Federal Court  Cour fédérale

Date: 20200416

Docket: T-741-18

Citation: 2020 FC 522

Ottawa, Ontario, April 16, 2020

PRESENT: The Honourable Mr. Justice Southcott

BETWEEN:

AMGEN INC. AND AMGEN CANADA INC.

Plaintiffs/
Defendants by Counterclaim

and

PFIZER CANADA ULC

Defendant/
Plaintiff by Counterclaim

PUBLIC JUDGMENT AND REASONS

I. OVERVIEW

[1] This decision relates to an action by the Plaintiffs, Amgen Inc. and Amgen Canada Inc. [collectively, Amgen], against Pfizer Canada ULC [Pfizer], and a related counterclaim by Pfizer. Amgen brings this action pursuant to section 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [Regulations], after being served with a Notice of Allegation by Pfizer pursuant to section 5(3) of the Regulations.

[2] Amgen Inc. is the current owner of Canadian Patent No. 1,341,537 [the 537 Patent]. Amgen Inc. has authorized Amgen Canada Inc. to list the 537 Patent on the Patent Register against Amgen's biologic drug NEUPOGEN, which the latter markets, sells, and distributes in Canada. The drug substance in NEUPOGEN and disclosed in the 537 Patent is generically known as filgrastim. Pfizer has filed with the Minister of Health a New Drug Submission [NDS] for the issuance of a Notice of Compliance [NOC] for its filgrastim biosimilar NIVESTYM. Pfizer's NDS refers to NEUPOGEN as a reference biologic drug for the purposes of regulatory approval.

[3] Amgen's claim in this action alleges the making, constructing, using, selling, offering for sale, importing or exporting of NIVESTYM in accordance with Pfizer's NDS would infringe certain claims of the 537 Patent. Pfizer's defence and counterclaim allege the 537 Patent is invalid and void, due to obviousness of the asserted claims, insufficiency of the 537 Patent's disclosure, and alleged misrepresentations to the Canadian Intellectual Property Office [CIPO].

Pfizer also asserts that, even if the patent is valid, it is protected against allegations of infringement by the defence of prior use.

[4] Some of the evidence adduced at trial is subject to a Confidentiality Order dated December 11, 2019 [the Confidentiality Order], in order to protect commercially sensitive confidential information of the parties. A draft confidential decision was therefore sent to the parties on April 6, 2020 to allow them to propose any redactions required for the issuance of the public version of the decision. Amgen proposed redactions to protect a non-party's private health information and to protect the dates and durations of certain steps in the invention process, which Amgen considers commercially sensitive information. Pfizer does not object to redaction of the private health information but does oppose the other redactions.

[5] In the course of exchanging written submissions on this issue, Pfizer pointed out that several of the proposed redactions relate to a date that is accessible to the public in the file history for the 537 Patent. Amgen agreed and withdrew its request that this date be redacted. With respect to the remaining proposed redactions, Pfizer disputes Amgen's assertion that these dates could affect its patent rights in other jurisdictions. Pfizer submits that Amgen is motivated by strategic litigation considerations and not by confidentiality interests in commercially sensitive information. Amgen responds, *inter alia*, that wishing to protect information because of litigation considerations would not diminish the confidential nature of the information.

[6] I agree with Amgen's position. It has consistently treated the information at issue as confidential, including obtaining the Confidentiality Order and redacting the information from

the publicly filed versions of its fact witness affidavits. While a party with which it is in litigation in another jurisdiction may be able to obtain this information though the discovery process, it will presumably then be protected by a version of the implied undertaking rule or by a protective agreement or order. As the proposed redactions will not affect the intelligibility of the decision, I am satisfied that the redactions appropriately balance the interests of protecting confidential information and the public interest in open and accessible court proceedings. As such, two versions of this decision, one public and the other confidential, will be issued simultaneously.

[7] For the reasons explained in detail below, I find that the claims of the 537 Patent asserted by Amgen are obvious and therefore invalid. I do not find the 537 Patent as a whole invalid due to misrepresentation or insufficiency. I also find that, if the claims asserted by Amgen had been valid, Pfizer would not have been protected by the defence of prior use.

II. BACKGROUND

[8] The Plaintiff, Amgen Inc., is a corporation incorporated and existing under the laws of the State of Delaware with its principal place of business in Thousand Oaks, California. Amgen Inc. is a biotechnology company and is the current owner of the 537 Patent. The Plaintiff, Amgen Canada Inc. [Amgen Canada], is a corporation incorporated and existing under the laws of the Province of Ontario and located in Mississauga, Ontario. Amgen Canada is also a biotechnology company and markets, sells and distributes various biologic drugs in Canada, including the filgrastim drug NEUPOGEN. Filgrastim is used to treat neutropenia (a disorder wherein the body cannot produce sufficient levels of white blood cells called neutrophils), which

can develop as a result of damage to the body's hematopoietic system (the system responsible for production of blood cells).

[9] The Defendant, Pfizer, is a corporation incorporated under the laws of Canada and has its head office and principal place of business in Kirkland, Québec. Like Amgen Canada, Pfizer sells pharmaceutical products including biologic drugs in Canada.

[10] The 537 Patent is entitled "Production of Pluripotent Granulocyte Colony-Stimulating Factor." It issued on July 31, 2007 from Canadian Patent Application No. 516,737 [the 737 Application], filed on August 25, 1986. The 537 Patent claims priority to US Patent Application No. 768,959 [the 959 Application], filed on August 23, 1985, and US Patent Application No 835,548 [the 548 Application], filed on March 3, 1986. Only the 959 Application is relevant to this proceeding, for reasons outlined below. Because of the dates surrounding this patent, the governing legislation in this action is the *Patent Act*, RSC 1984, c P-4 as it read immediately before October 1, 1989 [the Old Act]. The 537 Patent will expire on July 31, 2024. Amgen describes the patent as relating to a hematopoietic growth factor, made using recombinant genetic technology.

[11] By way of general scientific background relevant to this description, a hematopoietic growth factor is, in this case, a protein, which stimulates the growth of blood cells. A protein is composed of a string of amino acids. There are 20 different amino acids found in proteins of mammalian species. A recombinant protein is one produced in a laboratory through DNA technology. This involves, *inter alia*: (a) combining the DNA that codes for the target naturally

occurring protein with another piece of DNA, a process called cloning that forms recombinant DNA; (b) inserting that recombinant DNA into a host cell, referred to as transforming the cell; and (c) replicating the transformed host cell to form a colony of such cells, which express the target protein because of the presence of the protein's DNA.

[12] The 537 Patent refers to the target protein, i.e. the naturally occurring protein to be recombinantly produced, as "human pluripotent granulocyte colony-stimulating factor" or "hpG-CSF". A colony-stimulating factor [CSF] is a hematopoietic growth factor that stimulates the growth of progenitor cells into colonies. Progenitor cells develop from stem cells and in turn form mature blood cells. There are different categories of progenitor cells, which in turn develop into particular categories of mature cells. Granulocytes (the G in hpG-CSF) are one category of mature white blood cell that matures from relevant progenitor cells. As noted above, the protein to which the 537 Patent relates stimulates colonies of neutrophils, which are a type of granulocyte.

[13] The remaining term in the name the 537 Patent employs for the subject protein is "pluripotent." The meaning of this term, particularly in the context of the 537 Patent's disclosure, is controversial between the parties. As will be explained in greater detail later in these Reasons, the prior art describes the target protein as "pluripotent", meaning in that context that it stimulated growth of multiple lineages of mature blood cells from progenitor cells. However, either before or after the filing of the patent application (a point about which the parties disagree), it was discovered that this protein stimulates only the growth of granulocytes, not other cell lineages. The protein subsequently became known as granulocyte colony-

stimulating factor [G-CSF]. Other than where this controversy is engaged (in the analyses of the misrepresentation and insufficiency allegations), these Reasons use the terms "hpG-CSF" and "G-CSF" interchangeably.

[14] While the 537 Patent sets out 82 claims, Amgen's allegations of infringement assert only Claims 43 though 47 [the Asserted Claims]. Subject to the defences it has pleaded, Pfizer admits that the making, constructing, using or selling of filgrastim would infringe the Asserted Claims. As such, the outcome of this action turns on Pfizer's allegations of invalidity, all based on provisions of the Old Act, and the prior use defence.

[15] Pfizer's alleges three bases for invalidity: (a) the Asserted Claims are obvious; (b) Amgen has made wilfully misleading and untrue material allegations to CIPO, contrary to s 53 of the Old Act; and (c) the 537 Patent does not sufficiently disclose the alleged invention, contrary to s 34 of the Old Act. The prior use provision of the Old Act is s 56, although, for reasons that will be explained later, Pfizer relies on the common law to invoke that defence.

[16] As a preliminary matter, this proceeding also raises an issue surrounding the interaction between an action under s 6(1) of the current Regulations and an application under the former Regulations related to the same patent. In 2012, Amgen brought such an application in Court File No. T-2072-12, seeking a prohibition order against the Minister of Health to prevent an NOC from issuing to Apotex Inc. [Apotex] for its filgrastim biosimilar [the Apotex Application]. In *Amgen Canada Inc v Apotex Inc*, 2015 FC 1261, Justice Hughes dismissed the Apotex Application, finding Amgen had not shown Apotex's obviousness allegation in relation to Claim

43 of the 537 Patent was unjustified [the Apotex Decision]. Pfizer now argues this Court should adopt certain factual and legal findings of the Apotex Decision based on principles of abuse of process and/or judicial comity.

[17] Each of the parties supported its positions on the various issues in this action through the evidence of expert witnesses. Each expert presented a report and was cross-examined at trial. All experts were qualified at trial without objection, with the articulation of the experts' respective areas of qualification agreed between the parties. While Pfizer objected to various portions of Amgen's experts' evidence in advance of trial, including objections as to admissibility, the parties agreed the Court would receive the evidence and submissions on its admissibility at trial and adjudicate those objections in this Judgment and Reasons. Pfizer further advised during closing argument that it was pursuing objections to the expert evidence only as outlined in its closing submissions (all of which go to weight).

[18] The parties also introduced evidence through fact witnesses. By agreement, they adopted a process whereby the witnesses' direct evidence was presented in affidavit form, to be supplemented at the trial by a "warm up" examination-in-chief, followed by cross-examination. One of Amgen's witnesses, Dr. Hsieng Lu, was examined in advance of trial, with the video recording of the examination played and entered into evidence during trial.

III. THE ASSERTED CLAIMS

[19] The Asserted Claims in the 537 Patent read as follows:

> **43.** A polypeptide defined by the amino acid sequence:

> Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro [**Claim 43 Sequence**].
>
> **44.** A recombinant DNA encoding a polypeptide defined by the amino acid sequence: **Claim 43 Sequence**
>
> **45.** An expression vector comprising a DNA sequence encoding a polypeptide defined by the amino acid sequence: **Claim 43 Sequence**
>
> **46.** A transformed host cell comprising an expression vector comprising a DNA encoding a polypeptide defined by the amino acid sequence: **Claim 43 Sequence**
>
> **47.** A process for the preparation of a human granulocyte-colony stimulating factor (G-CSF) comprising transforming a host cell with an expression vector containing a DNA sequence encoding the amino acid sequence: **Claim 43 Sequence**, culturing said transformed host cell and collecting the granulocyte colony-stimulating factor expressed by said transformed cell.

IV. ISSUES

[20] By the time of trial, the parties had significantly narrowed the issues originally identified in the pleadings and agreed on a Joint Statement of Issues. With some re-ordering/re-grouping and minor changes in their articulation, I adopt those issues as follows:

A. Abuse of Process / Judicial Comity:

i. **Abuse of Process:** Is it an abuse of process for Amgen to relitigate factual and legal issues determined by Justice Hughes in the Apotex Decision?

ii. **Judicial Comity:** If it is not an abuse of process, should this Court nevertheless follow the legal findings and/or factual findings from the Apotex Decision by reason of judicial comity?

B. Validity:

i. **Skilled Person:** Who is the person skilled in the art to whom the 537 Patent is addressed [the Skilled Person]?

ii. **Claim Construction:** How should the Asserted Claims be construed?

iii. **Obviousness:**

(a) **Date of Invention:** Is August 23, 1985 the invention date of each of the Asserted Claims by virtue of the 959 Application? Or, was the subject matter of each of the Asserted Claims invented by no later than August 23, 1985?

(b) **Obviousness Analysis:** Was each of the Asserted Claims obvious as of the date of invention?

C. Material Misrepresentation: Is the 537 Patent void pursuant to section 53 of the Old Act?

D. Insufficiency: Is the disclosure of the 537 Patent insufficient pursuant to section 34 of the Old Act?

E. Prior use defence: Is Pfizer exempt from liability for infringement by reason of section 56 of the Old Act?

V. FACT WITNESSES

[21] The following is a brief summary, identifying the background and role of each fact witness and the areas to which their evidence relates. While particular details of the evidence will be considered later in the Reasons, in analysing the issues to which it relates, I will include in this summary some detail intended to provide an overall factual framework. The following also identifies my general observations as to the reliability of the individual fact witnesses' evidence.

