in other words, the key benefit of a RCT, namely randomization, is preserved. In contrast, with the exception of the Year 1 cohort, Dr. Madigan's analysis forfeits the benefits of randomization because the data for any particular year does not include all the patients in the AVERT trial. Data relating to those patients who had earlier experienced the complication is not included in the analysis of the rate ratios in subsequent years. As a result, data is being analyzed in subsets and there is no assurance that the Silzone and non-Silzone patients included in this subset are randomized. While the life table analysis also

presents data from a KM analysis on a yearly basis, Dr. Wells did not calculate hazard ratios for individual years. Thus, unlike Dr. Madigan's cohort analysis, Dr. Wells' analysis preserves randomization, and the life tables provide a means to understand trends in the KM curves by looking at the entire spectrum of randomized data.

[423] A further difficulty with the cohort analysis is that events in later years can skew the rate ratio and findings of statistical significance in earlier years. This was explained by Dr. Wells with reference to one of Dr. Madigan's slides:

> And so two things are going to come up. The first will be that if in year nine and the patient is in year nine, we find something that is quite statistically significant, which I have noted by that star, you have to remember that since year nine is also included in all the other cohorts, that the influence of that star could impact on all the other cohorts that he is going to look at. So that star, that yellow star in year nine could affect the year eight cohort; it could affect the year seven cohort, six, five, four, three, two, and even the one cohort. And an example that we have of this is death, okay, that the death reported in October 2009 in slide 78 of Dr. Madigan's, okay, and we saw this in the Kaplan-Meier curve, there was for whatever reason a big change in year nine and that big change in year nine, because the cohort, according to that yellow arrow, that particular cohort is embedded in all the others, it had the triggering effect of making all of those statistically significant. So to your eye, it may seem that something is going on all the time, but in reality, it may only be going on in the later years but impacting on the earlier years.

[424] As a result, with the cohort analysis, rate ratios and findings of statistical significance change from one data freeze to another, and not only for years where new data is obtained. This is illustrated by a comparison of the findings of Dr. Madigan's analysis of "all cause mortality" for the data freezes in September 2008 and October 2009.

Freeze	Yr 0	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Yr 7	Yr 8	Yr 9
Sept. 08	1.2	1.2	1.4	1.4	1.5*	1.6*	1.4	1.3	1.8	
Oct. 09		1.4*	1.6*	1.6*	1.8*	2.0*	1.8*	1.8*	2.6*	3.2*

*indicates a finding of statistical significance

[425] As can be seen from the above chart, the relative risk of "all cause mortality" changed between data freezes and now shows a statistically significant difference in this outcome throughout the life of the study. Based on data up until September 2008 (the top row), the

increased risk of mortality for Silzone patients was only statistically significant in years 4 and 5. When data from September 2008 to October 2009 is added to the analysis (the bottom row), it has the effect of making the risk ratio statistically significant for every year, despite the fact that the new data is only from year 9. A method of analysis in which data in later years can so drastically influence the calculated risk ratio for earlier years clearly provides an unreliable means for determining *when* a risk is present. In contrast, Dr. Wells' life table[101] shows that in terms of number of deaths, there are actually *more* deaths in the non-Silzone group up to the fourth year; the numbers are virtually identical at five years; and remain close up to 8 years. Unlike with life tables, it is impossible to know from the data in the cohort analysis what the risk of mortality was in any given year. Given our knowledge that there were actually more deaths in the non-Silzone group up until year 4, the fact that the cohort analysis for the October 2009 data freeze shows a risk ratio of 1.8 with statistical significance in that year graphically illustrates the unreliability of that analysis.

[426] The only expert testimony that was at all favourable to the cohort analysis came from Dr. Sackett who testified that it "made sense" to him. Dr. Madigan agreed that a cohort analysis is not recommended by the Edmunds Guidelines or Akins Guidelines or the Heart Valve Guidance. He acknowledged that he himself had not used this kind of analysis in any other study. There is no evidence that it has ever been used in the analysis of data from a prosthetic heart valve trial or in any RCT. Dr. Wells could not think of any example of either a randomized or non-randomized study where a cohort analysis had been used. For all these reasons, where the data shows an overall increased risk over the time period of the study (here, years 1 to 9 of AVERT), I find that the cohort analysis is not a scientifically reliable method of assessing *when* that risk is present within that timeframe. *When* the risk is present will be important in determining liability and damages, if any, at the individual stage of these proceedings. The most reliable evidence to assess this is Dr. Wells' KM analysis and accompanying life tables.

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[101] Exhibit#1443/14.

Dr. Sackett's Two-Part Test for Harm

[427] Dr. Sackett's two-part test for harm flows out of Dr. Madigan's cohort analysis. Until closing argument, it was unclear whether the plaintiffs were relying on the two-part test as a materiality standard under Common Issue 3, that is, a standard to determine whether the Silzone valve materially increases the risk of a particular medical complication. During oral submissions, the plaintiffs clarified that they were not relying on the two-part test for this purpose, but as a methodology to assess the risk of continuing harm. In fact, plaintiffs' counsel advised the court that "Drs. Madigan and Sackett decided they needed to come up with a method to assess whether the risk that was known to exist at one point in time was continuing".

[428] Dr. Sackett is an extremely distinguished epidemiologist, but his testimony was not persuasive. He admitted that the first time he proposed his two-part test for harm was during his direct examination at trial. Not only does his harm test not appear in any of his reports, but he provided no credible explanation for proposing this in his testimony, but not before. Given Dr. Madigan's admission that he had never before used a cohort analysis in any study, it appears that Dr. Sackett's two-part test and the cohort analysis to which it is linked were developed solely for the purposes of litigation and as such, must be looked at with considerable skepticism. As I have found the cohort analysis to be an unreliable methodology for determining when an increased risk is occurring, it follows that Dr. Sackett's application of his two-part test to the results of this analysis is similarly unreliable. Had I reached a different conclusion about the cohort analysis, I would nonetheless reject Dr. Sackett's two-part test for the following reasons.

[429] Dr. Sackett proposed applying two criteria to the rate ratios/relative risks derived from Dr. Madigan's analysis of the AVERT data. He testified there is evidence of harm if the point estimate of the relative risk for a particular year is greater than 1.0 and the upper end of the 95% confidence interval for that relative risk is greater than 2.0. Dr. Sackett supported his choice of the two criteria on the basis that while a point estimate greater than 1.0 can indicate there "might be a problem", the choice of a doubling of the risk at the upper end of the confidence level was "a low bar" and far greater than the one-third increase in risk that he said that a clinician or a patient would accept. He testified:

> A. Well, the approach that I used was, again, in terms of confidence would be a fairly low bar, but it would be, for the sake of argument, let's say that we would call it safe if it doesn't double the occurrence of some complication that occurs only once in awhile with our current treatment. In other words, would the confidence interval include a doubling of risk when we compare Silzone patients with standard valve patients as we continue this follow-up. I would have to admit that as a clinician, usually dealing with drug situations, most clinicians wouldn't tolerate a doubling as something that we would be willing to abide, that we would be quite concerned about increases of, you know, frequently increases of say 20 or 30 percent, not a hundred percent, would be a cause for concern among clinicians that I am dealing with. But I chose the doubling as a low bar.

[430] During his testimony, Dr. Sackett referred to a peer-reviewed paper co-authored by Dr. Wells as support for his two-part test, but Dr. Wells explained the many differences between the approach set out in that paper and Dr. Sackett's approach.[102] I am satisfied that to the extent Dr. Sackett was relying on the concept of minimally clinically important difference (MCID) as discussed in this paper, his reliance is misplaced. Importantly, the approach proposed in the paper is to compare the relative risk and confidence interval to the *predetermined* MCID for the study and not to the upper end of the confidence interval.

[431] An MCID refers to the smallest difference in the risk of an event that would lead a treatment provider to change a patient's management. MCIDs are selected *a priori* before a clinical trial begins as part of a study's design and are specific to certain outcomes. It is clear that Dr. Sackett did not do this, and it is unclear whether Dr. Sackett intended that 1.0 or 2.0 or some other number be considered the MCID for the purposes of his analysis. He offered no direct testimony on this, but the plaintiffs' submissions assume that the MCID in Dr. Sackett's two-part test is 2.0 "based on his clinical knowledge and judgment of patient values" and that this applies equally to all of the medical complications in issue. Dr. Wells testified that he also made the assumption that Dr. Sackett was using a MCID of 2.0 as this was the only way he could make sense of this criterion. The defendants submit that the only other choice for a MCID is 1.0

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[102] Man-Son-Hing et al. (2002).

because Dr. Sackett compares the point estimate relative risk to 1.0 to see if it is higher than 1.0. Dr. Wells testified that he had never seen a study where the MCID was set either *a priori* or *post hoc* at every number greater than 1.0.

[432] Dr. Wells' paper describes four different possible findings on clinical importance of study results: Definite, Probable, Possible and Definitely Not. The plaintiffs rely on the apparent choice of 2.0 as the MCID in Dr. Sackett's analysis and submit that his test contemplates that "if the point estimate of the relative risk is greater than one (whether statistically significant or not) and the upper end of the confidence interval includes the MCID, the study results are consistent with Silzone patients facing clinically important risks in later years".[103] The plaintiffs overlook that under the analysis used in the paper, this only shows results indicating *possible* clinical importance. Evidence that shows a possibility of harm is inconsistent with the plaintiffs' burden to prove causation on a balance of probabilities. In Dr. Wells' paper, it is only where both the upper end of the confidence interval and the point estimate of the relative risk are above the MCID that the study results show *probable* clinical importance.

[433] Dr. Sackett testified that he was concerned about the cases he described as "definite cases" of clinical significance, but under Dr. Wells' analysis, this requires that the *lower* end of the confidence interval be greater than the MCID. It is apparent that Dr. Sackett and Dr. Wells use very different definitions of "definite" clinical importance. Dr. Sackett's test would be met at its lowest threshold with a point estimate of just above 1.0 and an upper confidence interval just above 2.0, but the lower end of the confidence interval is never considered.

[434] To compound the lack of clarity around this evidence, Dr. Sackett, in response to a question from the court, prepared a diagram of his approach that showed the lower end of the confidence intervals in every case to be above 1.0, indicating statistical significance.[104] He

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[103] See Plaintiffs' submissions at paragraphs 1515 and 1574. The plaintiffs' Reply submissions appear to take a different approach and are confusing. They submit at paragraphs 679-681 that "the question should be about minimal clinically important differences" and that Dr. Sackett "established a specific range for [the MCID], that is, any relative risk between 1 and 1/3 and a doubling…" I am unable to reconcile this contradiction and can find no testimony of Dr. Sackett to support the proposition that he established a specific range for the MCID between 1 and 1/3 and a doubling. Indeed, it is unclear that he selected any MCID.

[104] Exhibit 641/1.

testified that even a statistically significant increased risk would not be clinically important unless the upper end of the confidence interval was above 2.0, indicating a doubling of the risk. Dr. Sackett recanted from this position in re-examination and testified that it did not matter to his approach if the lower end of the confidence interval was below 1.0. However, the diagram that he drew shows that for probable harm, the lower end of the confidence interval is above 1.0, indicating statistical significance, and the point estimate for the relative risk is above 2.0, or a doubling of the risk. This is in fact the standard that the defendants propose to determine if there is a material increase in risk.

[435] Dr. Hirsh testified that it was "flawed methodology" to ignore the lower end of the confidence interval simply because a treatment has been proven harmful in the past. As he testified: "[w]hy not just look at upper and lower confidence intervals because at a different point in time, it is possible that it moves in another direction. That it's no longer significant". Dr. Sackett was unable to identify any scientific paper that used a relative risk greater than 1.0 and the upper end of the confidence interval above 2.0 to draw conclusions about harm without statistical significance. Statistical significance is the widely accepted method of analyzing study results and was used in this trial by both Dr. Wells and Dr. Madigan. There is no evidence that Dr. Sackett's two criteria have been generally accepted by epidemiologists, statisticians or other research scientists. This leads me to conclude that his two-part test for harm is not reliable, and I reject it.

Does Silzone Materially Increase the Risk of Medical Complications?

[436] To determine whether Silzone materially increases the risk of medical complications, I must first identify the appropriate complications to consider. This is an area of considerable disagreement between the parties. For example, as I will discuss in more detail below, the parties disagree on whether or not all-cause mortality is a valid complication for me to consider. In addition, for many of the complications, the parties disagree on what evidence I ought to consider in making my determinations of materiality. In short, there are a number of complication-specific disagreements between the parties. I will now discuss my findings for each complication.

Paravalvular Leak (PVL)

[437] The risk of PVL is associated with all prosthetic heart valves. It is not defined in either the Edmunds or Akins Guidelines and is instead listed as a sub-category of non-structural dysfunction (NSD). The Heart Valve Guidance, discussed earlier in these reasons, refers to PVL as "any evidence of leakage of blood around the prosthesis between the sewing ring and the native annulus".

[438] The adverse event form in the AVERT Protocol had a box to record NSDs as adverse events, as well as a separate box to record whether the NSD was a PVL. It also included a box to note whether the PVL was "major" or "minor". However, "major" and "minor" PVL were not defined until after the recall of the Silzone valve. The proper category of PVL to analyze, including whether major and minor PVLs should be analyzed separately, is an area of contention between the parties.

[439] Based on the DSMB's finding of a significant increase in the rate of PVL leading to explants, the University of Pittsburgh worked with Dr. Schaff and in 2002 adopted a working definition of major PVL as "leaks that were followed either by a repair or an explant or a death". In January 2005, this definition was modified to mean a PVL that "results in reoperation, repair, re-intervention, explant, or death". Dr. Kennard explained the reasons for adopting the new definition as follows:

> After reviewing much of the data, we realized that this [the previous working definition of "major PVL"] really wasn't covering all cases correctly and, after discussions with Dr. Schaff again, we came up with a definition that was more precise and that definition was taken to the investigators for them to vote on whether they agreed with that definition of major paravalvular leak and they did agree.

[440] Once this definition was implemented, the DCC looked back at the previous data and adjudicated whether recorded PVLs met this definition. The plaintiffs argue that this process was flawed, and that Dr. Kennard and Sharon Lawlor performed inappropriate adjudications of the AVERT data that resulted in the underreporting of PVLs. I do not think it is necessary for me to go into detail discussing the plaintiffs' submissions in this regard, because, as I will explain below, I am not satisfied that any of the plaintiffs' alternative categories for PVL are reliable.