A. *Mr. Thomas Boone (Amgen Witness)*

1. Evidence in Brief

[22] The first and lengthiest witness to give evidence on behalf of Amgen was Mr. Thomas Boone. Mr. Boone is a molecular biologist and protein chemist. In the 1970s, he received a Bachelor of Science degree in genetics and then two Masters of Science degrees, in genetics and soil science. Mr. Boone started working at Amgen Inc. in September 1981 as a Research Associate under Dr. Lawrence Souza (the named inventor on the 537 Patent) and reported to him for several years. He retired from Amgen in 2009 as its Vice President of Protein Sciences, the group within Amgen that focus on expressing, purifying, and developing proteins that can be used in human beings. Mr. Boone now owns his own consulting company, which consults for many companies including Amgen.

[23] From 1981 through 1984, Mr. Boone worked as a Research Associate for Amgen, developing protocols and techniques for gene cloning and DNA sequencing, and working on projects focused on specific proteins. In this role, he developed experience in research strategies and molecular biology techniques involved in gene cloning, as well as experience with protein purification, both at the initial stage of isolating a naturally occurring protein and at the later stage of purifying a genetically engineered protein.

[24] Mr. Boone first joined Amgen's G-CSF project in late 1984. He was involved in this project through the clinical introduction of Amgen's genetically engineered G-CSF in late 1986 and continued to work with the protein into the early 1990s. He explains that the "kicking-off

point" for this project was a discovery made by a group of scientists at the Sloan-Kettering Institute [SKI] who were investigating the protein secreted by the "5637" human bladder carcinoma cell line. Dr. Karl Welte and other scientists at SKI had observed that a protein preparation derived from the conditioned culture medium of 5637 cells had a stimulatory effect on blood cell precursors in certain types of *in vitro* assays. (While not expressly noted in Mr. Boone's affidavit, the parties agree that this discovery was subsequently published in an article by Dr. Welte and others at SKI, entitled "Purification and biochemical characterization of human pluripotent hematopoietic colony-stimulating factor," in the March 1985 edition of the *Proceedings of the National Academy of Sciences* [Welte 1985]).

[25] Mr. Boone explains that the objective of Amgen's G-CSF project was to attempt to clone the DNA for this protein and to design a process for expressing a genetically engineered (or recombinant) version of the protein, having the same biological activity as the naturally occurring variant. In his affidavit, he provides detailed explanations of Amgen's process for attempting to produce the recombinant protein, broken down into the following five stages:

A. obtaining an adequately purified sample of the naturally occurring G-CSF protein;

B. identifying a partial amino acid sequence of the protein;

C. making a set of useful probes designed to bind to the cDNA (meaning complementary DNA) that encoded the identified partial amino acid sequence of the protein;

D. identifying the gene (i.e. DNA sequence) that encodes the protein, by creating a cDNA library for the 5637 cell line and employing the probes to attempt to hybridize (i.e. bind) one of the probes to the targeted cDNA in the library;

E. expressing a recombinant version of the G-CSF protein and purifying it in such a way that it retains at least some of the biological activities of the naturally occurring G-CSF protein.

[26] By the time Mr. Boone first joined the G-CSF project in late 1984, others on the Souza team had attempted throughout 1984 to obtain a partial amino acid sequence for the target protein by analysing samples of the conditioned medium that had been sent to Amgen by SKI, with which Amgen was collaborating. However, as adequate amino acid sequencing had not been achieved using the SKI samples, Dr. Souza decided Amgen would attempt to culture the 5637 cells itself to create its own conditioned medium and then purify the relevant protein to undertake further sequencing efforts. This in-house work involved modifications to SKI's original culturing and purification protocols as set out in Welte 1985. Mr. Boone was not directly involved in producing the conditioned medium. His work with the Souza team began with helping to purify Amgen's in-house samples.

[27] Mr. Boone's affidavit details the challenges and uncertainties at the various stages of the G-CSF project. He emphasizes the very real possibility that the project would fail. Those challenges will be explained and considered later in these Reasons.

(a) *General Observations on Reliability*

[28] Pfizer submits the Court should treat Mr. Boone's evidence with caution, arguing he is a paid advocate who has provided inconsistent and unreliable evidence. While Amgen no longer employs Mr. Boone, Pfizer notes he has worked with different Amgen legal teams on litigation involving the 537 Patent for years. Pfizer asserts that, while Mr. Boone is the witness Amgen has chosen to tell its invention story, he does not have first-hand knowledge of much of the evidence he seeks to provide to the Court. Pfizer also asserts that, by comparing Mr. Boone's current

evidence with that which he provided in past proceedings, it is apparent he has both stretched and curated his evidence to favour Amgen's position.

[29] In support of this last assertion, Pfizer notes that Mr. Boone's affidavit in the Apotex Application described Amgen's changes to Dr. Welte's purification protocol simply as "refinements", while his current affidavit describes those changes as "significantly re-worked". As another example, Pfizer refers to Mr. Boone's evidence regarding the purification and proper folding of the recombinant G-CSF, which he describes as "[…] a difficult challenge for us to overcome in August 1985." Pfizer points out that [REDACTED].

[30] My overall impression of Mr. Boone was that he attempted to testify accurately and honestly. At times, he was less than direct in answering cross-examination questions, but I interpreted this as wanting to ensure precision in his answers, rather than as being difficult. That said, Pfizer's points about Mr. Boone's subjective characterization of Amgen's work do resonate with me. Subject to concerns regarding evidence about which he does not have sufficient knowledge (which I will consider when addressing specific aspects of his evidence), I am inclined to treat his factual evidence surrounding Amgen's work as reliable. However, I will treat his characterizations of that work with more caution.

B. *Dr. Krisztina Zsebo (Amgen Witness)*

1. Evidence in Brief

[31] Dr. Krisztina Zsebo is a biochemist who worked at Amgen Inc. from April 1984 to 1992. She received a Bachelor of Science degree in biochemistry in 1977, a Masters degree in

biochemistry and biophysics in 1980, and a PhD in comparative biochemistry, with a minor in molecular biology, in 1984. Dr. Zsebo then joined Amgen as a Research Scientist. During her time at Amgen, she worked on the characterization, cloning, and/or recombinant expression of G-CSF and other factors. After the G-CSF project, she led the development of a stem cell factor, which was a hematopoietic growth factor like G-CSF. When Dr. Zsebo left Amgen in 1992, she was the Associate Director, Product Development for that stem cell factor. She is currently the Chief Executive Officer, Director, and Co-founder of a biotechnology company established in 2018.

[32] Dr. Zsebo believes her involvement with the G-CSF project began sometime in April 1985. She states she was heavily involved in the project and explains she was asked to provide information about that work, particularly the *in vitro* testing of the recombinant protein. Dr. Zsebo describes her involvement in the following aspects of the project:

A. Beginning around April 1985, she joined the Souza team that had been working on culturing 5637 cells and helped Joan Fare, a research associate on that team, to produce the conditioned medium from which the target protein was purified;

B. She conducted various *in vitro* tests, of both the purified target protein and Amgen's *E. coli* expressed, recombinant version of the protein, to characterize the protein and to confirm that the team had recombinantly produced the correct protein. This involved setting up and running a number of *in vitro* biological assays, as well as determining the carbohydrate structure (or glycosylation) of the protein by identifying its apparent molecular weight;

C. She helped to express a different version of the recombinant protein in mammalian cells (as opposed to *E. coli* cells); and

D. She assisted Dr. Arthur Cohen, an Amgen research scientist specializing in the pharmacology of drug candidates, with *in vivo* testing of the *E. coli* expressed recombinant protein.

2. General Observations on Reliability

[33] While Dr. Zsebo is not presently an Amgen employee, Pfizer notes she has acted as a consultant for Amgen in previous proceedings, including the Apotex Application. Notwithstanding that she may have an ongoing business relationship with Amgen, I identified no indications of bias or advocacy in her testimony. Dr. Zsebo struck me as a precise and straightforward scientist, and I found no basis to question her credibility. I remain conscious of arguments raised by Pfizer as to particular areas of her evidence that are not reliable, and I will take those into account when analysing her evidence in greater detail later in these Reasons.

C. *Dr. Hsieng Lu (Amgen Witness)*

1. Evidence in Brief

[34] Dr. Hsieng Lu is a protein biochemist who worked at Amgen Inc. in its protein sequencing group from September 1984 until his retirement on December 31, 2013. Dr. Lu graduated with a Bachelor of Science in agricultural chemistry in 1970, a Masters of Science in 1975, and a PhD in biochemistry in 1981. Protein sequencing was an important part of his thesis work, and he worked on several sequencing projects during his doctoral work from 1979 to 1981. From 1982 to 1984, Dr. Lu completed post-doctoral work, focusing on the study of protein structure, protein function, and protein sequencing.

[35] When Dr. Lu joined Amgen in 1984, he was the second research scientist to be recruited to its protein sequencing group. He joined another research scientist, Dr. Por Lai, who had already been working on the amino acid sequencing component of the G-CSF project. He

ultimately worked on the project with both Dr. Lai and two research assistants in the 1984 to 1986 timeframe.

[36] Dr. Lu explains the key responsibilities of the protein sequencing group were to determine the purity of protein samples provided to them and to try to determine the amino acid sequence of the protein of interest in each sample. With respect to cloning projects, the goal of the group was to determine, unambiguously, enough of the amino acid sequence of a protein of interest to permit Amgen's molecular biologists to attempt to clone the protein. Dr. Lu explains the equipment and process through which this work was conducted.

[37] In the period from March 1984 to late June 1985, Amgen's protein sequencing group tried to sequence the target G-CSF protein five separate times—three times using samples provided by SKI and twice using a protein sample independently purified by Amgen researchers—before Dr. Souza was satisfied his team had a sufficiently long and unambiguous amino acid sequence to proceed with the cloning project. By the time Dr. Lu joined the group in September 1984, the three unsuccessful sequencing efforts (or runs) using the SKI samples had already taken place.

[38] Dr. Lu states he was personally involved, with Dr. Lai, in the fourth and fifth runs using the sample purified in-house at Amgen. His involvement in the fourth run began on May 24, 1985, when the protein sequencing group received a sample that had been partially purified by Mr. Boone from protein secreted by cells cultured in-house at Amgen. He and Dr. Lai performed the final purification stage, employing a High Performance Liquid Chromatography [HPLC]

system. Dr. Lu states that, from the fourth sequencing run, they were able to obtain a sequence of 31 amino acids, most of which they were certain they identified correctly. However, Dr. Souza was not satisfied they could proceed with the cloning effort, and he directed the protein sequencing group to attempt another run on the same sample.

[39] Therefore, in late June 1985, Amgen performed another sequencing run, using approximately 50% more of the sample than in the previous run. In addition to the increased amount of the sample, for the fifth sequencing run, the protein sequencing group decided to reduce the sample with ß-mercaptoethanol to remove the protein's secondary structure. That is, they unfolded the protein under reducing conditions, with the hope of improving the effectiveness of the process (called Edman degradation) by which they cleaved individual amino acids from the protein chain, allowing them to call additional amino acids. Dr. Lu also states that, after weighing the pros and cons of using polybrene, which could sometimes make sequencing calls more difficult due to the presence of impurities, Dr. Lai made the judgment call to use polybrene at each cycle of the Edman degradation to try to improve the identification of the amino acids of interest.

[40] Dr. Lu explains they were then able to determine the identity of 44 amino acids before the chromatograms became too difficult to interpret. Based on the results of this fifth run, Dr. Souza was satisfied the amino acid sequence was sufficiently long and unambiguous that he could rely on it to move forward to the next steps of the cloning project. In his affidavit, Dr. Lu describes Dr. Souza and Mr. Boone selecting from this fifth run sequence a particular span of amino acids to design oligonucleotide probes. He also describes the sequencing group’s

uncertainty as to their results in the fifth run. In his view, Amgen was lucky that Dr. Souza chose the particular span that he did, as it later turned out that there were errors elsewhere in this fifth run sequence.

2. General Observations on Reliability

[41] Pfizer questions the level of first-hand involvement by Dr. Lu in the G-CSF project and the reliability of the recollections he claims to have of events that took place almost 35 years ago. It also emphasizes a portion of Dr. Lu's cross-examination, which Pfizer characterizes as follows: "Dr. Lu made up evidence that was wholly untrue, and was forced to recant when confronted with his fabrication."

[42] This argument relates to Dr. Lu's responses to questions by Pfizer's counsel as to whether an affidavit he swore in the Apotex Application attached all the same exhibits as his affidavit in the present proceeding. After reviewing the documents during a break, Dr. Lu testified that certain chromatograms attached to his Apotex affidavit were not attached to his current affidavit. When asked if these omissions were an unintentional oversight, Dr. Lu responded that probably an intentional decision was made to remove the chromatograms to reduce complexity.

[43] However, a short time later in the cross-examination, Dr. Lu located the missing chromatograms in the current affidavit, concluding they had all been included, just in a different order than in the Apotex affidavit. Under further questioning, Dr. Lu acknowledged that his

previous evidence, stating a decision had been made not to include certain chromatograms, was not true.

[44] Amgen argues that Pfizer has unfairly accused Dr. Lu of being untruthful. Amgen submits this allegation of dishonesty does not relate to any statement material to the issues in this litigation. Nor did it represent an effort to distort evidence in Amgen's favour. Amgen also asserts that Dr. Lu was initially speculating that a decision had been made to remove certain chromatograms from his present affidavit, and he described an actual recollection of such a decision only after being pressed by Pfizer's counsel.

[45] I agree with Pfizer that this portion of Dr. Lu's testimony raises concerns about his reliability as a witness. The point is not that this evidence was material to the issues. Rather, the concern is whether the Court can rely on Dr. Lu's professed recollections of events. While Pfizer's counsel pressed Dr. Lu to confirm whether the decision to leave out certain documents was speculation or an actual recollection, I consider the pursuit of this questioning to have been entirely fair, given the ambiguity in the manner he described this decision.

[46] I am not left with the impression of a deliberately dishonest witness, but rather of a witness who is prone to speculation and influence, and who cannot necessarily be relied upon to testify with precision as to what he actually remembers. Regardless, little actually turns on this impression. Amgen's closing submissions actually rely very little on the evidence of Dr. Lu. As will be noted later in these Reasons, Amgen does emphasize in its obviousness submissions his evidence that one of the amino acids within the stretch selected by Dr. Souza and Mr. Boone

(residues 23-30) to design oligonucleotide probes had been mis-called in the fourth run. However, this fact does not itself appear to be controversial.

D. *Ms. Anita Hammer (Amgen Witness)*

[47] Ms. Anita Hammer is the Director of Regulatory Affairs at Amgen Canada, which she explains is an indirectly wholly-owned subsidiary of Amgen Inc. Like the other fact witnesses, she provided direct evidence through an affidavit. However, as agreed between the parties, she was not called as a *viva voce* witness at trial and was not cross-examined. Pfizer raises no concerns with the veracity of her evidence.

[48] Ms. Hammer is responsible for completing regulatory requirements to list Amgen's patents on Health Canada's Patent Register, including the 537 Patent. She explains that process, including the means by which Amgen Canada obtained the consent of Amgen Inc. as patent owner.

[49] Ms. Hammer also explains that Dr. Souza, the named inventor of the 537 patent, left Amgen's employ in 2000. She describes her unsuccessful efforts to contact Dr. Souza, through his legal counsel, to discuss his possible participation as a witness in the trial of this action.

[50] Finally, Ms. Hammer describes contacting Joan Fare, a former Amgen employee who worked on the G-CSF project. [REDACTED].

E. *Ms. Sheila Ahmed (Pfizer Witness)*

[51] Ms. Sheila Ahmed is a Manager, Regulatory Affairs at Pfizer, a subsidiary of Pfizer Inc., and has worked in a regulatory role since 2015. Her responsibilities include managing Pfizer's Canadian regulatory portfolio for biosimilars. She prepares and files regulatory submissions to Health Canada, including Pfizer Canada's NDS concerning its filgrastim product NIVESTYM, which was filed on February 28, 2018.

[52] Ms. Ahmed's affidavit attaches excerpts from the NDS for NIVESTYM, copies of the product monographs for both NIVESTYM and Amgen's drug NEUPOGEN, and Health Canada's letter to Pfizer Canada dated February 8, 2019, advising that the review of its NIVESTYM submission was complete, but that an NOC would not be issued until the requirements of the Regulations are met. By agreement of the parties, Ms. Ahmed did not provide oral evidence at trial and was not cross-examined. Amgen raises no concerns about her evidence.

F. *Dr. Goran Valinger (Pfizer Witness)*

[53] Dr. Goran Valinger is the Director of Manufacturing Science and Technology at Hospira Zagreb d.o.o [Hospira Zagreb], which is a subsidiary of Pfizer. He holds both an undergraduate degree and a PhD in biotechnology. Dr. Valinger worked at PLIVA, a pharmaceutical company in Croatia, in various positions between 2001 and 2009. In 2006, he became the Director of Biotechnology Development, assuming responsibility for drug substance process development, including for filgrastim. In 2009, PLIVA was acquired by Hospira Inc. [Hospira], and Dr.

Valinger became the Director of Technical Support of Hospira Zagreb. In 2015, Pfizer acquired Hospira, and Dr. Valinger received his current title of Director of Manufacturing Science and Technology with Hospira Zagreb.

[54] Dr. Valinger explains Hospira Zagreb will manufacture the filgrastim to be sold by Pfizer Canada. He also explains the manufacturing process, employing a system with two cell banks (called a two-tiered cell banking system). The first tier is a Master Cell Bank [MCB], comprising *E. coli* host cells that were transformed by expression vectors containing the DNA sequence coding for filgrastim. The second tier is a Working Cell Bank [WCB], created by replicating cells from the MCB. The cells of the WCB are in turn grown to make additional cells, called production cells, which are used to make filgrastim. The MCB, WCB, and production cells are all identical.

[55] Dr. Valinger states that the MCB was created on or about April 6, 2004, the first WCB was created on or about April 19, 2005, and the first filgrastim protein was produced by December 23, 2005. Amgen does not challenge the reliability of Dr. Valinger's evidence.

VI EXPERT WITNESSES

[56] Each of the parties introduced expert evidence in support of its respective positions on construction of the Asserted Claims and the various grounds of invalidity that are at issue, including opining on the credentials and characteristics of the Skilled Person, the state of the art as of August 23, 1985, and the common general knowledge [CGK] of the Skilled Person as of August 23, 1985 and July 31, 2007. The following is a summary of each expert's qualifications

and the areas to which his evidence relates. As with the above fact witnesses, I will include in these summaries some level of detail, intended to support analysis of the issues later in these Reasons. The following also identifies my general observations as to the reliability of the individual experts.

A. *Dr. Richard Van Etten (Pfizer Expert)*

[57] The first expert to testify on Pfizer's behalf, Dr. Richard Van Etten, is presently the Director of the Chao Family Comprehensive Cancer Center and a Professor of Medicine and Biological Chemistry at the University of California Irvine. He also practices medicine as a physician in the Division of Hematology/Oncology at the University of California Irvine Medical Centre. Dr. Van Etten's academic research and clinical practice is focused on cancers of the human blood system.

[58] Dr. Van Etten earned Bachelor of Science degrees in Math and Biology from the Massachusetts Institute of Technology [MIT] in 1978 and a combined MD/PhD degree from Stanford University in 1984. He did his PhD research at Stanford from 1979 to June 1984 in the laboratory of Dr. David Clayton, who he describes as one of the world leaders in recombinant DNA technology. Dr. Van Etten then completed his internship and residency in Internal Medicine at Brigham & Women's Hospital in Boston from 1984 to 1988 and a subsequent fellowship in hematology at the same hospital. Then, from 1988 to 1991, he conducted post-doctoral research at the Whitehead Institute for Biomedical Research at MIT. Dr. Van Etten's research focused on the molecular structure and function of a particular protein involved in cell signalling that can cause chronic myeloid leukemia when it becomes dysregulated.

[59] Throughout his professional career, Dr. Van Etten has been a professor and researcher at several American universities, as well as practising medicine as a hematologist. For the past 27 years, he has operated a research laboratory dedicated to the study of leukemias. Dr. Van Etten has authored many peer-reviewed publications, frequently presents at conferences, universities, and hospitals on the subject of his laboratory's research, and has won many awards for that research. He was qualified at trial as an expert in hematology, protein biochemistry, and molecular biology, including recombinant DNA technology.

[60] Dr. Van Etten provided two reports. In his first and principal report, he explains that Pfizer's counsel assigned him several mandates. The following summarizes the mandates related to the issues in this action and Dr. Van Etten's opinion in relation to each of them.

1. Mandate 1 – Welte 1985

[61] First, Dr. Van Etten was asked to review and then summarize Welte 1985.

[62] He describes Welte 1985 as reporting on the discovery and isolation of a human protein—which Dr. Welte named "pluripotent CSF"—that was reported to act as a pluripotent hematopoietic growth factor in the laboratory. Dr. Van Etten opines that this was a significant discovery in the area of hematology and of considerable interest to scientists in biotechnology companies, particularly those interested in developing drugs to treat disorders of the hematopoietic system.

2. Mandate 2 - Research following from Welte 1985

[63] After he summarized Welte 1985, Pfizer's counsel asked Dr. Van Etten if scientists at the time would have thought there was any research that naturally followed from Welte 1985. When he answered in the affirmative, counsel asked him what the next research project would be.

[64] Dr. Van Etten responded that the last paragraph of Welte 1985 set out the next research project: to test the potential of "purified human pluripotent CSF […] in the management of clinical diseases involving hematopoietic derangement or failure." To do so, Welte 1985 suggests using recombinant DNA technology to allow for large-scale production of pluripotent CSF needed for clinical testing. Making recombinant pluripotent CSF for clinical testing would require two steps: (a) cloning the gene for pluripotent CSF; and (b) transforming the gene into host cells to cause them to produce biologically active pluripotent CSF.

3. Mandate 3 - Literature related to steps after Welte 1985

[65] After discharging Mandate 2, counsel asked Dr. Van Etten to identify sources of information scientists would have relied upon as of August 23, 1985 to carry out the recombinant expression of pluripotent CSF that he described in Mandate 2. Counsel asked him to focus on hematopoietic growth factors.

[66] Dr. Van Etten responded that a flurry of activity between 1982 and 1986 led to the isolation of genes for several hematopoietic growth factors, including the protein described in Welte 1985. He opines that, by August 23, 1985, there were laboratory manuals that explained in detail the techniques necessary to carry out the recombinant expression of pluripotent CSF. A

laboratory manual entitled *Molecular Cloning: A Laboratory Manual*, authored by T. Maniatis and others in 1982 [Maniatis 1982], was the leading and comprehensive guide to recombinant DNA technology. Maniatis 1982 would have taught scientists how to use this technology to make proteins such as pluripotent CSF in large scale.

4. Mandate 4 – The 537 Patent

[67] After completing the previous mandates, counsel provided Dr. Van Etten with a copy of the 537 Patent and asked him to: (a) summarize what the 537 Patent discloses; (b) identify the Skilled Person to whom the 537 Patent is addressed; (c) explain the Skilled Person's CGK as of the July 31, 2007 publication date of the patent; and (d) opine how the Asserted Claims would have been understood by the Skilled Person as of July 31, 2007.

[68] Dr. Van Etten opines that the 537 Patent begins where Welte 1985 left off—it describes how Amgen made a recombinant form of the protein that Welte 1985 isolated. The patent renames this protein "hpG-CSF". Dr. Van Etten states that the technical path described in the 537 Patent for achieving recombinant expression of this protein is the path that he stated earlier in his report would naturally follow from Welte 1985: (a) cloning the gene for hpG-CSF; and (b) transforming the gene into host cells to produce recombinant hpG-CSF.

[69] Dr. Van Etten concludes the Skilled Person to whom the 537 patent is addressed would have expertise in the fields of molecular biology, hematology, and protein biochemistry. Therefore, the Skilled Person would be a team, possessing the qualifications and experience to

understand and implement the teachings of the patent, consisting of one or more people with the following skills:

A. a molecular biologist with a PhD and several years of work experience in academia or industry;

B. a hematologist with an MD and board certification or, alternatively, a PhD in hematology and several years of work experience in academia or industry; and

C. a protein biochemist with a PhD and several years of work experience in academia or industry.

[70] Dr. Van Etten also provides scientific background information that he considers would have been included in the CGK of the Skilled Person as of the July 31, 2007 publication date of the 537 Patent. He explains this information was also CGK as of August 23, 1985, as the essence of protein biochemistry, molecular biology, and hematology had been largely worked out by 1985, including the basic tools of recombinant DNA technology. However, he also explains that, between 1985 and 2007, there were significant advances in the CGK concerning hematopoietic lineages and growth factors, including hpG-CSF (which had become known as G-CSF). It was CGK by 2007 that the naturally occurring and recombinant versions of this protein did not in fact have pluripotent hematopoietic biological activity.