[441] Because of the lack of a pre-specified definition of major PVL in the AVERT Protocol, the changing definition after recall, and the resulting adjudications, Dr. Madigan was concerned about the validity of analyzing major PVL as an endpoint and did not do so. Rather, he counted all PVL events together, whether designated as major or minor. He analyzed PVLs using four different categories:

- "Non-Structural Dysfunction (NSD)" which included, but was not limited to PVLs
- "PVL (Echo)" which included events reported in the AVERT Echo Substudy which recorded leaks that were detected by echocardiography but not diagnosed clinically
- "PVL (AE)" which combined all PVLs diagnosed in AVERT and reported in accordance with the AVERT Protocol ("AE" stands for "adverse events")
- "PVL (AE+Echo)" which combined the PVL (Echo) and PVL (AE) categories

[442] In contrast, Dr. Wells, Dr. Schaff, and the DCC each distinguished between major and minor PVLs in their analyses. The defendants argue that any bias that might arise out of the changing definition of major PVL and the subsequent adjudications is minimal and, in any event, would tend to make the Silzone valve look worse than if the definition from the Heart Valve Guidance were adopted. Dr. Schaff testified that he had no concerns about biasing the AVERT study by changing the definition of major PVL and adjudicating the data based on the new definition, stating that "the purpose was to make [the recording of events as major PVLs] more accurate". I will briefly consider each of the categories that were used to analyze PVL.

Non-Structural Dysfunction

[443] In my view, non-structural dysfunction is an inappropriate category to analyze for determining the relative risk for PVL. As the defendants' experts pointed out, NSD includes a range of complications other than PVL, including many which have nothing to do with the sewing cuff and thus could not be attributed to Silzone. As a result, any determinations with respect to NSD would be unhelpful in determining whether Silzone increases the risk of PVL. When asked why AVERT analyzed PVL and not NSD, Dr. Schaff testified that "major paravalvular leak seems to be a more precise definition. If we left it in the category – if I left it in the category of non-structural dysfunction, I suppose one could wonder what is the non-structural

dysfunction; it could be any one of several problems. If you leave it under paravalvular leak, you know exactly what the problem is [sic]". No expert testified that NSD is a reliable category for me to analyze.

[444] Because NSD includes a range of complications, many of which are unrelated to the sewing cuff, I have determined that it is an inappropriate category to analyze.

PVL (Echo)

[445] The data in this category comes from the AVERT Echo Substudy which considered PVLs that were detected only by echocardiography rather than through the recognition of clinical symptoms. The records of these PVLs were kept in a separate database at the DCC from the PVLs that were clinically diagnosed. According to Dr. Kennard, the Echo Substudy was conducted because the DSMB recommended that an echocardiography substudy be undertaken in order to determine whether any AVERT patients who had not demonstrated clinical symptoms of paravalvular leakage nonetheless had PVLs. Of the patients who were eligible to participate in the Echo Substudy, about 85% did so. Only Dr. Madigan conducted a statistical analysis of the results from the Echo Substudy.

[446] Dr. Wells had two reasons for not considering the Echo Substudy. First, as a substudy that did not include all of the AVERT patients as randomized, it does not possess the benefits of randomization. Second, he was concerned that many of the PVLs detected would not be clinically relevant. That is, they would not be PVLs that would result in a clinical diagnosis and be reported on the AVERT Adverse Effects Form. The inclusion of non-clinically diagnosed PVLs could result in the overstatement of the risk of clinical PVLs.

[447] To limit the possibility that his analysis of the Echo Substudy would overstate the risk of clinical PVLs, Dr. Madigan included in the analysis only those PVLs which were designated as "moderate" or "severe". According to Mr. Butchart and Dr. Christakis, this would include only cases for which a clinical diagnosis would be likely. However, the plaintiffs adduced no direct evidence from a cardiographer that all, or even most, of the cases of PVL labelled as moderate or severe in the Echo Substudy would result in clinical symptoms. Notably, the majority of PVLs detected by echocardiography did not later progress to clinical PVLs, as evidenced by the AVERT Adverse Effects Forms.

[448] In my view, the Echo Substudy is unreliable because it forfeits the benefits of randomization and because it includes PVLs that would not, and did not, result in clinical symptoms. As such, it is not useful to me in determining whether Silzone increases the risk of clinical PVLs.

PVL (AE)

[449] PVL (AE) is Dr. Madigan's analysis of all clinically diagnosed PVLs in AVERT, counting major and minor PVLs together. The defendants argue that this is an inappropriate category for analysis because it will not provide meaningful information to the Court in individual trials. In support of this argument, they note that major and minor PVLs have very different consequences. They also argue that because the relative risk obtained from the PVL (AE) analysis is not specific to major or minor PVL, it is not useful in establishing causation for individuals, since individuals suffer either a major or a minor PVL, not a "PVL (AE)". In addition, as the defendants point out, the Heart Valve Guidance directs that paravalvular leaks "must be reported as major or minor". The plaintiffs argued that analyzing major and minor PVLs separately understates the risk ratios for both categories. However, no expert testified directly on this point.

[450] In my view, in the absence of any expert testimony to the contrary, the fact that the Heart Valve Guidance clearly directs that major and minor PVLs be reported separately indicates that it is inappropriate to treat them as a single complication. I am also mindful that the risk ratios derived from the PVL (AE) analysis would not be useful in determining causation in respect of individuals who suffered either a major or a minor PVL. As a result, it would be inappropriate for me to use the results of the PVL (AE) analysis in determining whether Silzone increases the risk of PVL.

PVL (AE+Echo)

[451] This category simply combines the PVLs from the "AE" and "Echo" categories. I find the "AE+Echo" category to be unreliable for the same reasons I discussed above in respect of the "AE" and "Echo" categories.

Dr. Wells' Analysis of PVL

[452] Dr. Wells analyzed major and minor PVL as separate complications. This approach is consistent with the Heart Valve Guidance, all other AVERT investigators save Dr. Madigan, and that of peer-reviewed publications on the AVERT study.[105] It also does not suffer the failings of the categories analyzed by Dr. Madigan, discussed above.

Major PVL

[453] Based on Dr. Wells' analysis of major PVL using the October 2009 data freeze, the defendants concede that on an overall basis the point estimate for the risk ratio for major PVL is 3.03 and that the increase in the risk of major PVL in Silzone valve patients is statistically significant. Dr. Wells' log-rank test of significance found a p-value of 0.01 (where below 0.05 indicates statistical significance).[106] However, with respect to *when* the increased risk is present, the defendants argue that the life table for major PVL makes clear that it is only in the first two years. Therefore, according to the defendants it can only be said that Silzone increases the risk of major PVL for two years post implant. As Dr. Wells explained by reference to the KM curves for major PVL:

> I compared the overall experience of the 400 [patients] in each of the two groups with respect to paravalvular leak, major paravalvular leak, and I'm finding a statistical difference between the two groups.
>
> The next step is to go back and say, well, where [*when*] is that difference occurring? *And as you rightly pointed out with this changing slope in the first year or two years, that is where the major difference is between the Silzone and non-Silzone have occurred* [sic]*, and after that the two curves run roughly parallel, indicating they have a very similar experience*. [emphasis added]

[105] See e.g. The AVERT Annals Paper.
[106] Exhibit 1444.

[454] The life table from AVERT for major PVL is as follows:[107]

Number of Months post implant	Number of Events in Silzone Group	Number of Events in Non-Silzone Group
0-12	10	3
12-24	4	0
24-36	1	1
36-48	0	1
48-60	2	1
60-72	0	0
72-84	0	0
84-96	0	0
96-108	1	0
108+	0	0

[455] The life table demonstrates that of the 18 instances of major PVL in the Silzone group, 14 were in the first two years. Out of six events in the non-Silzone group, three were in the first two years. Of patients who reached at least two years post implant, there were four major PVLs in Silzone valve patients and three in conventional valve patients. As Dr. Wells testified, and as is obvious from looking at the life table, the difference in the rate of major PVL in Silzone versus conventional valve patients can be almost entirely attributed to events in the first two years post implant. The defendants also cite two other studies that came to similar conclusions.[108] In my view, the evidence clearly demonstrates that it is more likely than not that Silzone causes an increase in the risk of major PVL for two years post implant, but not thereafter. I will discuss whether or not this increase constitutes a "material" increase later in these reasons.

Minor PVL

[456] With respect to minor PVL, as with major PVL, the defendants concede that the AVERT data demonstrates a statistically significant increase in the risk of minor PVL for Silzone valve patients but they argue that this increased risk is only present in the first two years post implant.

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[107] Exhibit 1443.
[108] Exhibits 284 and 285.

Using the October 2009 data freeze, on an overall basis, Dr. Wells calculated a point estimate of the risk ratio for minor PVL of 2.29, with a p-value of 0.03. As with major PVL, the life table is instructive with respect to *when* the increased risk is present. Dr. Wells' life table for minor PVL is as follows:[109]

Number of Months post implant	Number of Events in Silzone Group	Number of Events in Non-Silzone Group
0-12	10	4
12-24	4	3
24-36	2	0
36-48	0	0
48-60	1	0
60-72	2	1
72-84	0	0
84-96	0	1
96-108	0	0
108+	1	0

[457] The life table demonstrates that the rate of minor PVL doesn't drop off as dramatically after two years as the rate of major PVL in Silzone valve patients. In the first two years post implant, there were 14 minor PVLs in the Silzone group and seven in the conventional group. After two years post implant there were six in the Silzone group and two in the conventional group. However, for years 3 to 6 post implant, there were five minor PVLs in the Silzone group and only one in the conventional group.

[458] Unlike for major PVL, Dr. Wells did not testify directly that the increased risk for Silzone patients is only apparent in the first two years post implant. Also in contrast to major PVL, the defendants do not cite any other studies that conclude that the risk of minor PVL is higher in Silzone patients for only two years post implant. As can be seen in the life table above, for years 3 to 6 post implant, there were five minor PVLs in the Silzone group and only one in the conventional group. In my view, given this evidence, and given that on an overall basis Dr. Wells' analysis found a statistically significant increase in the risk of minor PVL, I believe it is more likely than not that Silzone increases the risk of minor PVL for *six* years, rather than only

[109] Exhibit 1443.

two years, post implant. The evidence does not demonstrate an increased risk for minor PVL in Silzone patients following six years post implant. I will consider whether or not this increased risk is "material" later in these reasons.

Thromboembolism (TE Events)

[459] Thromboembolism is defined in the Edmunds Guidelines as "any embolic event that occurs in the absence of infection after the immediate perioperative period (when anaesthesia-induced unconsciousness is completely reversed)". An embolic event occurs when an embolus (a detached intravascular mass) lodges itself somewhere in the body, causing a blockage. This is different than a thrombus, which is a blockage at the site of origin of the embolus. The Edmunds Guidelines definition was incorporated into the AVERT Protocol's definition of embolism and was further broken down into Neurologic Embolic Events, Peripheral Embolic Events and Myocardial Infarction (heart attack). The AVERT Adverse Effect Form contained these categories and also broke them down by severity and type of event.

[460] Neurologic Embolic Events were broken down into the following categories: transient ischemic attack (TIA), which is a fully reversible neurologic event that last less than 24 hours; Reversible ischemic neurologic deficit (RIND), which is a fully reversible neurologic deficit that lasts between 24 hours and 3 weeks; and stroke, which is a neurologic deficit that lasts more than 3 weeks or causes death. Peripheral Embolic Events and myocardial infarction were both broken down by severity on the AVERT Adverse Effect Form as minor, major, or fatal.

[461] As I noted earlier in these reasons, the plaintiffs, primarily on the basis of testimony from Mr. Butchart, point to limitations in AVERT that they argue undermine its reliability in assessing the risk of TE events. They argue that inadequate data collection for TE events and the "improper" adjudication of TE events resulted in their under reporting in AVERT. They also argue that because AVERT was originally designed as an efficacy study with a primary endpoint of endocarditis, it was not properly designed to assess the risk of TE events. The plaintiffs adduce these arguments to support their submission that I should also consider data from CERFS, CLR and Top Accounts in assessing the risk of TE events posed by the Silzone valve. I do not agree.

[462] As I stated earlier in these reasons, despite the alleged deficiencies in AVERT that the plaintiffs point to, all of the experts in epidemiology and statistics relied only on the AVERT data in assessing the risk of complications, including TE events, associated with the Silzone valve. I find that this fact overwhelmingly demonstrates that AVERT provides the most reliable data.

[463] The only expert who testified in favour of my considering CERFS, CLR and Top Accounts was Mr. Butchart, who himself conducted both CERFS and CLR. Given that Mr. Butchart was alone in this regard, and given the clear opinion of all of the other experts that AVERT provides the most reliable epidemiological data, I do not find it necessary to consider his evidence in detail. Nor do I think it is necessary to consider the deficiencies the plaintiffs' perceive in AVERT in any great detail. What follows is a synopsis of the parties' opposing arguments with respect to CERFS, CLR and Top Accounts, as well as my reasons for rejecting this evidence.

Cardiff Embolic Risk Factor Study (CERFS) and Top Accounts

[464] CERFS was a study led by Mr. Butchart that commenced in 1995 at the Cardiff Hospital in Wales to investigate thromboembolic events and risk factors associated with mechanical heart valves generally. The protocol called for approximately 200 patients being enrolled over a period of two years and originally included four different valves, including the St. Jude standard bi-leaflet valve, but *not* the Silzone valve. Even though the study was coming to an end, Mr. Butchart agreed to include the Silzone valve in the study after discussions with St. Jude in late 1996. It was originally intended that 100 Silzone patients would be enrolled in CERFS and that these patients would be included in the study consecutively rather than on a randomized basis. As with AVERT, the withdrawal of the valve from the market terminated enrolment in the study.

[465] CERFS was a relatively small study of 167 patients who were implanted with St. Jude mechanical valves; 116 with conventional valves and 51 with Silzone valves. Of these patients, 65 had mitral valve replacement (mitral alone or double valve replacement), with 46 receiving non-Silzone valves and only 19 receiving Silzone valves. The study found an increased risk of major TE in these 19 mitral valve recipients.

[466] Mr. Butchart endeavoured to corroborate his findings in CERFS by referring to the Top Accounts Survey, which was a case series. As I explained earlier in these reasons, case series are at the bottom of the hierarchy of epidemiological studies. Dr. Flory, for the defendants, reviewed the Top Accounts Survey to determine whether it supported Mr. Butchart's reports of higher TE events, and determined that it did not. Given the unreliability of case series in determining causation and the fact that no experts other than Mr. Butchart – including Drs. Madigan and Sackett – placed any reliance on it in assessing the Silzone valve, I place no weight on the Top Accounts Survey.

[467] The plaintiffs argue that CERFS provides more reliable data than AVERT in assessing the risk of TE events associated with the Silzone valve. They note that unlike AVERT, CERFS was specifically designed to assess the risk of TE events. They also argue that patient follow up in CERFS was more thorough than in AVERT.

[468] The defendants argue that the data from CERFS is unreliable for several reasons. They note that CERFS was a non-randomized cohort study with no contemporaneous control group. As such, it sits below AVERT on the hierarchy of epidemiological studies. It also involved only one hospital and a fairly small number of patients.