[71] Dr. Van Etten then opines that the Asserted Claims claim the following:

A. **Claim 43 -** a recombinant hpG-CSF polypeptide with the 174 amino acid sequence of naturally occurring hpG-CSF and an additional N-terminal methionine (Met) [the Claim 43 Polypeptide];

B. **Claims 44 to 46:** recombinant DNA tools to express the Claim 43 Polypeptide; and

C. **Claim 47:** a process to make the Claim 43 Polypeptide.

[72] As discussed in more detail below, Dr. Van Etten finds the Skilled Person would not understand the polypeptide or tools in Claims 43-46 to possess any particular biological activity. However, the Skilled Person would understand the polypeptide resulting from the process of Claim 47 to possess granulocyte colony-stimulating activity.

5. Mandate 5 - Obviousness

[73] Pfizer's counsel then asked Dr. Van Etten whether any of the Asserted Claims were obvious. While he was asked to consider that question as of August 23, 1985 (the filing date of the 959 Application) and a subsequent date in 1986 (the filing date of the 548 Application), Amgen confirmed at trial that it is now relying only on the 1985 date.

[74] Dr. Van Etten opines that all of the Asserted Claims were obvious as of August 23, 1985. He concludes that, after Welte 1985 was published, a Skilled Person would inevitably make a recombinant form of hpG-CSF so that its clinical potential could be explored. In Dr. Van Etten's view, Welte 1985 clearly signalled the path forward, and the potential medical and commercial value of the protein was too great for this project not to have been pursued. He also concludes there was no inventiveness required to make this recombinant protein.

[75] Dr. Van Etten opines that Amgen's success in producing the recombinant protein was not surprising, as there were only a limited number of ways to use recombinant DNA technology to express the protein. After reading Welte 1985, the Skilled Person would have understood that achieving the goal of large-scale production of this protein would require the usual tools and standard techniques of recombinant DNA technology well known in the art. By August 23, 1985,

the Skilled Person would also have expected that recombinant hpG-CSF that was directly expressed in *E. coli* would likely have some or all of the biological activities of naturally occurring hpG-CSF.

6. Mandate 6 - Priority Application

[76] Counsel asked Dr. Van Etten whether the subject matter of the Asserted Claims is disclosed in the 959 Application. In Dr. Van Etten's opinion, it is not, for two reasons:

A. Each of the Asserted Claims relies on the amino acid sequence set out in Claim 43, which is different from the amino acid sequence in the 959 Application. (This opinion relates to what it appears the parties agree are typographical errors in the sequence in the 959 Application.); and

B. The 959 Application does not disclose that the recombinant protein has granulocyte colony-stimulating activity as set out in Claim 47 of the 537 Patent.

7. Mandate 7 - The Patent Specification

[77] Counsel asked Dr. Van Etten to describe the invention of the 537 Patent and then asked whether the 537 Patent specification (being the description and claims) contains the information necessary to make use of the invention as of July 31, 2007 (the issue date).

[78] Dr. Van Etten describes the invention of the 537 Patent as the production of recombinant pluripotent granulocyte colony-stimulating factor, referring to the patent as being replete with references to pluripotency. He states that, by 2007, it had been clearly shown that naturally occurring and recombinant hpG-CSF did not have pluripotent hematopoietic biological activity. As such, the 537 Patent did not contain the information necessary to allow the Skilled Person to produce a granulocyte colony-stimulating factor with pluripotent activity.

[79] Dr. Van Etten's second report responds to the claim construction opinion of one of Amgen's experts, Dr. Maloy. However, it became apparent at trial there are no material differences between the parties' respective constructions of the Asserted Claims.

8. General Observations on Reliability

[80] I found Dr. Van Etten to be a forthright witness. Amgen does not contend that he (or indeed any of Pfizer's experts) were dishonest or materially influenced by bias in any aspect of their opinions. Amgen acknowledges Dr. Van Etten was fair in responding to the propositions put to him by Amgen's counsel on cross-examination. Rather, Amgen submits that the differences between his opinion and its experts' opinions predominantly reflect differences in their respective approaches to answering the same questions. Amgen argues its experts' evidence, and evidence elicited from Pfizer's experts on cross-examination, is the more germane to the legal tests relevant to the issues in this action. I will consider the specifics of the evidence of the parties' respective experts later in these Reasons in relation to the individual issues to which it relates.

B. *Dr. Mark Hermodson (Pfizer Expert)*

[81] Pfizer's next expert, Dr. Mark Hermodson, is a protein biochemist with experience in protein structure and amino acid sequence analysis, having worked in these disciplines since the 1960s. Dr. Hermodson received a Bachelor of Arts degree in chemistry and mathematics in 1964 and a PhD in biochemistry in 1968. He then conducted post-doctoral research at the University of Washington from 1969 to 1972, working with professors who ran one of the world's largest amino acid sequencing laboratories. He spent most of his subsequent career at Purdue University, ultimately holding the position of Head of Biochemistry until 2001. He is the author of numerous peer-reviewed publications and estimates that, since 1977, he has personally conducted several hundred amino acid sequencings.

[82] Dr. Hermodson explains that during the early-to-mid 1980s, when the work leading to the 537 Patent was being performed, he was a Professor at Purdue University and actively engaged in protein biochemistry research and amino acid sequencing work. In particular, he managed a facility (often called a core facility) that conducted amino acid sequencing for other scientists. This work included, in particular, Edman degradation (a chemical reaction employed to remove each amino acid, one by one, from the protein chain to sequence that amino acid) and HPLC (which produces chromatograms that can be read to determine which amino acid has been removed).

[83] Dr. Hermodson was qualified at trial as a protein biochemist with experience in amino acid sequencing. Pfizer's counsel asked Dr. Hermodson to discharge two mandates. The following summarizes these mandates and Dr. Hermodson's opinion in relation to each of them.

1. Mandate 1 – Review of Welte 1985

[84] Counsel provided Dr. Hermodson with a copy of Welte 1985 and asked him to comment on the work done in that publication and what researchers working with proteins in 1985 would have done with the information in Welte 1985.

[85] Dr. Hermodson concludes that Welte 1985 describes the successful isolation, purification, and characterization of a human pluripotent hematopoietic colony-stimulating factor (referred to as "pluripotent CSF") from the human bladder carcinoma cell line 5637. He opines that researchers reading Welte 1985 would have recognized they could produce pluripotent CSF recombinantly using well-documented approaches that involved: (a) obtaining a partial amino acid sequence; (b) making oligonucleotide probes; (c) cloning the gene for pluripotent CSF; and (d) expressing pluripotent CSF in a host cell.

2. Mandate 2 – Review of the 537 Patent

[86] After Dr. Hermodson reviewed Welte 1985 and commented on it, counsel provided him with the 537 Patent and asked him to comment on the amino sequencing work described therein, in light of the state of the art in 1985. Counsel specifically asked Dr. Hermodson whether any of that work would have been outside the normal level of technical skill expected of the Skilled Person as of August 23, 1985.

[87] After receiving instructions as to the nature of the Skilled Person, he opines the patent is addressed to a protein biochemist with a PhD and several years of work experience in a discipline related to protein biochemistry. He explains that the skilled protein biochemist may oversee the work of a technician operating the sequencer (a machine that, by 1985, was widely used to perform Edman degradation) and HPLC column. Dr. Hermodson also provides scientific background information that he considers would have been included in the CGK of the skilled protein biochemist.

[88] The 537 Patent sets out in several Examples the steps undertaken by Amgen in producing the recombinant protein. As Dr. Hermodson's expertise relates to the amino acid sequencing step, he reviews Example 1, which sets out the process used for amino acid sequencing of the target protein. He reviews the information disclosed in the patent related to each of the five sequencing runs and concludes the 537 Patent does not describe any amino acid sequencing work that was outside the abilities of an ordinary skilled protein biochemist as of August 23, 1985. He opines that, through successive runs, Amgen used the same iterative process for amino acid sequencing that was used by skilled biochemists at the time.

3. General Observations on Reliability

[89] As with Dr. Van Etten, Amgen does not contend Dr. Hermodson was materially influenced by any bias in any aspect of his opinions, and it acknowledges he was fair in responding to the propositions put to him by Amgen's counsel on cross-examination. Consistent therewith, I found him to be a straightforward and knowledgeable witness.

C. *Dr. Steven Boxer (Pfizer Expert)*

[90] Dr. Steven Boxer is currently the Camille Dreyfus Professor of Chemistry at Stanford University. Since he started his laboratory at Stanford in 1976, the focus of his research has been investigating and researching the structure of biological systems, particularly proteins. Dr. Boxer's education includes a Bachelor of Science degree in Chemistry, earned in 1969, and a PhD in Physical and Physical-Organic Chemistry, earned in 1976. He has spent his academic career at Stanford University, where he became an Associate Professor in 1982 and a Full Professor in 1986. He has held his current position since 2000. Dr. Boxer has received many awards and has served as a member or elected fellow of several scientific organizations. He has authored over 325 publications, mostly in peer-reviewed journals, and has been invited to present his research at universities and scientific conferences around the world.

[91] Dr. Boxer was qualified at trial as an expert in protein biochemistry and molecular biology including recombinant DNA technology. Like Dr. Van Etten, he provided two reports, the second of which responds to the claim construction opinion of Amgen's expert Dr. Maloy, However, as previously noted, there are no material differences between the parties' positons on claim construction. In Dr. Boxer's first and principal report, he addresses the following four mandates:

1. Mandate 1 - Welte 1985

[92] Pfizer's counsel provided Dr. Boxer with a copy of Welte 1985. They asked him to review and summarize the article and provide his opinion on what, if any, research a Skilled Person would have wanted to pursue following the publication of this article.

[93] Dr. Boxer explained that Welte 1985 describes the isolation of a human protein called human pluripotent hematopoietic colony-stimulating factor (or pluripotent CSF) that is said to be involved in hematopoiesis. Welte 1985 also describes some aspects of the purified protein's structure and function.

[94] Dr. Boxer's opinion is that, following the publication of Welte 1985, the Skilled Person would have wanted to determine if pluripotent CSF had clinical promise. The Skilled Person would recognize that clinical testing would require large amounts of the protein and that the fastest and cheapest way to make large amounts was recombinant DNA technology. Therefore, the next logical steps would be for the Skilled Person to: (i) clone the gene for pluripotent CSF; and (ii) use the cloned gene to express recombinant pluripotent CSF in *E. coli*.

2. Mandate 2 – The 537 Patent

[95] After providing his opinion on Mandate 1, Dr. Boxer was provided with a copy of the 537 Patent. He was asked to summarize it and opine on how the Asserted Claims would have been understood by the Skilled Person as of July 31, 2007.

[96] Dr. Boxer describes the 537 Patent as presenting the work that he expected would follow from Welte 1985, that is: (i) the cloning of the gene for pluripotent CSF (which the inventor renames "hpG-CSF"); and (ii) the recombinant expression of this protein in *E. coli*. He construes the Asserted Claims as follows:

A. **Claim 43:** a recombinant polypeptide;

B. **Claims 44 to 46**: tools to express that polypeptide in a host cell such as *E. coli*;

C. **Claim 47:** a general process for making a biologically active form of the polypeptide.

Dr. Boxer notes that the polypeptide has the amino acid sequence of naturally occurring hpG-CSF, but with an additional N-terminal methionine (i.e., a particular amino acid at one end of the amino acid chain), which is required for expression in *E. coli*.

3. Mandate 3 – Obviousness of Claim 43

[97] Pfizer's counsel asked Dr. Boxer to opine whether Claim 43 was obvious as of August 23, 1985, focusing in particular on the portion of the process following isolation of the gene encoding naturally occurring hpG-CSF. He was also asked to provide this opinion with an additional assumption that the claimed polypeptide had to have one or more of the biological activities of naturally occurring hpG-CSF.

[98] In conducting this analysis, Dr. Boxer opines that the relevant CGK of the Skilled Person would include an understanding of the fundamentals of molecular biology and protein biochemistry, which would include the available tools and techniques of recombinant DNA

technology and protein biochemistry as of August 23, 1985. Earlier in his report, Dr. Boxer also states that the CGK included the following standard laboratory processes:

A. determining a partial amino acid sequence for a target protein;

B. using that partial amino acid sequence to make a probe that targeted the gene for the protein; and

C. using the probe to isolate the gene for the protein from a cDNA library.

[99] Dr. Boxer concludes Claim 43 was obvious as of August 23, 1995. Starting with the cloned gene, it would have been obvious to make recombinant hpG-CSF using direct expression in *E. coli*. It was standard practice to express mammalian proteins in *E. coli* by direct expression, and the Skilled Person would have anticipated that approach would work. Dr. Boxer also opines that the work described in the 537 Patent uses standard tools and procedures that were well known.