[469] As for the results of CERFS, I note that while Mr. Butchart found a higher incidence of TE events in patients with Silzone valves in the mitral position, this was based on only 19 patients in the study who were implanted with such valves. For all TE events overall, Mr. Butchart actually found the risks between Silzone and conventional valve patients to be almost identical. Mr. Butchart's finding in mitral valve patients is inherently unreliable because it constitutes a sub-group analysis, which, as Dr. Hirsh explained, is likely to be nothing more than a chance finding. The experts in epidemiology and statistics all agreed that sub-group analyses tend to be unreliable.

[470] While the plaintiffs note that CERFS, unlike AVERT, was designed to assess the risk of TE events posed by heart valves, the defendants point out that CERFS was not initially designed to consider Silzone valves at all. It was designed to assess the risk of TE events in conventional valves, not Silzone valves, and Silzone valves were only introduced into the study at the tail end of its originally planned duration.

[471] The defendants also argue that CERFS is unreliable because its findings have not been duplicated in other studies, and because Mr. Butchart used inappropriate methods to assess the data. They argue that his use of a linearized rates analysis, his comparison of Silzone complication rates to OPC rates, his use of complication rates reported in the medical literature for comparison purposes, and his failure to follow the Edmunds Guidelines in reporting complication rates from CERFS, all compromise the reliability of the data he derived from the study.

[472] It is not necessary for me to delve into the minutiae of either parties' arguments regarding the reliability (or lack thereof) of CERFS. The relatively small size of the study, and the fact that it took place entirely at one hospital counsel against its reliability. In addition, the most critical factor behind my determination that CERFS is less reliable than AVERT is that all of the experts in epidemiology and statistics, for both parties, relied on AVERT in making their determinations regarding causation. No expert other than Mr. Butchart testified that I ought to consider the findings in CERFS. I take this as compelling evidence that AVERT provides more reliable data than CERFS.

Cardiff Late Review (CLR)

[473] Sometime after the introduction of the Silzone valve into CERFS, the Cardiff Hospital began implanting Silzone valves in all mechanical heart valve patients. Following the recall of the Silzone valve, all patients who had been implanted with Silzone valves at the Cardiff Hospital were brought back for review by Mr. Butchart. This involved what the plaintiffs describe as a "full examination" by Mr. Butchart and his colleague Dr. Fraser of 55 Silzone patients. The majority of these patients were interviewed and examined in July, 2004. Hospital records and death certificates were also collected and examined for some patients who had died prior to the commencement of the review.

[474] In my view, CLR does not provide reliable evidence upon which to base findings of causation. It was a case series, and as such sits well below AVERT in the hierarchy of epidemiological studies. Unlike AVERT, CLR was conducted without the benefit of a control group and was not randomized. The data from CLR may be sufficient to support a hypothesis, but it is not sufficient to support a finding of legal causation. Dr. Hirsh testified that CLR does

not provide reliable evidence to support a causal relationship between Silzone and TE events. In addition, and most importantly, Drs. Madigan and Sackett did not rely on CLR in their analysis of the Silzone valve.

[475] For all of the above reasons, I will not consider the results of CERFS, CLR or Top Accounts in assessing the risk of TE events associated with the Silzone valve.

What the AVERT Data Demonstrates Regarding the Risk of Thromboembolism

[476] Based on the October 2009 data freeze, on an overall basis Dr. Wells found no statistically significant difference in the risk of any TE events in Silzone versus conventional valve patients.[110] Nor, in fact, did Dr. Madigan employing the Cox model. Thus, on an overall basis, employing time-to-first-event analyses, the data from AVERT demonstrate no statistically significant difference in the risk of TE events between Silzone and conventional valve patients.

[477] The only analysis to demonstrate any statistically significant difference in the risk of TE events facing Silzone versus conventional valve patients derives from linearized rates analyses. Earlier in these reasons, I determined that Dr. Wells' linearized rates analysis is reliable as a check on the findings of his KM analysis, but that Dr. Madigan's linearized rates analysis is unreliable. Dr. Wells only found a statistically significant difference in the risk of TE events in the Silzone versus the conventional valve for patients with valves in the mitral position, and only when he included outliers – that is, patients who experienced four or more events. When patients in the Silzone group who experienced four or more events are excluded, his finding loses statistical significance.

[478] As both Dr. Wells and Dr. Hirsh testified, analyzing data in sub-groups, such as by valve position, is problematic. As Dr. Hirsh testified:

> A. … Now, there is a statistical axiom that if the overall results were are [sic] not statistically significant, if you find a sub-group that is statistically significant… you've got to look at that with a great deal of circumspect because it means that there is another sub-group where the results goes in another direction [sic].

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[110] Exhibit 1444.

> Q. Just stopping there for a minute, which is then more important, the overall data or the sub-group data?
>
> A. Well, the overall data is the important data.

[479] Thus, Dr. Wells' finding of an increased risk of TE events in patients with mitral valves is unreliable as it is a sub-group analysis. In fact, Dr. Wells himself testified that this analysis is unreliable and explained that he only analyzed the data by valve position in order to respond to Mr. Butchart's analysis, which distinguished between aortic and mitral valve recipients. As indicated above, the overall data, which Dr. Hirsh testified is the most important, demonstrate no statistically significant difference in the risk of TE events facing Silzone versus conventional valve patients.

[480] Further, as Dr. Hirsh testified, because there was no randomization by valve position in AVERT, a sub-group analysis of the AVERT data by valve position is less reliable than the analysis of all positions together, because it is subject to confounding in a way that an analysis of the complete set of data – which maintains the benefits of randomization – is not.

[481] I find that the most reliable data with respect to TE events is Dr. Wells' KM analysis of the overall data from AVERT. As I stated above, Dr. Wells did not find a statistically significant difference in the risk of TE events facing Silzone versus conventional valve patients. The following table summarizes his overall findings, as of the October 2009 datafreeze, for TE events using the KM analysis:[111]

Complication	**Number of Events in Non-Silzone Group**	**Number of Events in Silzone Group**	**P-value (<0.05 = statistically significant)**	**Risk Ratio: point estimate (95% confidence interval)**
Thromboembolism	49	51	0.73	1.07 (0.77, 1.49)
Embolic Event - Stroke	14	18	0.41	1.34 (0.67, 2.69)
Embolic Event - RIND	7	11	0.31	1.62 (0.63, 4.18)
Embolic Event – Transient Ischemic Event	24	26	0.74	1.10 (0.63, 1.91)
Embolic Event – Myocardial Infarction	2	6	0.12	3.27 (0.66, 16.25)

[111] Exhibit 1444.

[482] I find that there is no reliable evidence demonstrating a statistically significant increased risk of TE events in Silzone versus conventional valve patients.

Bleeding

[483] Bleeding is defined in both the Akins and Edmunds Guidelines as "any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or necessitates transfusion". All mechanical heart valves require anticoagulation drugs to counter the thrombogenic potential of the housing and leaflets on the valve.[112] The thinner a patient's blood, the more likely the patient is to experience a bleeding event.

[484] The defendants argue that bleeding is not a meaningful endpoint to analyze because it was tracked without any analysis regarding whether each event was "valve related". They argue that without an analysis of valve relatedness, the category is not useful because it does not support a finding that observed differences between the Silzone and conventional groups are due to the presence of Silzone.

[485] In my view, the defendants' argument in this regard is not supported by the evidence. Both the Akins and Edmunds Guidelines require the collection and analysis of data on bleeding events without any mechanism to track whether such events are valve related. In addition, with a RCT like AVERT, there is no need to track events for valve relatedness because the whole objective of randomization is to ensure that observed differences between the two groups can be properly attributed to the fact that one group has Silzone valves while the other has conventional valves. No expert testified in support of the defendants' argument in this regard and I do not accept it.

[486] Nonetheless, the more significant fact is the fact that Dr. Wells' KM analysis found no statistically significant difference between the Silzone and conventional groups in terms of bleeding events. Dr. Wells' point estimate for the risk ratio was 1.35, with a p-value of 0.1. As discussed earlier in these reasons, a p-value above 0.05 indicates a lack of statistical significance.

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[112] Thrombogenic potential refers to the potential to produce thrombus that may cause a blockage either at the valve site or elsewhere in the body after breaking away and travelling through the bloodstream.

[487] The only analysis that found a statistically significant difference in the rate of bleeding events between the two groups was Dr. Madigan's Cox model analysis. However, for the reasons I discussed, Dr. Madigan's Cox model is less reliable than Dr. Wells' KM analysis. Where their results diverge, I prefer the analysis of Dr. Wells. I also note that Dr. Madigan's finding only barely reaches statistical significance, with a p-value of 0.04 and a confidence interval of 1.02 to 2.14.

[488] In the result, I find that there is no reliable evidence indicating a statistically significant difference in the rate of bleeding events between the Silzone and conventional valves.

Valve Thrombosis

[489] As I noted at the beginning of my discussion of TE events, above, valve thrombosis differs from TE events in that the former occurs on or near the operated valve whereas the latter occurs elsewhere in the body when a mass breaks away and travels through the bloodstream, eventually causing a blockage.

[490] Valve thrombosis is defined under the Edmunds Guidelines as "any thrombus, in the absence of infection, attached to or near an operated valve that occludes part of the blood flow path or that interferes with the function of the valve". This was the definition used in the AVERT Protocol. The plaintiffs argue that the AVERT investigators ought to have used the broader definition of valve thrombosis set out in the Akins Guidelines, and that the choice of the Edmunds Guidelines resulted in the underreporting of valve thrombosis. However, no expert testified that this is the case, and, in any event, I accept the defendants' argument that even if the choice of the Edmunds Guidelines definition resulted in underreporting, this would have affected both arms of the study equally due to the effect of randomization.

[491] As of the October 2009 data freeze, Dr. Wells calculated a point estimate for the risk ratio for valve thrombosis at 3.03, with a p-value of 0.31, indicating a lack of statistical significance. Notably, although the point estimate is high, the lack of statistical significance is a result of the fact that only 4 valve thrombosis events were recorded in AVERT; three in Silzone valve patients and one in a conventional valve patient. Both Dr. Madigan and Dr. Wells testified that

with so few events any statistical analysis is virtually meaningless. Both also agreed that there was no evidence of a statistically significant difference between the groups in terms of the rate of valve thrombosis.

[492] In my view, there is no reliable evidence of a difference in the risk of valve thrombosis in Silzone versus conventional valve patients.

TEB

[493] TEB is not a complication unto itself. Rather, it is a composite endpoint consisting of the last three complications considered above: thromboembolism, bleeding, and valve thrombosis. The defendants argue that for this reason TEB is not a meaningful endpoint for analysis. This is because even if I found that Silzone materially increases the risk of TEB, an individual bringing and individual claim would still need to demonstrate that they suffered one of the constituent complications in order to prove causation. For similar reasons, TEB was not an *a priori* complication for analysis under the AVERT Protocol. Rather, each of these three complications was analyzed separately.

[494] While it is not recognized by the Edmunds Guidelines, TEB first appeared in the Akins Guidelines in 2008. The plaintiffs note that Mr. Butchart, among others, has been advocating for the analysis of TEB as an endpoint because "thromboembolism and thrombus are part of the same complex, and the risk of bleeding is increased by the medical treatment of this complex".

[495] While the plaintiffs assert that TEB is a meaningful endpoint for analysis, they do not explain why. In their argument, the plaintiffs simply explain what TEB is, why it has developed as a newly recognized endpoint, and what the AVERT data shows. In my view, the reason TEB is suggested as an endpoint in the Akins Guidelines is to look at the combined hazards of thrombogenicity and anticoagulation and how they interact. TEB is not suggested as a useful endpoint for assessing the safety of a prosthetic heart valve. Indeed, other than repeating the general reasons for analyzing TEB as reflected in the Akins Guidelines, Mr. Butchart and Dr. Christakis provided no additional justification for analyzing TEB in the context of AVERT. As Dr. Hirsh testified, analyzing TEB as a category may be useful for comparing the efficacy or safety of anticoagulation drugs, but not for assessing the difference in the risks associated with Silzone versus conventional valves. Indeed, Dr. Hirsh "objected" to the plaintiffs' analysis.

[496] In the circumstances of AVERT, Dr. Hirsh's opinion was that there is no good reason to consider TEB as an endpoint. Similarly, Dr. Wells was of the opinion that an analysis of TEB was not useful for comparing the risks between the two valves. Dr. Wells was also concerned that analyzing TEB would introduce the risk of double-counting a finding of significance. For example, the risk ratio for TEB could reach statistical significance even where none of the risk ratios for the three constituent complications is statistically significant. If such were the case, a patient who suffered one of the constituent complications, for which statistical significance was not found, would be deemed to have suffered TEB, for which statistical significance was found. As such, the patient would erroneously be deemed to have suffered a complication for which statistical significance was not found. In the opinions of Dr. Wells and Dr. Hirsh, this demonstrates that TEB is not a useful endpoint for assessing the risk of complications.

[497] In my view, TEB is not an appropriate endpoint for me to consider. Dr. Wells and Dr. Hirsh clearly explained that TEB is useful for assessing the efficacy and safety of anticoagulation drugs, and not for assessing the risks associated with a prosthetic heart valve. Meanwhile, neither Mr. Butchart nor any other expert explained why TEB ought to be used as an endpoint. Rather, the only explanations given were the reasons for including TEB in the Akins Guidelines, which, as described above, only relate to assessing the impact of anticoagulation drugs and not to the efficacy of TEB in assessing the risk of a prosthetic heart valve.

[498] For all of the above reasons, I find that TEB is an inappropriate complication for me to consider under this common issue.

Death

[499] "Total deaths" is defined in the Edmunds Guidelines as "all deaths due to any cause after a valve operation". Those guidelines also define three subcategories: valve related mortality, sudden unexpected unexplained death, and cardiac death. The Akins Guidelines define "all-cause-mortality" as including "all deaths from any cause after a valve intervention". When deaths occurred in AVERT, the AVERT Adverse Effects Form directed that the cause of death be stipulated as "valve related", "other cardiac related", "other cause", or "unknown".

[500] The defendants argue that I should consider only the "valve related" category because it is the only category that can tell me whether a death can be properly attributed to the Silzone valve. The plaintiffs argue that I should consider only the broader category of "all-cause-mortality". I agree with the plaintiffs. In my view, the plaintiffs' position better accords with the expert testimony at trial.