[100] His conclusion remains the same if the polypeptide had to have one or more of the biological activities of naturally occurring hpG-CSF, as the Skilled Person would have expected the polypeptide to have such biological activity. As discussed in more detail below, Dr. Boxer is confident the Skilled Person would be able to purify and properly fold the polypeptide after direct expression in *E. coli*, so that it had biological activity. Welte 1985 provided information about the secondary and tertiary structure of the naturally occurring protein, which would encourage the Skilled Person about the recombinant protein's potential biological activity.

4. Mandate 4 - Obviousness of Claims 44 to 47

[101] Finally, Dr. Boxer was asked whether Claims 44 to 47 were obvious as of August 23, 1985, again focusing on the portion of the process following isolation of the cloned gene. He concludes these claims were obvious for the same reasons as Claim 43. The tools claimed in Claims 44 to 46 and the process claimed in Claim 47 were commonplace and therefore added nothing inventive to the Claim 43 polypeptide.

5. General Observations on Reliability

[102] As with Pfizer's other experts, Amgen does not contend that Dr. Boxer was materially influenced by any bias in any aspect of his opinion. I found him to be a credible and knowledgeable witness.

D. *Dr. Stanley Maloy (Amgen Expert)*

[103] Dr. Stanley Maloy is currently a Professor of Biology and the Associate Vice President for Research and Innovation at San Diego State University. He completed a Bachelor of Science degree in biological sciences in 1975, a Masters degree in microbiology in 1977, and a PhD in molecular biology and biochemistry in 1981. He conducted post-doctoral research until 1984, and then joined the faculty of the University of Illinois Urbana-Champaign as an Assistant Professor, leaving that institution as a full professor in 2002. His teaching focused on molecular genetics, and his research focused on genetics and biochemistry of membrane proteins. In the 1985-1986 timeframe, Dr. Maloy was actively researching in the fields of molecular biology and

biochemistry and had been doing so for a decade. He was also knowledgeable about developments in hematology and protein chemistry.

[104] Dr. Maloy has held leadership positions with the American Society for Microbiology, the Center for Microbial Sciences, the Center for Applied and Experimental Genomics, and the American Academy for Microbiology, and has authored numerous scientific publications and books. He was qualified at trial as an expert in microbiology, biochemistry, molecular biology and genetics, including recombinant DNA technology. Dr. Maloy notes that he does not consider himself an expert in protein sequencing, although he explains he is generally knowledgeable in that area, as he has experience accessing protein sequencing services in connection with his research projects.

[105] Dr. Maloy authored two reports on this matter. The first involves claim construction, providing his opinion on the characteristics of the person to whom the 537 Patent is addressed, as of July 31, 2007, and how that person would have understood the Asserted Claims. His second report responds to the reports of Drs. Van Etten, Boxer, and Hermodson, addressing particular tasks assigned to him by Amgen's counsel. His opinions in relation to the tasks relevant to the issues in this action are summarized below.

1. Report 1 – Construction Report

    (a) *Skilled Person*

[106] In Dr. Maloy's opinion, in 2007, the 537 Patent is addressed to a research scientist with a PhD in the field of molecular biology, biochemistry, hematology, or protein chemistry; graduate

students with at least three years of research experience in the fields of molecular biology, biochemistry, hematology, and protein chemistry; or an MD with a focus on research and at least two years of relevant, post-doctoral research that includes molecular biology, biochemistry, hematology, or protein chemistry.

(b) *Claim Construction*

[107] Dr. Maloy opines the Asserted Claims relate to a process for preparing a functional, synthetic version of human granulocyte colony-stimulating factor, the DNA sequence, expression vector and transformed host cell used in that process, and the polypeptide resulting from that process. He provides more detailed constructions for each of the individual Asserted Claims. However, as explained later in these Reasons, there is no material disagreement between the parties surrounding construction of the Asserted Claims. It is therefore not necessary to review this aspect of Dr. Maloy's opinion in any detail.

2. Report 2 –Validity Report

(a) *Identity of the Skilled Person*

[108] In his second report, Dr. Maloy was first asked to identify the Skilled Person as of August 23, 1985 (as well as dates in 1986 that are no longer relevant to this action). He disagrees with Dr. Van Etten's description of the Skilled Person, as he considers the Skilled Person described by Dr. Van Etten to have the same experimental skill as an expert in the field, lacking only their inventiveness. Dr. Maloy describes the person of ordinary skill as having less education or experience than Dr. Van Etten's Skilled Person.

(b) *Knowledge of the Skilled Person*

[109] Asked about the Skilled Person's CGK, in particular what the Skilled Person would have understood from Welte 1985 and Maniatis 1982, Dr. Maloy substantially agrees with Dr. Van Etten's and Dr. Boxer's identification of the various laboratory tools and techniques that would have been available to the Skilled Person. He also agrees that, by August 1985, there were published examples in which various combinations of these tools and techniques had been used to genetically engineer a recombinant version of a naturally occurring protein.

[110] However, Dr. Maloy states that in August 1985 recombinant protein expression was a long and complex process that was fraught with difficulty. He agrees that many of the tools and techniques involved in the gene cloning process could individually be characterized as standard or routine (noting as an exception the use of inosine probes, a technique that is explained later in these Reasons). Nevertheless, he opines that devising and successfully executing a strategy for how to combine those tools and techniques to clone a gene for a protein and express a functional recombinant version of the protein for the first time was not routine in August 1985.

(c) *Information Disclosed by the 537 Patent*

[111] Dr. Maloy was asked to summarize the information disclosed by the 537 Patent that is relevant to Claims 43 to 47, and that would not have been known to the Skilled Person. He opines that the patent discloses the 174 amino acid sequence of the naturally occurring colony-stimulating factor G-CSF and discloses a process for making biologically active recombinant G-CSF.

(d) *Obviousness*

[112] Next, Dr. Maloy was asked to consider whether the invention claimed in each of the Asserted Claims would have been obvious to the Skilled Person on August 23, 1985. He concludes the claims were not obvious. Specifically, Dr. Maloy opines that the amino acid sequence of G-CSF, and the process for making biologically active recombinant G-CSF, had not yet been discovered and were determined by Dr. Souza through a series of experiments that were not obvious to try. While he agrees there would have been a strong motive to clone and recombinantly express the gene of the protein identified by Welte 1985, there was no roadmap available to the Skilled Person that would have led them directly and without difficulty to achieving that objective.

[113] Dr. Maloy acknowledges published examples in which other genes were successfully cloned and other proteins expressed recombinantly. These would have provided the Skilled Person with ideas for what could be tried. However, Dr. Maloy opines that the Skilled Person would not have expected that what worked for a different protein ought to work for G-CSF. He states that, even within the narrow realm of hematopoietic growth factors (like G-CSF), there was no single cloning strategy that had consistently worked. Further, most of the strategies that had worked were significantly different from the strategy that the Souza team successfully executed for cloning and recombinantly expressing the gene for G-CSF.

(e) *Response to Pfizer's Experts' Claim Construction*

[114] Dr. Maloy responds to Dr. Van Etten's and Dr. Boxer's opinions as to how the Asserted Claims would have been understood (by what he refers to as the "skilled reader") as of July 31, 2007. He generally agrees with their opinions. However, he disagrees with a statement (related to Claim 44) by Dr. Van Etten that there is no limit to what the DNA sequence can be in the recombinant DNA as long as it includes sequences encoding the Claim 43 polypeptide. Dr. Maloy responds that, while the Skilled Person would appreciate the degeneracy of the genetic code (i.e. that different DNA sequences could code for the same polypeptide sequence), this reading would not have allowed for an unlimited DNA sequence in Claim 44 or the subsequent claims. However, this difference between those experts' opinions does not appear to be material to any of the arguments the parties are advancing.

(f) *959 Application*

[115] Asked to consider whether the 959 Application disclosed the same invention as Claim 47, including the granulocyte colony-stimulating activity that is part of the invention of Claim 47, Dr. Maloy concludes that it did. He opines that the Skilled Person would have understood the amino acid sequence in the 959 Application, realizing that it contained typographical errors and logically overcoming those errors. Also, while Claim 47 of the 537 Patent claims a process that allows production of a functional polypeptide having granulocyte-stimulating activity, the 959 Application showed that the functional polypeptide had granulocyte-stimulating activity when properly folded.

(g) *Sufficiency*

[116] Asked to consider whether the 537 Patent Specification contains the information necessary to produce "pluripotent granulocyte colony-stimulating factor" as of July 31, 2007, Dr. Maloy concludes that it does. He opines that, by July 31, 2007, the Skilled Person would have understood that the "pluripotent granulocyte colony-stimulating factor" described in 1985 referred to "granulocyte colony-stimulating factor", which the 537 Patent specification contains the information necessary to produce.

3. General Observations on Reliability

[117] In addition to several criticisms of the depth of Dr. Maloy's expertise and the methodology he employed in arriving at his opinions, Pfizer submits Dr. Maloy acted more as an advocate for Amgen than as an independent and impartial expert. While not all the points raised by Pfizer in support of this submission resonate with me, some do raise concerns that Dr. Maloy strayed into the role of an advocate. The following are the most compelling examples of this concern.

[118] One of the cloning techniques upon which both parties focus significantly is the use of inosine probes, because this technique had been developed only shortly before Amgen's work on the G-CSF project. This tool will be explained in greater detail later in these Reasons. For present purposes, the point is that Dr. Maloy asserts the use of inosine probes was not routine in 1985. In support of this assertion, he observes how long it took for the technique to appear in the handbook by Maniatis: "… it is telling that inosine probes were not included in the handbook

until the 1989 edition." However, on cross-examination, Dr. Maloy acknowledged there were no editions of Maniatis between 1982 and 1989.

[119] I agree with Pfizer's argument that Dr. Maloy's language suggests there were editions of Maniatis between 1985 and 1988 that did not include any reference to inosine probes, supporting his assertion the technique was not routine. In fact, the length of time that elapsed before these probes appeared in Maniatis was a function of the fact that 1989 was the next edition published after such probes were first developed and reported on in 1985. This aspect of his evidence supports Pfizer's assertion that Dr. Maloy demonstrated a tendency towards advocacy.

[120] I have a similar concern about the manner in which Dr. Maloy describes Amgen's purification procedure when it created its in-house samples of the target protein. He describes Amgen's protocol as a "complete rework" of the purification procedure described in Welte 1985. Following his statement of that opinion, Dr. Maloy provides in table form a summary of the differences between the Welte and Souza procedures. However, in cross-examination, Dr. Maloy acknowledged some of the items in the table used different terms to describe the same substance or technique.

[121] Amgen responds to this argument by pointing out that, in his "warm-up" direct examination, Dr. Maloy identified some of the items in the table represented similarities and others represented differences. Pfizer, in turn, asserts Dr. Maloy's oral evidence was an effort to improve his written evidence, because Pfizer had telegraphed in opening submissions that they

would be challenging Dr. Maloy's opinion that Amgen's purification process was a complete rework.

[122] I find Pfizer's argument the more compelling. Dr. Maloy's report clearly describes the table as a summary of the differences between the procedures of Drs. Welte and Souza. Moreover, the next paragraph of Dr. Maloy's report refers to this "particular combination of changes" as not being obvious to the Skilled Person. It is at best severely lacking in precision for Dr. Maloy to have supported an important element of his opinion in this manner and raises concern that, consciously or not, Dr. Maloy's work has strayed into advocacy. My concern does not rise to the level that I will necessarily prefer the evidence of other witnesses over Dr. Maloy, particularly if his evidence on a particular point is compelling for other reasons. However, I will treat his evidence with caution.

E. *Dr. David Speicher (Amgen Expert)*

[123] Dr. David Speicher is a protein biochemist, currently the Caspar Wistar Professor of Computational and Systems Biology at The Wistar Institute [Wistar] in Philadelphia, PA. Since 1986, he has also been the Scientific Director of the Proteomics and Metabolomics Core Facility at Wistar. He is the Co-chair of the Molecular & Cellular Oncogenesis Program and the Director of the Center for Systems and Computational Biology. Dr. Speicher is also an adjunct professor in the Department of Biochemistry and Biophysics at the University of Pennsylvania and an adjunct professor of Biochemistry and Molecular Medicine at Drexel University.

[124] Dr. Speicher received his undergraduate degree in biochemistry in 1972 and his PhD in biochemistry in 1977. He then received post-doctoral training at the Yale University School of Medicine and was promoted to Research Scientist in 1984. From 1980 to 1986, he was also Director of the Protein Chemistry Laboratory at the Yale School of Medicine, a core facility that provided protein sequencing, amino acid analysis, and HPLC technologies to Yale University faculty. Dr. Speicher has published numerous peer-reviewed papers, has acted in an editorial capacity for many scientific publications, and has authored numerous book chapters and reviews. He is also a member of several relevant professional organizations. He was qualified at trial to give expert opinion evidence in the fields of protein chemistry and amino acid sequencing.