[501] Both Drs. Madigan and Sackett testified that randomization in AVERT should equalize the influence of confounding variables between the two groups. I agree with this assessment. As I stated earlier in these reasons, a primary purpose of randomization is to ensure that observed differences in outcomes between the two groups (such as a difference in the rate of death) can be properly attributed to the difference in treatment between the two groups (one group has Silzone valves and the other has conventional valves). Dr. Sackett added that, in his opinion, all-cause-mortality is a more reliable category for analysis than the subcategories on the AVERT Adverse Effects Form because problems relating to data collection and reporting led to a disproportionate number of the deaths in AVERT being labelled as cause "unknown". In addition, Dr. Schaff testified that deaths that resulted from coronary embolism, cerebral bleed or stroke should be categorized as valve related under the Edmunds Guidelines. However, the listing of deaths prepared by Dr. Kennard and the DCC lists as non-valve related deaths that resulted from these very conditions. Thus, any analysis of deaths adjudicated as "valve related" is unreliable and likely underestimates the impact of the Silzone valve.

[502] The defendants submit that all-cause mortality is not a meaningful category because death can result from many causes that are unrelated to the Silzone valve. The defendants acknowledge that randomization can be expected to equalize the impact of confounding factors, but they argue that it cannot be expected to equalize for the "virtually unlimited" causes of death that may have arisen since the beginning of the AVERT trial. No expert testified in support of the defendants' position in this regard. The defendants also argue that the DSMB's request that the DCC investigate the causes of death after year 8 demonstrates their view that all-cause-mortality provides inadequate information. I do not agree. The reason the DSMB requested more information on the deaths that occurred after year 8 was because there was a substantial increase in the rate of death in the Silzone group after year 8. Their intention to investigate further was quite reasonable in the circumstances, but it does not demonstrate that all-cause-mortality is an

unreliable category for analysis. Dr. Wells testified that, like the DSMB, he would like more information about the causes of the deaths after year 8, but he did not testify that he thought all-cause-mortality was an unreliable category for analysis.

[503] In my view, all-cause-mortality is the most reliable category of death to consider. Drs. Madigan and Sackett testified directly on this point, and no expert contradicted their opinion. I am also concerned that, for the reasons detailed above, the "valve related" category of death underreports the true rate of deaths that can be attributed to the Silzone valve.

[504] Both Dr. Wells and Dr. Madigan performed statistical calculations to obtain risk ratios for all-cause-mortality on an overall basis using the October 2009 data freeze. Dr. Wells calculated a point estimate for the risk ratio of 1.33, with a p-value of 0.047 and a confidence interval of 1.01 to 1.75, indicating statistical significance. Dr. Madigan calculated a point estimate of 1.36, also with statistical significance.

[505] The striking characteristic of the data related to all-cause-mortality, however, is the dramatic increase in events in the two years prior to the October 2009 data freeze (more than 8 years post implant). Following is the life table for all-cause-mortality:

Number of Months post implant	Number of Events in Non-Silzone Group	Number of Events in Silzone Group
0-12	28	22
12-24	5	7
24-36	7	4
36-48	10	10
48-60	6	15
60-72	6	11
72-84	11	7
84-96	7	10
96-108	**5**	**17**
108+	**4**	**11**

[506] For the first eight years post implant, there were eighty events in the non-Silzone group and eighty-six in the Silzone group. In years 9 and 10, there were only nine events in the non-Silzone group versus twenty-eight in the Silzone group. It is clear that both Dr. Madigan's and Dr. Wells' findings of a statistically significant increase in the risk of death in Silzone patients are almost entirely attributable to the data from years 9 and 10.

[507] In my view, the data demonstrates that Silzone does not increase the risk of death for the first eight years post implant.

[508] The life table provides powerful evidence that Silzone does, in fact, cause an increase in the risk of death in Silzone patients beyond 8 years post implant. However, both Dr. Wells and Dr. Madigan testified that the statistical analysis of a study becomes less certain and can be less reliable later in the life of a study. This was one of the reasons Dr. Wells would have liked to see more clinical information about the causes of death in Silzone patients who died more than 8 years post implant.

[509] Dr. Wells performed "conditional probability" calculations for each year of data for all-cause-mortality. The conditional probability, in the present case, is the likelihood that a patient will die in a given year. For year 9, a non-Silzone patient who began the year had a 2.39% chance of dying that year (with a confidence interval of 0.87 to 5.62), whereas a Silzone patient had an 8.65% chance (with a confidence interval of 5.39 to 13.49). The available data from 9 years post implant and beyond indicates that non-Silzone patients had a 4.3% chance of death (1.34 to 10.89), and Silzone patients had a 13.02% chance (7.26 to 21.99).[113]

[510] The above data are indicative of an increased risk of death in Silzone patients in years 9 and beyond, but they do not demonstrate a statistically significant difference between the two groups. This is because the confidence intervals overlap. For year 9, the lower end of the confidence interval for Silzone patients is 5.39, while the upper end for non-Silzone patients is higher, at 5.62. For year 10 and beyond, the overlap is even larger, with an upper end in the non-Silzone group of 10.89 and a lower end in the Silzone group of 7.26. The overlapping confidence intervals demonstrate a lack of statistical significance, meaning there is an absence of evidence of a difference between the Silzone and conventional valves. In addition, as the experts testified, the wide confidence intervals are indicative of a great deal of uncertainty.

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[113] Exhibit 1443.

[511] In year 9 post implant and beyond, given the level of uncertainty and the lack of statistical significance in the data demonstrating an increased risk of death in those years, I am not satisfied that the data, by itself, demonstrates that Silzone increases the risk of death.

Explants

[512] Common Issue 3 asks whether Silzone increases the risk of *medical complications*. St. Jude argues that explants are not medical complications, but rather are a symptom that results from medical complications. However, the DCC and the AVERT investigators did use "explants for any reason" as an endpoint for analysis. Dr. Madigan also analyzed "explants for any reason". Dr. Wells, on the other hand analyzed the endpoint "explants except those occurring as a result of PVL". He testified that counting all explants would result in the double-counting of explants that were already counted in the major PVL category, which includes PVLs that result in explants.

[513] I note that the reason the Silzone valve was withdrawn from the market was an increased rate of explants *due to PVL* in the Silzone arm of AVERT. This supports the defendants' argument that explants are not a medical complication, but rather the symptom of a medical complication – in this case a symptom, or consequence, of PVL. It also supports Dr. Wells' position that counting all explants in a separate category will double-count patients whose valves were explanted due to a major PVL.

[514] The validity of Dr. Wells' concern, in fact, is graphically illustrated by the life table for "explants for any cause". In the first two years post implant, there were 19 explants in the Silzone arm of AVERT and only 2 in the conventional arm.[114] After two years post implant, as of the October 2009 data freeze, there were 6 explants in the Silzone group and 5 in the conventional group. It is clear that if Silzone does increase the risk of explants, it only does so for two years post implant. However, as Dr. Wells testified, most of the explants in the Silzone group in the first two years were the result of major PVLs.

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[114] Exhibit 564.

[515] I have already found that Silzone increases the risk of major PVL for two years post implant. And I agree with Dr. Wells' concern that it would not be sensible to conclude from the data that Silzone increases the risk of explants as a distinct complication. Rather, all that can be concluded is that Silzone increases the risk of major PVL, which correspondingly resulted in more explants in the Silzone group.

[516] In order to analyze explants as a distinct complication, one would have to consider explants other than those occurring as a result of PVL, as Dr. Wells did. Dr. Wells found that the risk ratio for this category was 1.78, with a p-value of 0.35, indicating a lack of statistical significance and a high degree of uncertainty. In my view, the data does not demonstrate that Silzone increases the risk of explants as a distinct complication. What the data does demonstrate is that Silzone increases the risk of major PVLs in the first two years post implant, many of which lead to explants.

Reoperation

[517] As with explants, the defendants argue that reoperation is not a valid endpoint to analyze because it is a symptom of a medical complication, rather than a complication itself. The defendants also point out that the Heart Valve Guidance refers to reoperation as a "*consequence* of a morbid event", rather than a morbid event itself. For this reason, Dr. Wells performed no statistical analyses of reoperation in AVERT.

[518] The DCC, using a KM analysis, and Dr. Madigan, using a linearized rates analysis, both analyzed reoperation as an endpoint and found a statistically significant increased risk in Silzone patients. However, in my view, it is abundantly clear from the life table for reoperation, that, as with explants, the difference is almost entirely due to major PVLs which required reoperation (it bears noting that to explant a heart valve requires, by definition, a reoperation). In the first two years post implant, there were 24 reoperations in Silzone patients and 4 in conventional patients. After two years post implant, there were 7 in Silzone patients and 8 in conventional patients. This is precisely the pattern observed in the life tables for major PVL and explants. As I stated above in considering explants, I have already found that Silzone increases the risk of major PVL in the first two years post implant. In my view, no other distinct conclusions can be drawn from

the fact that most of these major PVLs resulted in explants and/or reoperation. Thus, the data do not demonstrate that Silzone increases the risk of reoperation as a distinct event.

Endocarditis

[519] None of the statistical evidence indicates an increased risk of endocarditis in Silzone valve patients and the plaintiffs concede that no such increase exists. As such, I find that Silzone does not increase the risk of endocarditis.

The Meaning of "Materially"

[520] The legal test that is set out in Justice Cullity's certification decision is whether Silzone "materially" increases the risk of medical complications above the level observed in conventional valves. At paragraph 62 of his decision, Justice Cullity said:

> I believe the revised common issues produced at the hearing of the motion can be reduced slightly in number without affecting their content. I would also make a few changes in the wording. *The most important of these would be to substitute, in what would become issue #3, a reference to a material increase in the risk of complications for the existing words that might be considered to address even the remotest possibility of causation.* [emphasis added]

[521] The parties agree that the word "materially" modifies the word "increase" in Justice Cullity's formulation of Common Issue 3 – they agree that an increase is only legally significant under this common issue if it can be deemed "material". However, the parties disagree on how the word "materially" should be interpreted, or, in other words, what constitutes an increase that can be deemed "material". As I will discuss below, the parties' disagreement stems largely from their divergent interpretations of Justice Cullity's intentions in inserting the word "materially" into Common Issue 3.

[522] The plaintiffs argue that I ought to deem an increase in the risk for a given complication "material" where the risk for Silzone valve patients is at least one and one third times the risk for conventional valve patients. The defendants argue that an increase should only be deemed material where the risk for Silzone valve patients is double the risk for conventional valve

patients. In other words, the plaintiffs argue that for a complication to be material, the point estimate for the risk ratio must be at least 1.33, whereas the defendants argue that it must be at least 2.0.

The Plaintiffs' One and One Third Standard for Materiality

[523] The plaintiffs support their proposed standard by arguing that the significance of an increase in the risk of a complication from the perspective of a clinician should bear on my determination in this regard. They cite the concept of the "minimal clinically important difference" (MCID), which I described earlier when discussing Dr. Sackett's two-part test for harm. An MCID refers to the smallest difference in the risk of an event that would lead a treatment provider to change a patient's management. As the plaintiffs note, it makes sense that clinicians attribute MCIDs to complications in a manner that reflects the nature or seriousness of each complication. That is, the more severe the complication, the lower the risk of that complication needs to be in order for that risk to be deemed "clinically important". For example, the MCID would be lower for heart attacks than for headaches because heart attacks are more severe.

[524] The plaintiffs cite case law that uses the concept of MCIDs to aid in determining whether certain risks must be disclosed to a patient. For example, they cite informed consent case law, such as *Hopp v. Lepp*,[115] for the proposition that a risk which is a mere possibility is material if its occurrence carries serious consequences. The plaintiffs note that such risks must be disclosed to the patient.

[525] In my view, the plaintiffs' one and one third standard is not supported by the evidence, but rather is based only on one offhand comment by Dr. Sackett that an increase of 1/3 would be of concern to physicians or patients. Neither Dr. Sackett nor any other expert gave evidence that the fact that a given degree of risk may concern physicians means that degree of risk is "material" for the purposes of determining this common issue. There is no evidence from Dr. Sackett that a matter of concern to physicians is equivalent to a material increase in risk. In

[115] [1980] 2 S.C.R. 192.

addition, Dr. Sackett conceded that the degree of risk that would be of concern to physicians would depend on the severity of the complication at issue, yet the plaintiffs led no evidence regarding the relative severity of the complications at issue in this case. Thus, in my view, the concept of MCIDs and the informed consent case law cited by the plaintiffs is not relevant to my determination of general causation.

[526] I also note that the plaintiffs did not propose the one and one third standard for materiality until they filed reply submissions, after they saw that the defendants had proposed a standard for materiality – a doubling of the risk standard – in their closing submissions. In my view, if the plaintiffs truly believe that this is the proper standard of materiality, they ought to have presented evidence of this at trial. The circumstances under which the plaintiffs proposed the one and one third standard give rise to serious concerns of reliability. It is apparent that not only was the test adapted by counsel from one comment made by Dr. Sackett, but this was done late, after the evidence was concluded, and only in reply submissions.

[527] In attributing significance to MCIDs, the plaintiffs conflate Justice Cullity's use of the word "material" in Common Issue 3 with notions of clinical significance by reference to informed consent case law. In the context of this case, "material increase" does not equal "clinically significant". As the plaintiffs acknowledge, the word "material" in Common Issue 3 modifies the word "increase". Common Issue 3 queries whether the *increase in the risk* of a complication is material, not whether the complication itself is material having regard to its severity. I do not agree with the plaintiffs' submission that the word "materially" in Common Issue 3 ought to be interpreted by reference to MCIDs, the basis for Dr. Sackett's casual reference to a one and one third increase in risk.

[528] The true nature of Justice Cullity's use of the word "material" in Common Issue 3 can be understood by considering his reasons for inserting it. Justice Cullity was concerned that the previous language in Common Issue 3 ("can cause or contribute to") "might [have been] considered to address even the remotest possibility of causation". Justice Cullity did not have in mind the severity of complications when he inserted the word "material". Rather, he 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.

[529] I find that the plaintiffs' one and one third standard for materiality is not supported by the evidence and derives from considerations that do not bear on questions of causation. I therefore reject it as the standard for materiality under this common issue. The only other standard proposed is the defendants' doubling of the risk standard.

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 (something the reader should find effortless after this painful journey through the statistical evidence).

[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.[116] 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.

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[116] *Resurface Corp. v. Hanke*, [2007] 1 S.C.R. 333 at paras. 21-23.

[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. In 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 it 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. The problematic nature of this outcome is recognized in the U.S. Federal Judicial Center's *Reference Manual on Scientific Evidence*:[117]

> The use of probabilities in excess of .50 [which corresponds to a risk ratio of 2.0] to support a verdict results in an all-or-nothing approach to damages that some commentators have criticized. The criticism reflects the fact that defendants responsible for toxic agents with a relative risk just above 2.0 may be required to pay damages not only for the disease that their agents caused, but also for all instances of the disease. Similarly, those defendants whose agents increase the risk of disease by less than a doubling may not be required to pay damages for any of the disease that their agents caused.

[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. I have explained why I have rejected the plaintiffs' one and one third standard. A doubling of the risk standard is an approach that is used by the WSIAT and in American courts to demonstrate causation. Also, unlike the plaintiffs' one and one third standard, I believe it accords with Justice Cullity's intention in revising Common Issue 3.

[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

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[117] Federal Judicial Center, *Reference Manual on Scientific Evidence*, 2d ed. (Washington D.C.; Federal Judicial Center, 2000) [*Reference Manual*] at p. 362, footnote 82.

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 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.

The Proper Application of the Doubling of the Risk Standard (A Presumptive Threshold, Rather than a Prescriptive one)

[539] The defendants argue that patients who suffered complications for which the risk ratio is below 2.0 should not be able to proceed to the individual stage of these proceedings on the basis that the increase in the risk of the complication they suffered is not material. However, for patients who suffered complications for which the risk ratio is above 2.0, the defendants seek to retain the right to rebut the finding of causation that would result from a strict application of the arithmetic detailed above. That is, in the example where 201 patients suffer a complication in the Silzone group, the defendants seek to retain the right to argue that any particular claimant out of the 201 potential claimants would not have suffered the complication but for Silzone; in other words, that the claimant was amongst the 100 patients who would have suffered the complication anyway as part of the background rate. Presumably, the defendants would need to adduce probative evidence other than the epidemiological evidence in order to do this.

[540] The defendants' arguments in this regard are contradictory. On the one hand, they seek to retain the right to rebut individual causation where the risk ratio is above 2.0. But on the other hand, they argue that class members who suffered from complications for which the risk ratio is below 2.0 should be barred from proceeding to the individual stage of these proceedings; meaning they would be barred from having the opportunity to adduce evidence to rebut the negative finding of causation that would arise having regard only to the epidemiological evidence.

[541] However, in seeking to retain the right to rebut individual causation where the risk ratio is greater than 2.0, the defendants implicitly acknowledge that probative individualized evidence could be adduced at the individual stage of these proceedings. By "individualized evidence", I mean evidence that pertains only to an individual class member, rather than to the class as a whole. Individualized evidence is evidence of causation that is specific to an individual. This contrasts with evidence of general causation, such as the epidemiological evidence from AVERT.

[542] If, at the individual stage of these proceedings, probative individualized evidence could be adduced to rebut the positive finding of causation that would result having regard only to the epidemiological evidence where the risk ratio is greater than 2.0, then in follows that the reverse must also be true: probative individualized evidence could also be adduced to rebut the negative finding of causation that would result where the risk ratio is below 2.0. This being the case, it would be unreasonable to bar class members from proceeding to the individual stage of these proceedings on the basis that the risk ratio for the complication they suffered is below 2.0.

[543] To support their argument that class members who suffered from complications for which the risk ratio is below 2.0 ought to be barred from proceeding to the individual stage of these proceedings, the defendants would have to argue that there is no probative individualized evidence that could rebut the negative finding on causation that would result where the risk ratio is below 2.0. The defendants do not make this argument. Rather, as discussed above, they implicitly acknowledge that there *will* be probative individualized evidence at the individual stage of these proceedings.

[544] Further, because this is a common issues trial, the plaintiffs made no submissions regarding what individualized evidence they would adduce at the individual stage of these proceedings, nor should they have been expected to. Since the parties made no submissions regarding individualized evidence (other than the 14 patient study), I cannot make a finding that would assume that no probative individualized evidence will be adduced at the individual stage of these proceedings. Thus, I cannot direct that class members who suffered from complications for which the risk ratio is below 2.0 will be barred from proceeding to the individual stage of

these proceedings. Whether or not the epidemiological evidence demonstrates that the risk ratio for a complication is greater than 2.0 is only determinative of individual causation where there is no evidence other than the epidemiological evidence.

[545] This interpretation is consistent with the case law relied upon by the defendants. In *Daubert v. Merrill Dow Pharmaceuticals, Inc.* ("*Daubert II*"),[118] the U.S. Ninth Circuit Court of Appeals dismissed the plaintiffs' claim on the basis that the epidemiological evidence relied upon by the plaintiffs did not demonstrate that the defendant's drug, Bendectin, doubled the risk of the birth defect suffered by the plaintiff. Two critical facts demonstrate that *Daubert II* does not support the defendants' position:

> (1) *Daubert II* was an individual trial, not a common issues trial. As such, the plaintiffs *did* have the opportunity to adduce individualized evidence.
>
> (2) The plaintiffs did not present individualized evidence. As the Court in that case stated, "*[p]laintiffs do not attempt to show causation directly*; instead, they rely on experts who present circumstantial proof of causation." [emphasis added]

[546] *Daubert II* is simply an example of an individual trial in which the epidemiological evidence was the only evidence of causation relied upon by the plaintiffs. In that case, the epidemiological evidence could not by itself prove causation because it did not demonstrate a risk ratio greater than 2.0. This is not controversial. As I explained above, absent individualized evidence to the contrary, a risk ratio of less than 2.0 cannot support a finding of causation in an individual case. However, *Daubert II* does not support the defendants' contention that class members who suffered a complication for which the risk ratio is below 2.0 should be barred from proceeding to the individual stage of these proceedings.

[547] *Young v. Memorial Hermann Hospital System* is another example of an individual trial in which the plaintiff adduced no evidence other than epidemiological evidence which demonstrated a risk ratio below 2.0.[119] Thus, it too does not support the defendants' argument

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[118] 43 F. (3d) 1311 [*Daubert II*].
[119] 573 F. (3d) 233 (5th Cir. 2009).

that class members who suffered complications for which the risk ratio is below 2.0 should be barred from making claims at the individual stage of these proceedings.

[548] *Hanford Nuclear Reserve Litigation* explicitly cautions against the approach advocated by the defendants.[120] The court stated that the lower court's application of a doubling of the risk standard "forced the plaintiffs to prove that they were exposed to specific levels of radiation, *without regard to individualized factors*".[121] As such, the court determined that the lower court "erred in requiring epidemiological evidence which would… require a plaintiff to prove exposure to a specific threshold level of radiation that created a relative risk of greater than 2.0".[122] The court noted that its decision was consistent with the "Reference Guide on Epidemiology" contained in the U.S. Federal Judicial Center's *Reference Manual on Scientific Evidence*. As the court explained:[123]

> The Manual explains how epidemiological proof can be adapted to meet the "more likely than not" burden of proof by requiring statistics to reflect a relative risk factor of 2.0 before a plaintiff can recover. The discussion there, however, recognized that when available, known individual risk factors are also relevant. The Manual states that it limits its discussion to the role of epidemiology in proving individual causation.

[549] Thus, the most that can be said of the case law relied upon by the defendants is that it directs that, *in the absence of any other evidence*, a risk ratio below 2.0 does not support an inference of causation, whereas a risk ratio above 2.0 does.

[550] Both parties make reference to the practice of the WSIAT in determining issues of causation. The plaintiffs note that the WSIAT does not bar individuals who suffered a medical complication from recovering on the basis that the risk ratio for the complication they suffered is below 2.0. In fact, the defendants also acknowledge that WSIAT decisions have only required a relative risk of greater than 2.0 to establish causation *absent factors specific to an individual worker's case* that would impact a balance of probabilities analysis.

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[120] 292 F. (3d) 1124 [*Hanford Nuclear*].
[121] *Hanford Nuclear* at 1137 [emphasis added].
[122] *Hanford Nuclear* at 1137.
[123] *Hanford Nuclear* at 1137.

[551] WSIAT *Decision No. 600/97*, which considers how to determine causation in respect of workers who were exposed to asbestos and later contracted cancer, neatly demonstrates the WSIAT approach.[124] Note that instead of risk ratios, the WSIAT employs "standardized incidence ratios", or "SIRs", where an SIR of 200 is the equivalent of a risk ratio of 2.0. In the context of *Decision No. 600/97*, the SIR for the condition for which causation was being considered was 150, which corresponds to a risk ratio of 1.5. Following is a helpful excerpt:[125]

> 116. [E]pidemiological statistical measures look at "group risk" because they study populations rather than the cause of a particular worker's cancer. There is no way of knowing with certainty whether an individual worker would be one of the majority of workers who, in this example, would have developed the cancer even without occupational exposure, or whether he/she would be one of the minority of workers who would not have developed the cancer "but for" the occupational exposure. Nonetheless, the statistical probability of any individual worker being one of the minority of workers who would not have developed cancer "but for" the occupational exposure is 50/150 x 100 = 33%. That does not establish, on a "balance of probabilities" that the individual worker's cancer arose out of, or was due to, his/her employment.
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> 117. *But it also does not necessarily prevent such a finding on the "balance of probabilities" when epidemiological evidence is considered in light of all other evidence.*
>
> 118. *Adjudicative decisions about causation do not simply convert statistical probabilities into decisions about causation using the legal standard of "balance of probabilities".*
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> 119. Even in cases such as this where most of the evidence associating a workplace with a cancer is epidemiological evidence, *there may be factors about the individual worker or his/her exposure that increase that individual's risk such that an adjudicator will be persuaded that it is more likely that he/she is one of the workers whose cancer would not have developed "but for" the work exposure* (i.e. that it is more likely that he/she was one of the 50 out of 150 workers whose cancer would not have developed "but for" the work exposure)…
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> 120. We understand the OWA argument that a substantial number of cases in the relative risk of 1.5 example would meet the "but for" test of causation and be compensated if they could be identified – and that requiring a relative risk of 2

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[124] *Decision No. 600/97*, 2003 ONWSIAT 2153, [2003] O.W.S.I.A.T.D. No. 2106 [*Decision No. 600/97*].
[125] *Decision No. 600/97* at paras. 116-122.

> (i.e. an SIR of 200) would mean that this group (1/3 of the miners in the example above) would be unfairly denied compensation.
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> 121. In our view, this does not mean the legal test of causation for adjudicating claims under the Act changes. But it does illustrate the importance of attempting to identify those who are more likely to be in the "excess risk" group of cases – particularly when the SIR is less than 200.
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> 122. *To decide a claim from an individual worker in the population used in the OWA example, the Tribunal would consider not only the epidemiological evidence about the group risk, but also any evidence about the individual worker that might indicate whether his risk was greater than, or less than, the group risk. The Tribunal would, for example, consider specific medical evidence about the worker as well as evidence about whether he was exposed to other risks (such as smoking if that is a risk factor for the disease the worker developed).* The Tribunal would also consider evidence about the particular worker's work exposure to see whether the worker had a different risk associated with his/her work exposure than did other workers in the group for which the relative risk of 1.5 was calculated. [emphasis added]

[552] As I will outline in more detail below, I believe the practice of the WSIAT provides a useful framework for the adjudication of individual claims at the individual stage of these proceedings.

[553] Since this is a common issues trial, I am to determine general causation, not individual causation. For the reasons described above, had I found the defendants liable under Common Issue 1, I would not have applied the doubling of the risk standard prescriptively such that class members who suffered a complication with a risk ratio below 2.0 would be denied the opportunity to present individualized evidence of causation in their cases. Rather, as I will describe in more detail below, I would have applied the doubling of the risk standard *presumptively*.

[554] Below, I will discuss how the doubling of the risk standard ought to be applied if I had found the defendants liable under Common Issue 1.

The Doubling of the Risk Standard is a Presumptive Threshold

[555] While the above discussion demonstrates that it would be inappropriate to bar class members from proceeding to the individual stage of these proceedings on the basis that the risk ratio for the complication they suffered is below 2.0, it also demonstrates that whether or not a

risk ratio is above 2.0 bears on how questions of individual causation ought to be determined. It is apparent to me, as the plaintiffs point out, that the WSIAT employs a risk ratio of 2.0 as a *presumptive* threshold, as opposed to a prescriptive threshold, for individual claimants.

[556] Where the epidemiological evidence demonstrates a risk ratio above 2.0, then individual causation has presumptively been proven on a balance of probabilities, absent evidence presented by the defendant to rebut the presumption. On the other hand, where the risk ratio is below 2.0, individual causation has presumptively been disproven, absent individualized evidence presented by the class member to rebut the presumption. That is, whether or not the risk ratio is above 2.0 determines upon whom the evidentiary responsibility falls in determining individual causation. *Daubert II* and *Hanford Nuclear* also support the use of a risk ratio of 2.0 as a presumptive threshold in the manner practiced by the WSIAT.

[557] I also note that the level of a risk ratio relative to 2.0 determines the *extent* of the evidentiary responsibility for the party on whom it lies. In other words, a class member faces a greater evidentiary hurdle where the risk ratio for the complication he/she suffered is 1.2, than when it is 1.8. Indeed, in the present case, a class member who suffered a complication for which the risk ratio is 1.2 (corresponding to a presumptive percentage chance of causation of 20/120 X 100 = 16.7%) would have a substantial evidentiary hurdle to overcome in order to persuade the trier of fact in his/her individual action that Silzone was more likely than not the causal factor driving his/her complication. Likewise, the defendant faces a greater hurdle where the risk ratio is 4.0, than where it is 2.2. Thus, the risk ratio for any given complication determines both the *direction* and the *extent* of the evidentiary responsibility when individual claims are brought forward.

[558] This approach is entirely consistent with the case law. The defendants did not present any case law that supported their contention that I should use a risk ratio of 2.0 as a *prescriptive* standard without regard to the potential for individualized factors relevant to particular class members. In fact, as detailed above, *Hanford Nuclear*, *Daubert II*, the U.S. *Reference Manual on Scientific Evidence*, and the procedure employed by the WSIAT all support the use of a risk ratio of 2.0 as a presumptive, rather than prescriptive, standard for individual causation.

[559] As such, this is the approach that I believe is appropriate. If I had found the defendants liable under Common Issue 1, I would have applied the doubling of the risk standard for materiality presumptively, as described above. Patients who suffered complications for which the increase in the risk is not "material" (i.e. below 2.0), or even not statistically significant, would still be able to recover at the individual stage of these proceedings provided they presented sufficient individualized evidence to rebut the presumption of a lack of causation that flows from a risk ratio below 2.0 and persuade their trier of fact that Silzone was the "but for" cause of their complications.

[560] I believe this approach is consistent with Justice Cullity's formulation of this common issue. A presumptive doubling of the risk standard for materiality does more than "address the remotest possibility of causation".[126] Indeed, it defines materiality as the point at which the evidence of general causation is sufficient to permit a presumption of individual causation in an individual case. But at the same time it does not shut the door on individual class members solely on the basis of evidence regarding group risk. As no class member in this case has yet had the opportunity to adduce individualized evidence of causation, had I found liability, I would not have made a determination that implicitly assumes that no such evidence would be probative.