[125] Having been asked by Amgen's counsel to discharge three mandates, Dr. Speicher's opinions can be summarized as follows:

1. Mandate 1 – Skilled Person and Common General Knowledge

[126] Focusing in particular on Example 1 of the 537 Patent, which relates to his area of expertise, Dr. Speicher opines this Example is addressed to a biochemist with an advanced degree related to protein biochemistry. Such a person would have a PhD with two years of experience or a Masters degree with substantially more years of relevant experience.

[127] Dr. Speicher identifies the CGK possessed by that Skilled Person as comprising the general approaches to protein purification and partial amino acid sequencing in 1985; the operation of automated Edman degradation amino acid sequencers; and some ability to make

"calls" of partial amino acid sequences when provided a sufficient amount of a sufficiently pure experimental protein that produced strong and straightforward signals.

[128] Dr. Speicher further opines that, armed with that CGK, the number of contiguous residues (i.e. amino acids) a Skilled Person would be able to correctly assign in an experimental protein sequence would vary substantially depending upon the protein's properties, but the length of sequence determined would typically not be extensive and may or may not be sufficient to allow the construction of oligonucleotide probes.

2. Mandate 2 – Obviousness of Example 1 of the 537 Patent

[129] Next, Amgen's counsel asked Dr. Speicher to review Amgen's protein purification and amino acid sequencing work as described in Example 1 of the 537 Patent and to opine whether the Skilled Person could successfully carry out that work as of August 1985 without ingenuity, inventiveness or creativity.

[130] Dr. Speicher concludes this work required substantial specialized skill, judgment, and creativity and was beyond the capabilities of the Skilled Person as of August 23, 1985. He opines it would not have been more or less self-evident to the Skilled Person that any accurate N-terminal amino acid sequence information could be obtained. Even if a partial sequence could be obtained, it would not have been more or less self-evident that the sequence would correspond to the N-terminus of the protein (and biological activity) that the researchers were attempting to identify, or that the sequence would be sufficiently long, unambiguous, or useful for a cloning project.

3. Mandate 3 – Response to Pfizer's Experts

[131] Amgen's counsel asked Dr. Speicher to review and further respond to the opinions provided by Drs. Hermodson, Van Etten and Boxer in their respective reports that fall within his expertise, indicating the areas of agreement and disagreement with those opinions.

[132] Dr. Speicher strongly disagrees with the opinions of Drs. Hermodson and Van Etten that the amino acid sequencing work described in the 537 Patent was, respectively, straightforward and routine. He states that their opinions ignore the many challenges faced by the Skilled Person in correctly calling amino acid sequences of sufficient unambiguous length to render them useful in a cloning project, when working with small amounts of an unknown, experimental protein. He states that their opinions rely on several references reporting on the work of other protein biochemists and greatly exaggerate the abilities of the Skilled Person and what was routine in 1985. Dr. Speicher describes many of the references cited by Pfizer's experts as reporting on the work of extraordinarily skilled protein biochemists whose skills far exceeded the abilities of the Skilled Person.

4. General Observations on Reliability

[133] Dr. Speicher is the only expert witness in this matter who also gave evidence in the Apotex Application. Pfizer submits he is acting as an advocate, having changed his evidence from the Apotex matter to make the amino acid sequencing process appear more challenging, as well as adding new information favourable to Amgen's case and removing other less favourable information.

[134] For example, Pfizer refers to Dr. Speicher's testimony that Amgen's amino acid sequencing Run 2 did not produce more information than the previous run, which conflicts with the opinion in his Apotex affidavit. Also, his current affidavit describes Amgen's failed attempt on Run 3 as a highly innovative attempt, as it used a different sequencing method than the other runs, while his Apotex affidavit is silent on that run. In his Apotex affidavit, Dr. Speicher did not discuss the use of a reducing agent or a problem with loading protein sample onto the sequencer, but in his current affidavit, these are portrayed as matters of significance.

[135] Pfizer also notes Dr. Speicher tried to distance himself from a statement in a patent of which he was a co-inventor, to the effect that since a particular protein had been purified to homogeneity, oligonucleotide probes can identify the relevant gene, thereby allowing the protein to be produced by known recombinant DNA techniques.

[136] I do not find Pfizer's submissions on these points particularly compelling. In my view, Dr. Speicher adequately explained in cross-examination the differences in language surrounding Run 2. With respect to Run 3, I accept Amgen's submission that, in his current report, Dr. Speicher was providing a response to an opinion by Dr. Hermodson's opinion related to that run. Apotex's expert had provided no similar opinion. I do not find the fact that Dr. Speicher offered opinions on some points that did not arise in the Apotex Application to undermine his reliability as a witness.

[137] Nor does such a result arise from Dr. Speicher's testimony surrounding his patent. He explained in cross-examination that, while he signed the patent application and considered its

details correct, he did not write the patent himself and did not agree with the particular statement from the patent put to him by Pfizer's counsel. That testimony, and his demeanor generally, left me with the impression of an honest witness.

[138] I therefore reject Pfizer's submission to the effect that Dr. Speicher deliberately tailored his evidence to favour Amgen. Pfizer raises other arguments in support of its position that I should prefer the opinions of its experts to those of Dr. Speicher, which arguments I will address when considering the particular issues to which that evidence relates.

F. *Dr. James Griffin (Amgen Expert)*

[139] Dr. James Griffin is a Senior Physician at the Dana-Farber Cancer Institute and a Professor of Medicine at Harvard Medical School. He obtained his MD in 1974 and then completed a residency in medicine followed by a series of fellowships, including a research and clinical fellowship in hematology and a clinical and research fellowship in medical oncology. In 1977, Dr. Griffin obtained board certification from the American Board of Internal Medicine. In 1978, he obtained board certification in the hematology subspecialty, and in 1981 he obtained a further board certification in the medical oncology subspecialty.

[140] Dr. Griffin has been a member of the faculty of Harvard Medical School and a member of the staffs of the Dana-Farber Cancer Institute and Brigham & Women's Hospital since 1980. He has authored or co-authored numerous scientific publications, has contributed to reviews, commentaries and book chapters, has held dozens of roles on research committees and with professional societies, and has served on the editorial boards of several scientific journals. Dr.

Griffin has run his own independent laboratory at the Dana-Farber Cancer Institute since 1981, with major research focuses on the regulation of hematopoiesis and the biology and treatment of myeloid leukemia (a cancer affecting blood cells). He was qualified at trial as an expert in the areas of hematopoiesis and oncology.

[141] Amgen's counsel asked Dr. Griffin to provide opinions in the following areas, including responding to the report of Dr. Van Etten within his areas of expertise.

1. Mandate 1 – Identity of Skilled Person

[142] Asked to identify the Skilled Person of the 537 Patent as of August 23, 1985, Dr. Griffin opined the Skilled Person would have the same advanced degrees as described by Dr. Van Etten, but less experience. In his opinion, the Skilled Person has one to three years post-graduate experience, is skilled enough to use the techniques in the area, and encounters the subject matter in the regular course of their work. Dr. Griffin refers to the Skilled Person seeking out expert advice in order to adapt things to their own use. He describes Dr. Van Etten's Skilled Person as more like an expert. Although Dr. Griffin states he has performed his analyses from the perspective of each of Dr. Van Etten's and his Skilled Person, his evidence does not demonstrate a distinct analyses from the perspective of a Skilled Person with less experience.

2. Mandate 2 - State of the Art of Hematopoiesis in August 1985

[143] Asked to describe the state of the art in the area of hematopoiesis relating to the subject matter of the 537 Patent before August 23, 1985, Dr. Griffin explains that CSFs were of great interest in the field of hematology and particularly hematopoiesis. At least four CSFs had been

identified, although there was no consistent nomenclature used to describe these CSFs and no agreed-upon identification of their functions.

[144] Dr. Griffin states that expert teams at the leading edge of industry and academia were assembled to confront and overcome the difficulties associated with purifying CSFs isolated from the cells of humans and animals, and, if successful, to confront and overcome the difficulties associated with trying to clone the genes that code for those proteins. Each CSF presented a unique challenge. By 1985, several such groups were attempting to prepare partially purified human CSF preparations. Among these were SKI, under the supervision of Dr. Welte, and the Walter and Eliza Hall Institute [WEHI] of Australia, under the supervision of Dr. D. Metcalf.

[145] The SKI lab had prepared a protein preparation of a human CSF that it identified as "pluripotent CSF". The WEHI lab, using the same human cell line that the SKI lab had used, distinguished two different human CSFs, which it identified as "CSF-α" and "CSF-ß". The WEHI lab identified that CSF-ß was the human analog of mouse G-CSF; and, like mouse G-CSF, CSF-ß specifically stimulated growth of granulocyte colonies. However, neither SKI nor WEHI had identified the equivalence of CSF-ß with pluripotent CSF, and neither group had published the entire amino acid sequence of either factor.

3. Mandate 3 - 959 Application

[146] Asked whether the 959 Application disclosed the same invention as Claim 47 of the 537 Patent—and, in particular, granulocyte colony-stimulating activity —Dr. Griffin responded that

it did. Claim 47 claims a process for making biologically active recombinant G-CSF. The 959 Application showed that Amgen's recombinant G-CSF was biologically active by using an assay (a scientific test) known as the WEHI-3B (D+) assay [the WEHI Assay]. This assay tested the ability of a protein to induce differentiation of WEHI-3B (D+) leukemic cells into mature granulocytes, a known and unique property of human G-CSF.

[147] Dr. Griffin explains that the ability to differentiate WEHI-3B (D+) cells had been shown by the WEHI lab to be a distinguishing property of CSF-β (not shared by the other CSF produced by 5637 cells, CSF-α). In this way, the WEHI Assay allowed the Souza team to confirm the gene they cloned was the "pluripotent CSF" of Dr. Welte. Drs. Welte and Souza went on shortly thereafter to fully characterize all the biological activities of Amgen's recombinant G-CSF, but the WEHI Assay was instrumental in initially confirming that this recombinant G-CSF was the analog to Dr. Welte's naturally occurring factor.

4. Mandate 4 - Meaning of "Pluripotent" in the 537 Patent

[148] Amgen's counsel then asked Dr. Griffin how the Skilled Person would have understood the term "pluripotent" or the acronym "hpG-CSF" throughout the 537 Patent when it was published on July 31, 2007. He opines the Skilled Person would have understood these references as that term was used at the time the 537 Patent was written, i.e., as describing a manufactured, recombinant version of the naturally occurring protein previously described in Welte 1985 as "pluripotent CSF". In other words, the 537 Patent used that term to maintain continuity with the naming convention established in Welte 1985.

5. Mandate 5 - Contribution to the Field of Hematology

[149] Asked to describe the impact of recombinant G-CSF on the field of hematology and oncology, Dr. Griffin explains that recombinant G-CSF, once purified, was quickly put into clinical use to fill an urgent need. It ultimately became the drug filgrastim, which revolutionized the treatment of cancer and has prevented deaths caused by infections due to neutropenia (a side effect of chemotherapy caused by its effect on hematopoiesis). When administered after chemotherapy, filgrastim typically shortens or eliminates levels of neutropenia and significantly reduces the risk of serious bacterial infections.

6. General Observations on Reliability

[150] In cross-examination, Pfizer elicited from Dr. Griffin the acknowledgement that, in 1991, he provided a series of declarations [the Declarations] in a proceeding before the US Patent and Trademarks Office [USPTO proceeding], in which he considered the 959 Application and Dr. Welte's purification work. Neither these Declarations nor his participation in the USPTO proceeding are mentioned in Dr. Griffin's report.

[151] Pfizer argues the Declarations are directly relevant to the issues in the present litigation and should have been disclosed under the Code of Conduct for Expert Witnesses [the Code of Conduct] prescribed by the *Federal Courts Rules*, SOR/98-106. Paragraph 3(k) of the Code of Conduct requires disclosure of particulars of any aspect of the expert's relationship with a party to the proceeding or the subject matter of his or her proposed evidence that might affect his or her duty to the Court. Pfizer also advances arguments as to the substance of those Declarations, which arguments will be considered later in these Reasons.

[152] Pfizer notes that the failure to provide disclosure, as required by the Code of Conduct, has been found to affect the weight to be given to expert evidence (see *Kwicksutanaieuk Ah-Kwa-Mish First Nation v Attorney General of Canada*, 2012 FC 517 at paras 69-70). While I accept this principle, I do not find it applicable in the present case. Dr. Griffin explained in cross-examination that his recollection of the Declarations (now 30 years old) was that the issues were perhaps overlapping but different. He did not see any way that his comments back then would stop him from entirely telling the truth and having his own faithful opinions today. My impression of Dr. Griffin's overall testimony is that he answered questions directly and honestly, and I found him to be credible. I similarly accept his explanation surrounding the Declarations and do not find failure to disclose those documents to affect the weight due to his evidence.