This Approach Succeeds in Significantly Advancing the Litigation

[561] The defendants suggested that to allow plaintiffs who suffered a complication for which the risk ratio was below 2.0 to proceed to the individual stage of these proceedings would fail to significantly advance this litigation and would result in the justice system being overwhelmed as every class member brought forward an individual claim. I disagree. I have described the evidentiary responsibility that such individuals would face. Proceeding with individual claims would be costly for those plaintiffs that did so both financially and personally. As such, they could only be expected to do so where they had the ability to present the court with probative individualized evidence that had a real chance of overcoming the presumption against causation

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[126] *Anderson v. St. Jude Medical Inc.*, (2003) 67 O.R. (3d) 136 at para. 62.

that flows from a risk ratio below 2.0. As such, in my view, the defendants' suggestion that to allow these claims to proceed to the individual stage would result in a "stampede" to the courts is without merit.

[562] In addition, as the plaintiffs argued, this approach to materiality succeeds in substantially advancing the present litigation. Guided by American case law and the procedure of the WSIAT, I have outlined how triers of fact at the individual stage of these proceedings could properly utilize the risk ratios as ascertained by the epidemiological data in this case. I have also determined that the AVERT data is the most reliable and that the KM / life table analysis employed by Dr. Wells provides the best method of analyzing that data. Further, I have made determinations with respect to the parties' numerous arguments under each complication. Thus, I have analyzed and distilled all of the evidence before me regarding general causation, under both Common Issue 2 and this common issue, significantly advancing the litigation.

The Evidence does not Support an Inference of Causation

[563] The plaintiffs direct me to a number of authorities which, they argue, support the proposition that, employing a "robust and pragmatic approach" to evaluating the evidence, I ought to find that the "totality of the evidence" supports an inference that Silzone causes medical complications. I am mindful of the Court of Appeal's reasoning in *Fisher v. Atack*, where the Court stated that "the robust and pragmatic approach does not shift the burden of proof away from the plaintiffs", but rather "offers a method for evaluating evidence", and "is not a substitute for evidence that the defendant's negligence caused the plaintiff's injury; nor does it change the amount of proof required to establish causation".[127]

[564] Much of the plaintiffs' submissions regarding my authority to make inferences of causation are seemingly directed at circumstances where the statistical evidence demonstrates a lack of statistical significance. In such cases, the plaintiffs seek to demonstrate that positive findings of causation may still be made. They argue that the statistical evidence is only one part of the evidence, and that I must consider the totality of the evidence in making findings of

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[127] 2008 ONCA 759, at paras. 56-57.

causation. The plaintiffs place great emphasis in this regard on *Snell v. Farrell*, in which the court stated that "[c]ausation need not be determined by scientific precision".[128] *Snell* was cited with approval in *Athey v. Leonati*, in which the Court noted that "[a]lthough the burden of proof remains with the plaintiff, in some circumstances an inference of causation may be drawn from the evidence without positive scientific proof".[129] The plaintiffs also cite the Supreme Court's cautionary language regarding the use of statistical evidence in *Laferriere v. Lawson*:[130]

> 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… [P]roof as to the causal link must be established on the balance of probabilities taking into account all the evidence which is before [the court], factual, statistical and that which the judge is entitled to presume.

[565] *Laferriere* was cited in *Goodman v. Viljoen*,[131] which the plaintiffs also cite for the proposition that statistical evidence ought not to be considered in a vacuum, but rather forms just one piece of the totality of the evidence.

[566] In my view, the Court's reasoning in *Snell* does not support the plaintiffs' submission that it would be appropriate for me to make an inference of causation in this case. In *Snell*, the Court noted that "[w]hether an inference is drawn is a matter of weighing evidence… The legal or ultimate burden remains with the plaintiff, but in the absence of evidence to the contrary adduced by the defendant, an inference of causation may be drawn although positive or scientific proof of causation has not been adduced". In the present case, the defendants *have* adduced a considerable amount of evidence contrary to my making an inference of causation. For example, the defendants adduced expert evidence, including expert testimony on the 14 patient study, the sheep studies and the scientific literature, demonstrating that it is unlikely that Silzone impairs tissue healing, despite the finding in AVERT that Silzone materially increased the risk of PVL for some patients for some period of time post implant.

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[128] [1990] 2 S.C.R. 311 at para. 29 [*Snell*].
[129] [1996] 3 S.C.R. 458 at para. 16 [*Athey*].
[130] [1991] 1 S.C.R. 541 at paras. 156-157 [*Laferriere*].
[131] [2011] O.J. No. 463 (S.C.J.) at para. 198 [*Goodman*].

[567] Further, the Court's reasoning in *Snell* with respect to the treatment of scientific evidence was driven largely by its other findings. In that case, the Court had already found that the plaintiff suffered blindness as a result of atrophy of the optic nerve caused by the loss of blood supply to the nerve; that the loss of blood supply was caused by a stroke; that a stroke is the destruction of a blood vessel due to interruption of the blood supply; and that there were two possible causes of the stroke, one of which was natural and the other due to the defendant surgeon's decision to continue an operation to remove a cataract from the plaintiff's eye in the face of obvious retrobulbar bleeding. It was this series of findings that gave the trial judge a factual basis to infer causation on the totality of the evidence, despite the lack of definitive scientific evidence.

[568] In the present case, I have made no similar series of findings regarding how Silzone might cause medical complications that would permit such an inference. Under Common Issue 2, I have found that the plaintiffs have failed to demonstrate on a balance of probabilities that impaired tissue healing is the mechanism by which (or how) Silzone causes medical complications. I recognize that, as the plaintiffs point out, they do not have to demonstrate *how* Silzone causes medical complications in order to prove *that* it does so. However, reliable evidence as to how Silzone would cause medical complications would be able to support an inference that it does so. Here, however, there is none, as I have rejected the plaintiffs' theory of impaired tissue healing under Common Issue 2. Thus, while the epidemiological evidence demonstrates that Silzone causes PVL in some patients, unlike in Snell, we may never know, as the defendants argue, how it causes that or any other complication, if it does in fact do so. In *Snell*, the trial judge was able to reduce the number of possible causes of the plaintiff's injury down to two and it was established *that* the plaintiff had suffered an injury. In the present case I have no reliable evidence upon which to make any findings about how Silzone causes medical complications, if it does indeed do so. Thus, unlike in *Snell*, other than the epidemiological evidence, I have no evidentiary basis upon which to make an inference of causation.

[569] In the present circumstances, I believe the British Columbia Court of Appeal's words in *Moore v. Castlegar and District Hospital* are apposite.[132] In that case, the Court held that it is not open to a trial judge to draw a common sense inference of the cause of the medical complication where both parties have led expert medical evidence of causation. *Moore* was cited with approval in *Sam v. Wilson*, a case in which *Snell* was distinguished for similar reasons.[133]

[570] In the present case, the two sides have adduced conflicting expert testimony. Further, there is simply no reliable evidence, other than the epidemiological evidence, upon which I could base an inference of causation. Thus, I cannot apply the robust and pragmatic approach as it was outlined in *Aristorenas v. Comcare Health Services* to draw an inference of causation. In that case, the court stated that "a series of facts and circumstances established by the evidence led at trial may enable the trial judge to draw an inference even though medical and scientific expertise cannot arrive at a definitive conclusion".[134] In the present case, the "series of facts and circumstances" upon which I could base such an inference is absent. The only reliable evidence of causation is epidemiological evidence, and I have interpreted that evidence consistently with how it is treated by qualified experts in the medical and scientific communities.

[571] I also do not believe the court's decision in *Goodman* assists the plaintiffs' submissions in this regard. The plaintiffs note that in that case causation was found despite epidemiological evidence that did not reach statistical significance. However, I note that the epidemiological data in that case was derived from over 20 RCTs, as opposed to one in the present case, and it came very close to statistical significance. Further, the trial judge had the benefit of reliable clinical evidence of causation that was specific to the individual plaintiff, whereas in the present case I have rejected the plaintiffs' impaired tissue healing theory under Common Issue 2 and have not accepted any clinical evidence of causation as reliable.

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[132] (1998), 49 B.C.L.R. (3d) 100 [*Moore*].
[133] 2007 BCCA 622 at paras. 139-146.
[134] (2006), 83 O.R. (3d) 282 at para. 56.

[572] Moreover, *Goodman* was an individual case, whereas in the present case I am assessing general causation. In an individual case, it makes sense that where epidemiological evidence falls short of statistical significance a trial judge could nonetheless find causation on the basis of individualized clinical evidence supportive of such a finding, as in *Goodman*. However, it does not follow that I may make a finding of *general* causation absent any reliable clinical evidence whatsoever. Further, had I found liability, there would be nothing in my reasons under this common issue to bar an individual plaintiff from bringing an individual claim in these proceedings. In such a case, where the individual suffered a complication for which no statistically significant increase in risk in Silzone valve patients was found, it would have been open to the trier of fact to nonetheless find that Silzone caused the particular plaintiffs' injuries on the basis of individualized clinical evidence combined with the epidemiological evidence – as occurred in *Goodman*. Outcomes such as the one in *Goodman*, therefore, would still have been possible in respect of individual plaintiffs in the present case.

[573] I also note that the plaintiffs' submissions with respect to my ability to draw inferences of causation were confusing and, in some cases, contradictory. For example, in their closing submissions, the plaintiffs acknowledge that "Common Issue 3 does not address whether the risks posed by Silzone would be considered significant in the eyes of a clinician",[135] a statement with which I agree. Yet, shortly thereafter, the plaintiffs again refer to informed consent case law and the importance of the seriousness of the injuries suffered by the plaintiffs. They state that

> [t]he concept of materiality… is… dependent on consideration of the seriousness of the injuries and whether the risk was sufficiently substantial that an implanting cardiac surgeon would consider the risk significant from a clinical perspective… Even if there is only a slight chance of serious injury or death, a risk may be material. In contrast, a significant chance of a slight injury may not be material.[136]

[574] In discussing the plaintiffs' one and one third standard for materiality, above, I explained why the informed consent case law and the relative seriousness of the complications at issue are not relevant to my determinations under Common Issue 3. The same analysis applies here. This

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[135] At para. 1802.
[136] At para. 1811.

line of case law does not assist the plaintiffs in establishing that, "on the totality of the evidence", an inference of causation ought to be drawn.

Conclusion under Common Issue 3

[575] A Silzone coating on heart valves does not materially increase the risk of medical complications, with the exception of major PVL for two years post implant, and minor PVL for six years post implant.

THE REMAINING COMMON ISSUES

[576] The remaining common issues address the plaintiffs' entitlement to the remedies of medical monitoring (Common Issues 4 and 5), 'waiver of tort' (Common Issues 7 and 8) and punitive damages (Common Issue 10(a)). In view of the conclusions I have reached on Common Issues 1, 2 and 3, the plaintiffs have no entitlement to these remedies and these questions must be answered in the negative.

[577] I realize that there has been considerable anticipation that this trial, with the benefit of a full factual record, would finally decide whether or not there is a basis in Canadian law for applying the doctrine of waiver of tort in a product liability negligence case. As I have found no wrongdoing, any analysis I engage in would be academic. Nonetheless, due to the considerable interest in this issue, I will provide one or two comments that may be helpful in moving this vexing question closer to resolution.

The Waiver of Tort Debate

[578] Our courts have had occasion to consider the question of whether waiver of tort exists as an independent cause of action, and if so, under what circumstances. The debate was neatly captured by Blair J.A. in the following passage from *Aronowicz v. Emtwo Properties Inc.*: [137]

> 80 Waiver of tort is a restitutionary remedy. There is considerable controversy over whether it exists as an independent cause of action at all or whether it is "parasitic" in the sense that it requires proof of an underlying tort and - since a tort

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[137] [2010] ONCA 96.

requires damage - proof of harm to the plaintiff. By invoking waiver of tort, a plaintiff gives up the right to sue in tort but seeks to recover on the basis of restitution, claiming the benefits the wrongdoer has derived from the wrongful conduct regardless of whether the plaintiff has suffered damages or not. See, for example, *Serhan Estate v. Johnson & Johnson* (2006), 85 O.R. (3d) 665 (Div. Ct), at paras. 45-69, leave to appeal to S.C.C. dismissed, [2006] S.C.C.A. No. 494.

81 The claim is not so much "novel" - it has its roots in the ancient action of *assumpsit* - as it is "mysterious" or "mystical". In their text, *The Law of Restitution*, Maddaugh and McCamus describe it in this fashion: [138]

> The doctrine known as "waiver of tort" is perhaps one of the lesser appreciated areas within the scope of the law of restitution. From the outset, it seems to have engendered an undue amount of confusion and needless complexity. The *almost mystical quality* that surrounds the doctrine is attested to by the following famous couplet penned by a pleader of old [J.L. Adolphus, "The Circuiteers - An Eclogue" (1885) 1 L.Q. Rev. 232, at p. 233]:
>
> Thoughts much too deep for tears subdue the Court
>
> When I *assumpsit* bring, and god-like waive a tort.
>
> One source of this confusion stems from the doctrine's very name. As one writer has pointed out, not entirely facetiously, it has "*nothing whatever to do with waiver and really very little to with tort*". [Emphasis added.]

82 While waiver of tort appears to be developing new legs in the class action field - see *Serhan Estate* and *Heward v. Eli Lilly & Co*. (2008), 91 O.R. (3d) 691 (Div. Ct.), for example - it is of no assistance to the appellants here. 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

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[138] Peter D. Maddaugh and John D. McCamus, *The Law of Restitution*, looseleaf (Aurora: Canada Law Book, 2009), at p. 24-1.

> record discloses no wrongful conduct on the part of the respondents in respect of any of the causes of action pleaded."

[579] As the above excerpt says, the primary debate about waiver of tort has been whether the doctrine exists as an independent cause of action in restitution (the independence theory) or is parasitic of an underlying tort (the parasitic theory). Under the parasitic theory, waiver of tort may only be invoked where all of the elements of the underlying tort have been proven, including damage to the plaintiff if that is an element of the tort. If, however, waiver of tort exists as an independent cause of action, by invoking the doctrine, a plaintiff can claim the benefits that accrued to the defendant as a result of the defendant's wrongful conduct, even if the plaintiff suffered no harm. It is also noteworthy that the independence theory of waiver of tort is not the same as an action for unjust enrichment, as the plaintiff does not have to demonstrate a deprivation that corresponds to the defendant's enrichment.

[580] In *Serhan Estate v. Johnson & Johnson*,[139] an appeal from a Superior Court order certifying waiver of tort as a cause of action, the Divisional Court provided, at paragraphs 45 to 67, a detailed account of the contemporary academic and judicial debate on the issue. The court in *Serhan* noted that both the parasitic and independence theory of waiver of tort can claim the support of academic writings and case law, and the majority concluded, at paragraph 67, that while it had concerns about eliminating the need to prove loss in products liability cases (as is directed by the independence theory), the issue "should be considered and resolved on the basis of a full record". The court stated further, at paragraph 68, that "the resolution of the questions the defendants raise about the consequences of identifying waiver of tort as an independent cause of action in circumstances such as exist here, involves matters of policy that should not be determined at the pleadings stage". Finally, at paragraph 69, the court concurred with the certification judge's determination that "whether waiver of tort is an independent cause of action should be resolved in the context of a factual background of a more fully developed record".