[153] With the above evidence and issues in mind, I turn to the Analysis portion of these reasons. I will first address Pfizer's argument that the within action is an abuse of process in light of the Apotex Application, or that I should follow Justice Hughes' factual and legal findings in the Apotex Decision because of judicial comity. Next, I will address Pfizer's allegations of invalidity: (1) obviousness, (2) material misrepresentations; and (3) insufficiency. Finally, I will address Pfizer's affirmative defense that its activities fall under the prior use exception and are not infringement.

VII. ABUSE OF PROCESS

[154] As a threshold issue in this action, Pfizer argues it is an abuse of process for Amgen to re-litigate factual and legal issues that were decided by Justice Hughes in the Apotex Decision. At an earlier stage in this proceeding, Pfizer presented a motion seeking dismissal of Amgen's

action, on the basis that it was an abuse of process in light of the Apotex Decision, under s 6.08 of the Regulations. Prothonotary Milczynski dismissed that motion, and the Federal Court of Appeal upheld her decision (see *Amgen Inc v Pfizer Canada Inc*, 2018 FC 1078; *Pfizer Canada Inc v Amgen Inc*, 2019 FCA 249 [*Pfizer Canada*]). However, relying significantly on its decision in *Apotex Inc v Pfizer Ireland Pharmaceuticals*, 2011 FCA 77 [*Pfizer Ireland*], the Federal Court of Appeal held Pfizer was not precluded from raising the abuse of process doctrine at trial in connection with individual factual and legal findings in the Apotex Decision:

> [83] The Court's decision in *Pfizer Ireland* leaves no doubt, in my respectful opinion, that the commencement of a section 55 action cannot be prevented by reason of a decision made under section 6 of the Former Regulations. Hence, I am satisfied that the same conclusion must be reached in respect of an action commenced under section 6 of the Amended Regulations which, for all intents and purposes, is a proceeding identical to a section 55 action.
>
> [84] Thus, although Pfizer cannot succeed on the motion now before this Court, it remains open to it to raise issue estoppel and abuse of process once Amgen's action goes to trial. Whether or not Pfizer can succeed on those grounds in respect of factual findings and legal determinations made by the Hughes Decision, shall, as Sexton J.A. made clear in *Pfizer Ireland*, depend on the trial judge's assessment of these issues in light of the evidence.

[155] Pfizer identifies several findings by Justice Hughes that it argues would represent an abuse of process to re-litigate;

A. Dr. Welte had already identified the critical protein, isolated it, purified it, and characterized it in several respects;

B. Welte 1985 was motivational for leading edge scientific labs such as Amgen to undertake the task laid out by Dr. Welte;

C. Dr. Welte found the protein and said to the readers of his paper to go out and make it in quantity, which Amgen did;

D. Amgen obtained a product having an amino acid sequence beginning with a methionine, the addition of which was simply part of the process necessary in order to create the recombinant protein that Dr. Welte said should be made;

E. Amgen's steps in carrying out the G-CSF project were routine in the sense that they were carried out by skilled persons operating with the science as it was known at the time;

F. Amgen did not utilize any hitherto unknown step or technique; and

G. Amgen's end product, which is simply the protein made by whatever process, was not itself inventive.

[156] As explained in *Pfizer Canada* at paragraph 57, the principles informing an abuse of process analysis were identified by the Supreme Court of Canada in *Toronto (City) v CUPE, Local 79*, 2003 SCC 63, and include the need to address attempts to re-litigate a claim already determined by the Court that would have a negative impact on judicial economy, consistency, finality, and the integrity of the administration of justice.

[157] *Pfizer Ireland* explains the application of these principles to the interaction between NOC applications and subsequent infringement actions (at paras 24-25 [emphasis added]):

> [24] This court has repeatedly said that NOC proceedings are quite different from subsequent infringement or impeachment actions. In my view, there is scope for applying the bars of issue estoppel and abuse of process in the later proceedings to prevent the relitigation of subsidiary factual and legal issues in order to preserve judicial resources, promote the integrity of the justice system, prevent inconsistent findings, and prevent abuse. The difference between the NOC proceeding and later proceedings is an important consideration for the judge in the later proceedings, along with all of the other discretionary considerations discussed in *Danyluk* and *C.U.P.E.* Simply put, *Danyluk* and *C.U.P.E.* can apply in proceedings such as these.
>
> [25] Given the foregoing analysis to the effect that *res judicata* does not apply to the determination of validity and infringement,

> the parties remain free to launch proceedings on those issues in other fora. Where a party introduces significant and important new evidence or raises significant and important new argumentation in the subsequent action, the trial judge should reconsider the issue in light of the full record before him or her (*Ratiopharm* at paragraphs 25 and 26). In applying the rule that issue estoppel generally precludes parties from raising arguments or issues that could have been raised at the original hearing, courts should be cognisant of the summary nature of NOC proceedings and the fact that no discoveries or live evidence are permissible.

[158] Noting the language highlighted above, Pfizer argues that Amgen bears a burden to lead evidence capable of unseating the findings from the Apotex Decision and that it has failed to discharge that burden. Pfizer submits that all Amgen's fact witnesses in this case were heard by Justice Hughes and that, while two of Amgen's three experts are new, none points to any step taken by Amgen that was not described in the prior art.

[159] Amgen disputes that it bears a burden as articulated by Pfizer. Instead, it reads the same language in *Pfizer Ireland* as describing one scenario in which the trial judge should reconsider the issues in light of the full record. That is, the introduction of significant new evidence is not the only circumstance in which the trial judge should do so. To support its position that the Court should reconsider the issues upon which Justice Hughes has already pronounced, Amgen argues Justice Hughes erred in his legal analysis of obviousness for Claim 43. It notes there has been no substantive appellate consideration of such alleged errors, as the Federal Court of Appeal dismissed Amgen's appeal of the Apotex Decision on the basis of mootness (see *Amgen Canada Inc v Apotex Inc*, 2016 FCA 196 [*Amgen Canada*]).

[160] I do not consider it this Court's role, when assessing abuse of process submissions, to consider whether another decision of this Court demonstrates legal error (see *MacDougall v Lake Country (District)*, 2012 BCCA 408 [*MacDougall*] at para 36, for a similar conclusion in the context of *res judicata*). However, the fact that Amgen has not had an opportunity to subject those alleged errors to appellate review is relevant to my discretion whether to apply the principle of abuse of process.

[161] *Pfizer Ireland* notes (at para 24) that the difference between the NOC proceeding and later proceedings is an important consideration, along with all of the other considerations discussed in the applicable Supreme Court jurisprudence, in exercising this discretion. The unavailability of appellate review of the NOC decision forms part of this important consideration. In *Penner v Niagara Regional Police Services Board*, 2013 SCC 19 [*Penner*] at paragraph 41, the Supreme Court identified the availability of an appeal as an important consideration in an issue estoppel analysis. In the absence of an opportunity to have an earlier decision reviewed, it may be unfair to hold a party to the results of that decision for purposes of later proceedings. I find this factor similarly relevant to an abuse of process analysis.

[162] I note *Penner* provides this guidance in the context of an earlier decision by an administrative decision-maker. Pfizer refers to jurisprudence to the effect that, when the earlier decision is from a court (as opposed to a tribunal), the discretion to decline to apply the abuse of process doctrine is limited in its application (see *Procter & Gamble Pharmaceuticals Canada Inc v Canada (Minister of Health)*, 2003 FCA 467 [*Proctor*] at paras 28-29; *MacDougall* at para 34).

[163] However, I do not read these authorities as suggesting that the inability to appeal an earlier decision, even a decision of a court, cannot be a circumstance where the applicable discretion is available. In deciding to apply the doctrine of issue estoppel in relation to a decision of a court of competent jurisdiction, the British Columbia Court of Appeal in *MacDougall* took into account the fact that there was an available right of appeal, which simply had not been exercised (at para 35). Indeed, in *Assiniboine v Meeches*, 2013 FCA 177 at paragraph 37, the Federal Court of Appeal noted that the comments at paragraphs 40-41 of *Penner* were made in the context of a claim of issue estoppel following an administrative decision, but the Court held they were nevertheless applicable to that case, which involved decisions of the Federal Court.

[164] In my view, it is unfair to hold Amgen to the results of the Apotex Decision in the current proceedings, when it did not have the benefit of substantive appellate review of that decision. As Amgen emphasizes, the Federal Court of Appeal in *Amgen Canada* dismissed Amgen's appeal for mootness in part because it could pursue a subsequent infringement action (at para 22). In conclusion on this issue, regardless of the scope of Amgen's burden to identify evidence warranting reconsideration of the issues before Justice Hughes, I have decided to exercise my discretion not to apply the abuse of process doctrine and will therefore address the issues in this action on their merits.

VIII. JUDICIAL COMITY

[165] In in its opening written submissions, Pfizer argued the Court should defer to the Apotex Decision by reason of judicial comity, even if I decide I am not bound by that decision as a

matter of abuse of process. As Pfizer did not pursue this argument in its closing submissions, I will address it only briefly.

[166] Pfizer refers to *Allergan Inc v Canada (Minister of Health)*, 2012 FCA 308 [*Allergan*] at paragraph 50, in which the Federal Court of Appeal held the Federal Court should have applied principles of comity and adhered to findings of law in another Federal Court decision, involving the same patent but different parties. To similar effect, in *Apotex Inc v Pfizer Canada Inc*, 2013 FC 493 at paragraph 18, Justice O'Reilly held an earlier decision by Justice Snider as to the construction of the same patent was binding on him unless it was, for strong reasons, necessary to depart from it.

[167] I accept the importance of *stare decisis* and its cousin, judicial comity. However, the authorities upon which Pfizer relies apply these principles to prior findings of law, not to findings of fact or mixed law and fact. Indeed, in *Allergan*, the Federal Court of Appeal notes the doctrine of comity has no application with respect to findings of fact (at para 50). As Justice Fothergill explained in *Bayer Inc v Apotex Inc*, 2016 FC 1013 [*Bayer*] at para 54, in the context of an action for patent infringement following an earlier NOC decision:

> [54] Previous findings of fact or mixed fact and law made in the NOC context are potentially persuasive, but they must be approached with caution. For example, Justice Hughes previously defined the "person of ordinary skill in the art" […] in the NOC proceedings, but this is a question of mixed fact and law. It must therefore be determined anew based upon the evidence adduced in these proceedings. Obviousness is generally considered to be a question of fact or mixed fact and law, to which the principle of comity does not apply (*Wenzel Downhole Tools Ltd v National-Oilwell Canada Ltd*, 2012 FCA 333 at para 44 [*Wenzel*]; *Allergan* at para 44). The same holds true for the issues of ambiguity, overbreadth, utility, and insufficiency.

[168] The findings in the Apotex Decision that Pfizer argues would represent an abuse of process to re-litigate are all findings of either fact or mixed law and fact. The only finding of law that could be relevant to the present action is Justice Hughes' construction of Claim 43. However, even that finding was a function of the particular evidence adduced in that application. Moreover, claim construction is not one of the findings Pfizer ask the Court to adopt. Rather, as will be explained in more detail below, the parties are largely agreed on the issue of claim construction in the present action. As such, I find good reason not to adopt the claim construction from the Apotex Decision (see *Bayer* at paras 52-53).

[169] With respect to questions involving findings of fact and mixed fact and law, I recognize they are potentially persuasive (see *Bayer* at para 54), and I will therefore afford them respectful attention. However, those questions must be answered based upon the evidence adduced in the present action.

IX. CLAIM CONSTRUCTION - THE SKILLED PERSON

[170] Although the parties largely agree on the construction of the Asserted Claims, the task of claim construction rests with the Court (see, e.g., *Zero Spill Systems (Int'I) Inc v Heide*, 2015 FCA 115 at paragraph 41).

[171] Analytically, claim construction first requires identifying the Skilled Person to whom the patent and its claims are addressed. In general, the qualities and capabilities of the Skilled Person are the same for purposes of construing the patent and for the assessment of obviousness that will

be required later in these Reasons (see *Leo Pharma Inc v Teva Canada Limited*, 2015 FC 1237 at para 103 [*Leo Pharma*]).

[172] The Skilled Person is a hypothetical person possessing the ordinary skill and knowledge of the particular art to which the invention relates and a mind willing to understand a specification that is addressed to them (see, e.g., *Tetra Tech EBA Inc v Georgetown Rail Equipment Company*, 2019 FCA 203 at para 25, citing *Free World Trust v Électro Santé Inc*, 2000 SCC 66 [*Free World Trust*] at para 44). The Skilled Person is understood to be a technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right (see *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Plavix*] at para 52). The Skilled Person may be conceived of as a team of people possessed of different skills (see *Teva Canada Limited v Jansen Inc*, 2018 FC 754 at para 66).