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[139] (2006) 85 O.R. (3d) 665 (Div. Ct.), leave to appeal to C.A. ref'd Oct. 16, 2006, leave to appeal to S.C.C. ref'd. [2006] S.C.C.A. No. 494 [*Serhan*].

[581] Similarly, in *Heward v. Eli Lilly & Co.*,[140] in which waiver of tort was again certified as a common issue in a class proceeding, at paragraph 48, the certification judge, citing *Serhan*, noted that the consideration of whether and when waiver of tort should be an available remedy involves "important issues of policy… that must surely be confronted on the basis of a full factual record".

[582] Other courts have followed this pattern, and since *Serhan* waiver of tort has been routinely certified in most class actions. It has also found its way into pleadings in cases such as *Aronowicz* (a garden variety shareholders' dispute), presumably in the hope of avoiding the hammer of summary judgment on the basis that it is a novel and uncertain claim.

[583] I could not agree more that it is time to decide the question.

[584] There is no case law before me on waiver of tort that was not also before the courts in *Serhan* and *Eli Lilly*, although the related academic debate continues to develop.[141] Neither of those courts found that this was sufficient to determine the issue. In fact, both found that a full evidentiary record would be necessary. The Court of Appeal and the Supreme Court of Canada refused leave to appeal the decision in *Serhan* and as neither Court is obliged to give reasons for this, we do not know why. If these Courts did so because they agreed with the courts in *Serhan* and *Eli Lilly* that a full factual record is necessary to decide whether or not there is a basis in Canadian law for applying the doctrine of waiver of tort in a product liability negligence case, I must respectfully disagree.

[585] The extensive factual record that was developed during a 138 day trial did not illuminate for me the important issues of policy that were meant to arise from the trial record. The written submissions of the parties did not rely on any evidence from the factual record in advancing

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[140] [2007] O.J. No. 404 (S.C.J.), leave to appeal to Div. Ct. granted, [2007] O.J. No. 2709 (Sup. Ct. J.), aff'd (2008), 91 O.R. (3d) 691, [2008] O.J. No. 2610 (Div. Ct.) [*Ely Lilly*].

[141] H. Michael Rosenberg, "Waiving Goodbye: The Rise and Imminent Fall of Waiver of Tort in Class Proceedings" (2010) 6:1 Can. Class Action Rev. 36; The Honourable Mr. Justice Todd L. Archibald and Christian Vernon, "No Harm, No Foul? The Existence of Waiver of Tort as an Independent Cause of Action in Canadian Law" (2008) *Annual Review of Civil Litigation* 409; Shantona Chaudhury and Paul J. Pape, "Damages in Waiver of Tort" (Paper delivered at the Continuing Professional Development workshop on "The Law of Damages", 27 March 2012).

arguments to support or oppose extending the waiver of tort doctrine to a negligence case. The plaintiffs did not lead any policy evidence to explain why waiver of tort should be available in a product liability negligence case.

[586] In fact, the only policy evidence brought before the court was adduced by the defendants from Professor Michael Trebilcock, a law and economics scholar at the Faculty of Law, University of Toronto. The kind of analysis that Professor Trebilcock offered was certainly outside the experience and knowledge of the court, but I hasten to add that where the court is engaged in an analysis that may result in changes to the law, this kind of social science evidence is frequently brought before the court by way of application and is evaluated on the basis of affidavit evidence and cross-examination thereon.[142] The plaintiffs objected to the admissibility of the evidence of Professor Trebilcock and argued that waiver of tort is a matter for legal argument and does not require expert evidence on policy. If they are correct, the recognition (or not) of the waiver of tort doctrine can be determined under section 5(1)(a) of the *Class Proceedings Act*.

[587] While generally, courts are reluctant to determine unsettled matters of law at a pre-trial stage and particularly on a pleadings motion, there is certainly precedent for doing this. It may be lost in the mists of time, but *Donoghue (or McAlister) v. Stevenson* reached the House of Lords on a pleadings motion.[143] No one can dispute that the outcome in that case represented a 'sea-change' in the law. As well, appellate courts have struck claims in regulatory negligence on pleadings motions based on an *Anns* analysis of whether there were policy reasons to negate a common law duty of care.[144] My experience from this trial suggests that deciding the waiver of tort issue does not necessarily require a trial and that it may be possible to resolve the debate in some other way.

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[142] See, "Ruling on Admissibility of Evidence of Professor Michael Trebilcock", 2011 ONSC 2178.
[143] [1932] All E.R. Rep. 1; [1932] A.C. 562 (H.L.).
[144] See, for example, *Cooper v. Hobart*, [2001] S.C.J. No. 76, [2001] 3 S.C.R. 537 (S.C.C.); *Attis v. Canada*; but see *contra*, *Sauer v. Canada (Attorney General)* (2008), 225 O.A.C. 143 (C.A.), leave to appeal ref'd, [2007] S.C.C.A. No. 454.

Policy Considerations

[588] The policy considerations did not arise from the factual record. The plaintiffs adduced no expert evidence on policy, but there is one policy consideration that they advance in their submissions that merits consideration. The plaintiffs argue that "[a]s a matter of policy, the courts should not encourage manufacturers to take unreasonable risks in circumstances where, *due to the complexities of establishing causation, it is unlikely that every individual harmed by a defective product will be able to successfully sue for compensation*" [emphasis added].

[589] In the present case, had I found that the defendants had breached their duty of care, the defendants would have, through their negligence, exposed a population of Silzone valve patients to an increased risk of a serious medical condition (PVL). However, whether the defendant was required to pay for this – and thus, whether this would deter medical product manufacturers from engaging in negligent behaviour that puts populations at risk – would depend on whether individuals within that population could demonstrate that, on a balance of probabilities, Silzone caused their particular injuries. While epidemiological evidence can show that the defendant placed a group of people at risk, it is a more burdensome evidentiary hurdle to demonstrate that it is more likely than not that any one individual within the group suffered damages as a result of that increased risk. Tort law may be inadequate to the task of regulating the conduct of medical device manufacturers and other manufacturers whose products put populations at risk. Recognizing an independent tort based on wrongdoing, rather than proof of harm, can arguably overcome this problem and serve a useful social purpose.

[590] When a population is put at risk, one might rightly ask whether this constitutes a *public* problem inviting public oversight, or a *private* problem the resolution of which can be left to a court applying private law. It bears noting that if the latter approach is taken, whether or not a person who puts a population at risk experiences any consequences will, in many cases, depend on whether a member of the bar sees fit to initiate a class action lawsuit. The factors that drive a lawyer's decision in this regard will be specific to that lawyer's practice, and generally will not include safeguarding the public interest. If putting populations at risk of serious medical complications is construed as a public problem, then it is unsurprising that private law constructs,

such as the requirement that individual causation and damages be proven on a balance of probabilities, can become virtually insurmountable hurdles for those within the population who suffered from the risk and are seeking redress.

[591] There are, of course, countervailing policy considerations. The defendants submit that the plaintiffs have fundamentally failed to explain why, as a matter of law and policy, waiver of tort should be extended to a product liability negligence case. Professor Trebilcock's law and economics public policy evidence indicates that the recognition of waiver of tort in this context will have a negative impact on product innovation and will over deter socially desirable behaviour on the part of health product manufacturers. Law and economics policy considerations strongly support the idea that damages for negligence should be calculated based on the injury suffered by the plaintiff, rather than the gain realized by the defendant. Professor Trebilcock discussed the negative consequences that might be expected to arise from a "super-compensatory" regime in negligence law, that is, one where plaintiffs receive compensation in excess of their actual injuries. If waiver of tort were recognized as an independent cause of action, plaintiffs could be overcompensated in this manner as a defendant's gain from its wrongful conduct could exceed the damages suffered by plaintiffs. Professor Trebilcock noted there is considerable risk that overcompensating a plaintiff through waiver of tort in a negligence case would destabilize the deterrence and insurance functions of tort law. He testified that such a regime has the potential to deter socially productive activities. For example, allowing waiver of tort in negligence cases may:

- cause sellers to take socially excessive precautions on the market;
- cause sellers to take products off the market;
- cause sellers to under-invest in product innovation;
- cause sellers to charge higher prices for their products; and,
- cause consumers to have to pay more for products than they would prefer to pay.

[592] While acknowledging their limitations, Professor Trebilcock cited empirical studies that suggest some negative consequences that might flow from a super-compensatory regime. A study by Steven Garber found that super-compensatory liability in medical products markets in the United States had the effect of causing companies to withdraw products from the market that

had widespread support in the medical community.[145] He also found that the regime caused major price increases and deterred development efforts for socially valuable products. Another set of studies by Richard L. Manning suggested that exposure to super-compensatory liability caused manufacturers to increase prices for major childhood vaccines at a rate that outpaced increases in wholesale prices for drugs and pharmaceuticals generally.[146]

[593] The debate between the independence theory and the parasitic theory engages fundamental philosophical questions about the nature of tort law. As Professor Trebilcock noted, negligence has been predicated on a system of compensation for actual loss for nearly 200 years. The requirement that a plaintiff demonstrate damages has long been considered a fundamental tenet of tort law. Does this requirement exist because the law only considers a person's conduct wrongful where it harms another person? If so, recognizing waiver of tort as an independent cause of action would result in punishing defendants for conduct that has never before been deemed wrongful. Under this view, the requirement that damages be demonstrated is meant to serve a foundational philosophical purpose. On the other hand, is it only the violation of the duty of care that makes a defendant's conduct wrongful? In that case, the requirement that the plaintiff demonstrate damages may merely perform some practical purpose and the philosophical foundations of tort law would not be offended by recognizing waiver of tort as an independent cause of action. Thus, the discussion surrounding the waiver of tort debate touches on questions as fundamental as what exactly it is that directs the law to deem certain conduct wrongful.

[594] Given the philosophical and policy considerations mentioned above, it is my view that the fundamental question for a court to answer is whether the recognition (or not) of the waiver of tort doctrine is within the capacity of a court to resolve, or whether it has such far-reaching

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[145] Steven Garber, "Product Liability, Punitive Damages, Business Decisions and Economic Outcomes" (1998) Wis. L. Rev. 237.

[146] Richard L. Manning, "Is the Insurance Aspect of Producer Liability Valued by Consumers? Liability Changes and Childhood Vaccine Consumption" (1996) 13 *Journal of Risk and Uncertainty* 37; Richard L. Manning, "Changing Rules in Tort Law and the Market for Childhood Vaccines" (1994) 37 J.L. & Econ. 247.

and complex effects that it is best left to consideration by the Legislature.[147] On the basis of my experience, the answer to this and the other questions surrounding the waiver of tort doctrine is not dependent on a trial with a full factual record and may require no evidence at all.

ANSWERS TO THE COMMON ISSUES

Common Issue 1

The defendants exercised reasonable care in the design and testing of the Silzone valve and in the warnings of the risks inherent in their use.

Common Issue 2

A Silzone coating on a heart valve sewing ring has no different or adverse effect on tissue healing than uncoated Dacron.

Common Issue 3

A Silzone coating on heart valves does not materially increase the risk of medical complications, with the exception of major PVL for two years post implant, and minor PVL for six years post implant.

Common Issues 4 and 5

Silzone patients do not require additional or different medical monitoring than conventional heart valve patients. Common Issue 5 is moot.

Common Issue 6

The plaintiffs are not entitled to a presumption that explanted valves and tissue samples from the sheep studies would have been unhelpful to the defendants' case and helpful to the plaintiffs.

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[147] *Watkins v. Olafson*, [1989] 2 S.C.R. 750, [1989] S.C.J. No. 94 at paras. 13-15; see also *Friedman Equity Developments Inc. v. Final Note Ltd.*, [2000] S.C.J. No. 37 at paras. 42-49.

Common Issues 7 and 8

Members of the Class cannot elect to have damages determined through an accounting and disgorgement remedy. Common Issue 8 is moot.

Common Issue 10(a)

The defendants' conduct does not merit an award of punitive damages.

DISPOSITION

[595] The action is dismissed. I encourage the parties to attempt to resolve the question of costs. If they are unsuccessful, they should arrange an attendance.

"J.L. Lax, J."

LAX J.

Released: June 26, 2012

SCHEDULE I

Certified Common Issues*

1. Did the defendants breach a duty of care owed to class members by reason of the design, pre-market testing, regulatory compliance, manufacture, sale, marketing, distribution and recall of Silzone-coated mechanical heart valves and annuloplasty rings implanted in such members?

2. What effect, if any, does such Silzone coating have on tissue healing?

3. Does a Silzone coating on heart valves, or annuloplasty rings, materially increase the risk of various medical complications including, but not limited to, paravalvular leakage, thrombosis, thromboembolism, stroke, heart attacks, endocarditis or death?

4. Do Silzone implanted-patients need additional or different medical monitoring than that for conventional mechanical heart valve patients?

5. Should the defendants be required to implement a medical monitoring regime and, if so, what should the regime comprise and how should it be established?

6. Is the burden of proof of causation or negligence affected by spoliation of evidence by the defendants?

7. Can all or a part of the Class elect to have damages determined through an accounting and disgorgement of the proceeds of the sale of the mechanical heart valves, or annuloplasty rings, coated with Silzone implanted in patients?

8. If part, but not all, of the Class can so elect, which part or parts of the Class can so elect?

9. If all or part of the Class can so elect, in what amount and for whose benefit is such an accounting to be made?

10. (a) Does the defendants' conduct merit an award of punitive damages?

(b) Should an award of punitive damages be made against the defendants?
If so, in what amount?

*The common issues were certified by order of the Honourable Justice Cullity, dated January 16, 2004, and amended by order of the Honourable Justice Lax, dated January 20, 2010. Common issues 9 and 10(b) were bifurcated to the end of the trial of common issues.

SCHEDULE II

The Expert Witnesses

Area of Expertise	Plaintiffs' Experts	Defendants' Experts
Biomaterials Science	• Dr. Kevin Healy, Professor of Bioengineering and Materials Science, University of California, Berkeley	• Dr. David Williams, Professor Emeritus, Clinical Engineering, University of Liverpool
Biostatistics / Epidemiology	• Dr. David Madigan, biostatistician; Professor and Chair, Department of Statistics, Columbia University • Dr. David Sackett, Professor Emeritus, Clinical Epidemiology and Biostatistics, McMaster University	• Dr. George Wells, biostatistician and epidemiologist; Director, Cardiovascular Research Methods Centre, University of Ottawa, Heart Institute
Cardiac Surgery / Cardiology / Haematology	• Mr. Eric Butchart, University Hospital of Wales, Senior Cardiovascular Surgeon • Dr. George Christakis, cardiac surgeon, Sunnybrook Health Science Center, Toronto	• Dr. Lee Errett, Chief, Division of Cardiovascular and Thoracic Surgery, St. Michael's Hospital, Toronto • Dr. Jack Hirsh, Professor Emeritus, Department of Medicine (Haematology), McMaster University • Dr. Henry Mizgala, Professor Emeritus, Department of Medicine (Cardiology), University of British Columbia
Infectious Diseases		• Dr. Daniel Sexton, Professor, Department of Medicine, Division of Infectious Diseases, Duke University
Microbiology		• Dr. Robert Hancock, Professor of Microbiology and Immunology, University of British Columbia
Neurology		• Dr. Bruce Snyder, Clinical Professor of Neurology, University of Minnesota
Pathology	• Dr. Gregory Wilson, Staff Pathologist, Division of Pathology, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto	• Dr. Stephen Factor, cardiac pathologist, Albert Einstein College of Medicine • Dr. Frederick Schoen, cardiac pathologist, Brigham and Women's Hospital; Professor of Pathology, Harvard University
Regulatory / Industry Standards		• Diane Johnson, former FDA Scientific Reviewer, heart valve applications
Social Science (Law and Economics)		• Michael Trebilcock, Professor of Law and Economics, University of Toronto, Faculty of Law
Toxicology	• Dr. George Cherian, Professor Emeritus, Department of Pathology, Faculty of Medicine, University of Western Ontario • Dr. André McLean, Professor Emeritus, Department of Toxicology, University College London	• Dr. Joseph Rodricks, Visiting Professor, School of Hygiene and Public Health, Johns Hopkins University; former Chair, FDA task force on toxicological risks in medical devices
Veterinary Medicine / Animal Testing	• Dr. Merle Olson, Research Director, Innovotech Inc.; Research Director, Alberta Veterinary Laboratories	• Dr. William Wustenberg, Regulatory Consultant on animal testing, AlterNet Medical Consulting

SCHEDULE III

Scientific Articles

Akins et al. (2005), "Guidelines for reporting mortality and morbidity after cardiac valve interventions," *European Journal of Cardio-thoracic Surgery*.

Arom et al. (1996), "St. Jude Medical Prosthesis: Health Status of the Patients after 15 Years," *Annals of Thoracic and Cardiovascular Surgery*.

Bambauer et al. (2004), "Large Bore Catheters with Surface Treatments versus Untreated Catheters for Vascular Access in Hemodialysis," *Artificial Organs*.

Bambauer et al. (1996), "Scanning Electron Microscopic Investigation of Catheters for Blood Access," *Blood Purification*.

Bambauer et al. (1995), "New Surface Treatment Technologies for Catheters used for Extracorporeal Detoxification Methods," *Dialysis & Transplantation*.

Batt et al. (2003), "In situ revascularization with silver-coated polyester grafts to treat aortic infection: Early and midterm results," *Journal of Vascular Surgery*.

Boosalis et al. (1987), "Serum and urinary silver levels in thermal injury patients," *Surgery*.

Bradford Hill, A. (1965), "The Environment and Disease: Association or Causation?" *Proceeding of the Royal Society of Medicine*.

Bull and Braunwald (1971), "Human histopathologic response to a completely fabric-covered prosthetic heart valve," *Annals of Surgery*.

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SCHEDULE IV

Glossary of Medical Terms

Adsorption – molecules of gas or liquid adhere to the surface of a solid. It is different from "absorption" where molecules actually enter the absorbing medium.

Albumin – major blood protein.

Aliquot – a smaller portion of a sample taken for experimental purposes; fractional; pertaining to a part of the whole.

Anastomosis – to make such connection surgically.

Angstrom – unit of measurement; 1/100,000,000 of a centimetre.

Annular – related to the *annulus*.

Annuloplasty – surgical procedure involving repair of a heart valve.

Annulus (plural "annuli") – a ring of tough fibrous tissue at the base of a heart valve. This ring supports and anchors the heart valve(s) into the heart itself. There are 4 valve annuli: one each for the *tricuspid*, *mitral*, *aortic*, and *pulmonary* valves.

Anticoagulant – a drug that inhibits blood from clotting.

Antimicrobial – a substance that kills or inhibits the growth of microbes such as bacteria, fungi, or viruses.

Aorta – the largest artery in the human body, originating from the left ventricle of the heart and bringing oxygenated blood to all parts of the body.

Aortic Valve – a one-way valve that allows blood to flow only out of the left ventricle (left lower chamber) and into the *aorta*.

Bactericidal – capable of killing *bacteria*.

Bacteriostatic – inhibiting the growth or reproduction of bacteria.

Bileaflet Valve – a heart valve prosthesis consisting of a circular orifice to which are attached two semicircular occluding discs that swing open and closed to regulate blood flow.

Bioavailability – the extent to which a drug or other substance is absorbed by and becomes available to the body.

Biocompatibility – the ability of a material to perform with an appropriate host response in a specific application.

Biofilm – an aggregate of tiny organisms with a distinct architecture.

Clostridium – a kind of bacteria.

Coumadin – anticoagulant; also known as *Warfarin*.

Culture-negative Endocarditis – an infection and inflammation of the lining of one or more heart valves in which no *endocarditis*-causing germs can be identified on a blood culture.

Cytoskeleton – a network of proteins making up the internal skeleton of a cell.

Cytotoxic – any agent or process that is toxic to cells; ("cyto" denotes a cell).

Dacron – DuPont trade name for polyester.

Dehiscence – a rupture or opening of a sutured area or surgical wound, or of an organ or structure.

Duke Criteria – diagnostic criteria *for infectious endocarditis* originally proposed in 1994. The criteria are based on a combination of *echocardiogram*, laboratory and physical examination findings. These criteria include major and minor criteria. Clinical criteria for *infective endocarditis* requires: any of: (a) two major criteria; (b) one major criteria and three minor criteria; or (c) five minor criteria.

Echocardiogram – like an ultrasound, it provides a three dimensional view of the heart in real time.

Elution – in chemistry, separation of material by washing; the process of pulverizing substances and mixing them with water in order to separate the heavier components, which settle in solution, from the lighter.

Embolism – obstruction of a blood vessel by foreign substances or a blood clot.

Endocarditis – an infection of the lining of the heart (called the *endocardium*).

Endothelial – relating to the flat layer of cells lining the heart.

Endotheliazation – the growth of a layer of cells lining the circulatory system including the blood and lymphatic vessels of the heart.

Endothelium – protective cells that line the heart.

Epidemiology – the study of factors affecting the health and illness of populations.

Etiology – assignment of a cause, an origin, or a reason for something.

Explant – removal of an implanted prosthesis such as a heart valve or knee joint.

Fibrin – a stringy protein needed for blood to clot.

Fibroblasts – cells that help make up the support structure for tissues and organs; they are cells found in connective tissue.

Fibrous – containing, consisting of, or resembling fibres, for example, *collagen* is a fibrous protein.

Foreign Body Giant Cell – a collection of fused *macrophages* (giant cell) which are generated in response to the presence of a foreign body.

Free Radicals – compounds with an unpaired electron (and no charge). They may be involved as short-lived, highly-active intermediates in various reactions in living tissues, notably in photosynthesis.

Galvanic – electric; producing a direct current of electricity.

Galvanic Corrosion – Galvanic corrosion is an electromechanical process in which one metal corrodes preferentially when in electrical contact with a different type of metal and both metals are immersed in an *electrolyte*.

Glutathione – a tri-peptide found in plant and animal tissues that has various functions in a cell, which include acting as an antioxidant and protecting cells from toxins.

Hemolysis/Haemolysis – the destruction of red blood cells by the body.

In situ – Latin meaning “in place” or not removed, in its original position.

In vitro – in a test tube or a lab dish.

In vivo – in the living subject/the body.

Infection – a state in which the body is invaded by a disease-causing agent (like a microorganism or virus).

Infectious Endocarditis – an infection of the lining of the heart chambers and heart valves that is caused by bacteria, fungi, or other infectious substances.

INR or International Normalized Ratio – used to measure the effectiveness of blood thinning drugs such as warafin (Coumadin).

Interstices – a small area or gap in tissue or structure of an organ.

Ion Beam Assisted Deposition (IBAD) – a process of applying materials to a surface through the application of an ion beam.

Ischemic Stroke – a stroke in which blood supply to part of the brain is decreased leading to dysfunction of the brain tissue.

Leukocytes – white blood cells that help the body fight infections and disease.

LIMRA – Limited Initial Market Release Authorization.

Lymphocytes – white blood cells that are a major component of the immune system; they fight infection and disease.

Lysis – rupture, disintegration or destruction of cells.

Macrophages – large, white blood cells found at the site of infection or injury that are capable of engulfing and ingesting cells or particles.

Mammalian – any of the higher vertebrate animals comprising the class Mammalia.

Mechanical – in the context of heart valve prostheses, it means manufactured non-tissue prosthetics made to replicate the function of native heart valves.

Metallothionein – a small metal-binding protein, rich in sulphur-containing *amino acids*, that is synthesized throughout the body and in the liver, heart and kidney and important in ion transport. It is important in detoxification.

Microbiology – the study of all aspects of microorganisms, organisms which individually are generally too small to be visible other than by microscopy.

Micron – a unit of length equal to one millionth of a meter.

Microorganism – a minute living body not perceptible to the human eye.

Microvasculature – the portion of the circulatory system composed of the smallest vessels, such as the *capillaries*.

Mitral Valve – a valve of the heart located between the *left atrium* (receives oxygen-rich blood) and *left ventricle* (chamber on the left side of the heart that receives blood from the *left atrium* and pumps it into the *aorta*, a large artery of the heart); the mitral valve regulates blood flow between the left atrium and the left ventricle.

Monocytes – a type of *leukocyte* (white blood cell) and part of the human body's immune system. Monocytes can move quickly to sites of infection in the tissues to elicit an immune response.

Necropsy – post-mortem examination/autopsy.

Necrosis – the death of one or more cells or a portion of tissue or an organ through injury or disease.

Neo-intimal – the inner lining of a vessel, artery or vein.

Pannus – fibrotic tissue which grows around a newly implanted prosthetic heart valve. The term may be used either to refer to such tissue generally, or refer to excessive tissue (*i.e.* pannus tissue that may grow to the point where it obstructs the leaflets of a prosthetic valve).

Paravalvular Leak – the leakage of blood through an opening between the upper and lower chambers of the heart around the outside of the valve.

Paravalvular Regurgitation – a complication associated with heart valve replacement surgery to which the blood leaks backwards between the native annulus and the prosthetic valve sewing ring.

Pasturella – a bacterium; many Pasturella species are zoonotic pathogens (meaning an infectious disease that is able to be transmitted from wild and domestic animals to humans or from humans to animals).

Pathology – the study of the characteristic causes and effects of disease.

Phagocyte – a cell, such as a white blood cell, that engulfs and absorbs waste material, harmful microorganisms, or other foreign bodies in the bloodstream and tissues.

Platelets – the part of a blood cell that helps prevent bleeding by causing blood clots.

Pledget – a small piece of material, usually felt, that is used to buttress or reinforce sutures during surgery.

Polyester – a category of *polymers* which contain the ester functional group in their main chain. Although there are many polyesters, the term "polyester" as a specific material most commonly refers to polyethylene terephthalate (PET).

Prosthetic Valve Endocarditis – infection based in the area of a prosthetic heart valve.

Prosthetic Valve Thrombosis – an obstruction of prosthesis by non-infective thrombotic material (blood clotting material).

Reversible Ischemic Neurologic Deficit ("RIND") – a temporary loss of functioning brain tissue caused by an interruption in the cerebral blood supply that lasts between 24 hours to three weeks.

Sewing Ring – a portion of a heart valve prosthesis that allows the valve to be sutured into place.

Silver Sulfadiazine – a topical antibacterial agent used primarily as a topical burn cream on second- and third-degree burns. The cream is applied to the burned skin for the duration of the healing period or until a graft is applied. It prevents the growth of a wide array of bacteria, as well as yeast on the damaged skin. Silver sulfadiazine is typically delivered in a 1% solution suspended in a water-soluble base.

Stroke – a stroke is the rapidly developing loss of brain functions do to a disturbance in the blood vessels supplying blood to the brain.

Thrombin – an enzyme formed in shed blood that converts *fibrinogen* into *fibrin* (proteins necessary in blood clotting), and forms the basis of a blood clot.

Thromboembolic – the blocking of a blood vessel by a blood clot dislodged from its site of origin.

Thromboembolism – the formation in a blood vessel of a clot (*thrombus*) that breaks loose and is carried by the bloodstream to plug another vessel.

Thrombogenicity – the tendency of a material in contact with the blood to produce a *thrombus* or clot.

Thrombosis – the presence or formation of a blood clot which obstructs veins (venous thrombosis) and *arteries* (arterial thrombosis).

Thrombus (plural "*thrombi*") – a blood clot within a blood vessel or within the heart.

Toxicity – the quality, state or relative degree of being toxic or poisonous.

Toxicology – the study of symptoms, mechanisms, treatments and detection of poisoning, especially the poisoning of people.

Transient Ischemic Attack or "TIA" – caused by the changes in the blood supply to a particular area of the brain, resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours.

Valve Thrombosis – an obstruction of a prosthesis by non-infective thrombotic material (blood clotting material).

Vascular graft – synthetic or biological materials used to patch injured or diseased areas of *arteries*, or for replacement of whole segments of larger *arteries* (such as the *aorta*), and for use as sewing cuffs (as with the heart valve).

Vegetation – in the medical context, an abnormal growth of tissue around a valve that can develop following the presence of bacteria in the blood. Vegetation is composed of blood *platelets*, the infecting *bacteria*, a few white blood cells, and *fibrin* (a protein involved in clotting).

Warfarin – a drug that prevents blood from clotting. Also called *anticoagulant* (blood thinner).

Zone of Inhibition – an area on an agar plate where growth of a control organism is inhibited.

CITATION: Andersen v. St. Jude Medical, Inc., 2012 ONSC 3660
COURT FILE NO.: 00-CV-195906CV, Toronto
DATE: 20120626

ONTARIO

SUPERIOR COURT OF JUSTICE

BETWEEN:

YVONNE ANDERSEN ON HER OWN BEHALF AND AS EXECUTRIX OF THE ESTATE OF ERIK ANDERSEN, SHARON FROST and HER MAJESTY THE QUEEN IN RIGHT OF THE PROVINCE OF ALBERTA, AS REPRESENTED BY THE MINISTER OF HEALTH AND WELLNESS

Plaintiffs

– and –

ST. JUDE MEDICAL, INC. and ST. JUDE MEDICAL CANADA, INC.

Defendants

REASONS FOR JUDGMENT

LAX J.

Released: June 26, 2012