[173] There is no material dispute over the areas in which the Skilled Person in this case must be qualified. All experts performed their analyses using the definition supplied by Dr. Van Etten: a team consisting of a molecular biologist with a PhD and several years of work experience in academia or industry; a hematologist with an MD and board certification (or, alternatively, a PhD in hematology and several years of work experience in academia or industry); and a protein biochemist with a PhD and several years of work experience in academia or industry.

[174] I note that Amgen's experts opined that the Skilled Person might be less experienced than suggested by the definition supplied by Dr. Van Etten. Nevertheless, they were instructed to use

Dr. Van Etten's definition for purposes of their analyses and do not conduct distinct analyses from the perspective of a Skilled Person with less experience. I am also mindful that Amgen's expert Dr. Maloy opined the Skilled Person would not necessarily have had the technical skills or equipment required to put the teachings of the 537 Patent into action. This characterization is inconsistent with the legal requirement that the Skilled Person is able to practice the invention disclosed in the patent (see, e.g., *Pfizer Canada Inc v Novopharm Ltd*, 2012 SCC 60 at para 71 [*Novopharm SCC*]). Taking that principle into account, as well as Amgen's general adoption of Dr. Van Etten's definition, I prefer Dr. Van Etten's definition of the Skilled Person and adopt it for purposes of these Reasons.

X. CLAIM CONSTRUCTION - ANALYSIS

[175] Having identified the Skilled Person, I must determine how the Skilled Person would construe the Asserted Claims of the 537 Patent. As explained below, there is no material disagreement between the parties on this issue. As such, I need not comment in any detail on the expert evidence, other than to confirm that I consider the evidence to support the constructions I adopt below.

[176] While they are all independent claims, Claims 44 to 47 all build upon Claim 43, and specifically the Claim 43 amino acid sequence. Amgen's and Pfizer's proposed constructions of Claim 43 are as follows:

A. **Amgen:** Claim 43 pertains to a polypeptide with the specified sequence of 175 amino acids.

B. **Pfizer:** Claim 43 pertains to a polypeptide with a specified sequence of 175 amino acids, comprising an N-terminal methionine followed by the 174 amino acid sequence of the natural protein that by July 31, 2007 was named human granulocyte colony-stimulating factor (G-CSF). Claim 43 does not require that the polypeptide has biological activity.

[177] While these are not identical, nothing turns on the additional level of detail in Pfizer's proposed construction. In particular, while only Pfizer's construction states that biological activity is not an essential element of the claim, Amgen's counsel confirmed at trial it is not asserting Claim 43 includes such a requirement. I adopt Amgen's language for the construction of Claim 43.

[178] Similarly, with respect to Claim 44, the only difference in the parties' proposed constructions is the point surrounding biological activity. For the same reasons as explained above in relation to Claim 43, I adopt Amgen's language for the construction of Claim 44, as follows:

> Claim 44 pertains to a recombinant DNA molecule that instructs cellular machinery to synthesize a specified sequence of 175 amino acids, namely the Claim 43 polypeptide. The DNA molecule can have variations in its sequence because the genetic code is degenerate, meaning that most of the amino acids are encoded by more than one codon (i.e., a triplet of deoxyribonucleotides in the DNA). "Recombinant" means sections of DNA from different sources, joined together in a laboratory.

[179] With respect to Claim 45, Amgen's and Pfizer's proposed constructions are as follows:

A. **Amgen:** Claim 45 pertains to an expression vector, which is a recombinant DNA molecule that can drive synthesis of a specified sequence of 175 amino acids, namely the Claim 43 polypeptide, when inside an appropriate host cell.

B. **Pfizer:** Claim 45 pertains to an expression vector, which is a recombinant DNA molecule that can drive synthesis of a specified sequence of 175 amino acids, namely the Claim 43 polypeptide, when inside an appropriate host cell. The DNA molecule can have variations in its sequence for the same reasons as in Claim 44. Claim 45 does not require that the Claim 43 polypeptide has biological activity.

[180] Again, I can disregard the difference in the language surrounding biological activity. The other difference is Pfizer's inclusion of the language about variations in the sequence of the DNA molecule. While that difference does not appear to be material to any of the arguments the parties are advancing (in relation to either Claim 44 or 45), I adopt Pfizer's language because of its consistency with the construction of Claim 44. Therefore, I construe Claim 45 as follows:

> Claim 45 pertains to an expression vector, which is a recombinant DNA molecule that can drive synthesis of a specified sequence of 175 amino acids, namely the Claim 43 polypeptide, when inside an appropriate host cell. The DNA molecule can have variations in its sequence for the same reasons as in Claim 44.

[181] Other than the point about biological activity, the parties' constructions of Claim 46 are identical, and I adopt Amgen's language, as follows:

> Claim 46 pertains to a living cell that contains the expression vector of Claim 45, introduced using genetic engineering techniques in such a way that the cell can express the Claim 43 polypeptide.

[182] The parties agree upon, and I adopt, the following construction of Claim 47:

> Claim 47 pertains to a process for making the Claim 43 polypeptide that has granulocyte colony-stimulating activity. The process involves inserting the expression vector of Claim 45 into a living cell, reproducing that cell, and purifying the polypeptide away from other host cell proteins.

[183] As will be apparent, the parties agree that, unlike the other Asserted Claims, Claim 47 does include a requirement for biological activity, i.e. granulocyte colony-stimulating activity. For ease of reference, the language of Claims 43 to 47, and the above constructions, are set out in Appendix "A" to these Reasons.

XI. OBVIOUSNESS – DATE OF INVENTION

[184] Under the Old Act, obviousness is assessed as of the invention date, rather than the claim date. The invention date is presumptively the filing date of a priority application, if one has been filed, or the filing date of the Canadian patent application, if a priority application has not been filed (*Ratiopharm Inc v Pfizer Ltd*, 2009 FC 711 at para 32 [*Ratiopharm*], aff'd 2010 FCA 204). A patentee can rely on its priority application only if that application was for the "same invention" as the Canadian application (see Old Act, s 28(1); *Canadian Marconi v Vera Prinzen*, 46 CPR 97 (1964) at para 75). A patentee can also demonstrate an earlier invention date with evidence of when the inventor(s) first reduced their invention to a definite and practical shape or first formulated, either in writing or verbally, a description which affords the means of making that which is invented (see *Ratiopharm* at para 32; *Christiani & Nielsen v Rice*, [1930] SCR 443 [*Christiani*] at 454, 456).

[185] In this case, Amgen asserts an invention date of August 23, 1985 for the Asserted Claims on the basis of: (a) the 959 Application, providing the 537 Patent with a priority date of August 23, 1985; or (b) evidence establishing the Souza team achieved the invention no later than August 23, 1985. Amgen does not argue or present evidence that the Asserted Claims were not

obvious as of any later date of invention (e.g., the 548 Application's filing date, or the Canadian filing date).

A. *Priority Date from the 959 Application*

1. Legal Principles

[186] Turning first to the 959 Application, Amgen's position relies on s 28(1) of the Old Act, which provides as follows [emphasis added]:

***Patent Act,* RSC 1985, c P-4, as it read immediately before October 1, 1989 [Old Act]**	***Loi sur les brevets*, LRC 1985, ch P-4, telle que parue avant le 1 octobre 1989 [La loi antérieure].**
28. (1) An application for a patent filed in Canada by any person entitled to protection under the terms of any treaty or convention relating to patents to which Canada is a party who has, or whose agent or other legal representative has, previously regularly filed an application for a patent for the same invention in any other country that by treaty, convention or law affords similar privilege to citizens of Canada, has the same force and effect as the same application would have if filed in Canada on the date on which the application for a patent for the same invention was first filed in that other country, if the application in Canada is filed within twelve months after the earliest date on which any such application was filed in that other country.	**28. (1)** Une demande de brevet, déposée au Canada par toute personne ayant le droit d'être protégée aux termes d`un traité ou d'une convention se rapportant aux brevets et auquel ou à laquelle le Canada est partie, qui a, elle-même ou par son agent ou autre représentant légal, antérieurement déposé de façon régulière une demande de brevet couvrant la même invention dans un autre pays qui, par traité, convention ou législation, procure un privilège similaire aux citoyens du Canada, a la même force et le même effet qu'aurait la même demande si elle avait été déposée au Canada à la date ou la demande de brevet pour la même invention a été en premier lieu déposée dans cet autre pays, si la demande au Canada est déposée dans un délai de douze mois à compter de la date la plus éloignée à laquelle une telle demande a été déposée dans cet autre pays.

[187] Amgen argues the 959 Application discloses the same invention as its application for the 537 Patent (i.e., the 737 Application). In *Sanofi-Aventis Canada v Apotex Inc*, 2009 FC 676 [*Sanofi-Aventis*] at paragraph 270, Justice Snider explained:

> [270] Obviousness must be assessed as of the date of the invention. In the absence of proof of an earlier invention date, the date of invention is presumed to be the first priority date (see, for example, *Pfizer Quinipril (FC)*, above, at paragraph 89). Should a party wish to assert an earlier date, that party bears the burden of establishing that the date of invention was different than the first priority date (*Westaim Corp. v. Royal Canadian Mint* (2001), 23 C.P.R. (4th) 9 at para. 87). […]

[188] Amgen therefore argues that, while it bears the burden of proving an invention date other than the priority date, it is entitled to a presumption that the priority date applies. Pfizer takes a different position, asserting Amgen bears the burden of establishing the priority application is for the same invention as the 737 Application. Pfizer relies on the following description of the relevant principle by Justice Hughes at paragraph 33 of the Apotex Decision [emphasis added]:

> [33] Obviousness of an "old" *Act* patent is to be determined as of the "date of the invention". The date of invention of the '537 patent is presumptively taken to be the Canadian filing date, August 25, 1986. <u>That date can be established at an earlier date with reference to foreign priority applications if the substance of the description is essentially the same as the Canadian patent.</u> Here, two United States patent applications were named as priority applications; United States Application No. 768,959, filed August 23, 1985, and United States Application No. 835,548, filed March 3, 1986. An even earlier date of invention can be proven upon evidence before the Court. In the present case, Amgen relied upon the earlier of two priority filing dates, namely August 23, 1985, and Apotex was apparently content to deal with obviousness as of that date.

[189] I need not reach a conclusion on which party bears the burden of proof on this point, as the outcome of my analysis below does not turn on which party bears the burden. I note Justice Hughes adopted the August 23, 1985 priority date from the 959 Application, for purposes of his obviousness analysis of Claim 43 in the Apotex Decision. However, as that date was not in dispute in the Apotex Application, this particular finding has no instructive value in the present case.

[190] In the above excerpt from the Apotex Decision, Justice Hughes expresses the relevant question as whether the substance of the descriptions are essentially the same. To similar effect, Amgen submits priority will be lost only where the Court concludes from the disclosures and claims of both applications that they are in substance directed to different inventions (see D H MacOdrum, *Fox on the Canadian Law of Patents*, 5th ed (Scarborough: Carswell, 2019) [*Fox on Patents*] at § 9:36(c)). I consider these expressions of the relevant principle to be compatible, and I will apply them in conducting the required analysis.

[191] While the expert evidence was directed toward the 537 Patent, as opposed to the 737 Application, I note Amgen's submission that this perspective does not alter the resulting analysis. I accept this submission, as both parties' evidence and arguments focused upon the text of the patent itself.

[192] Pfizer's position that the two applications are not for the same invention turns on two points. First, it submits the 959 Application does not disclose the correct amino acid sequence or DNA sequence related to the protein that is the subject of the application, which is an integral

part of the invention of the 537 Patent. Second, Pfizer submits the 959 Application also does not disclose any biological testing that shows granulocyte colony-stimulating activity, which is required for Claim 47.

2. Errors in Table VII Sequences

[193] Pfizer's first submission turns on errors in the amino acid and DNA sequences set out in Table VII of the 959 Application. That Table sets out the sequences of (i) amino acids making up the naturally occurring G-CSF; (ii) the DNA codons that instruct cellular machinery to create those amino acids; and (iii) the complementary strand of DNA corresponding to those codons. There are errors in all three sequences.

[194] First, the experts who speak to this point agree the amino acid sequence in the 959 Application contains an incorrect amino acid "Alu" instead of "Glu" at position +122. No amino acid exists with the name "Alu". Second, in three positions in the DNA sequence, the stated codon does not match the amino acid it purports to encode. Finally, there are three positions in the complementary DNA line where the nucleotides listed are not complementary to the DNA codons above.

[195] Dr. Van Etten opines that, using the information disclosed in the 959 Application, the Skilled Person would not have known how to resolve the errors in the sequences without redoing the work of cloning the gene for hpG-CSF. He explains the position +122 amino acid labelled "Alu" could have been a typo for one of two amino acids, either "Glu" or "Ala". Also, in relation to the errors in the DNA sequence, the Skilled Person would not have known whether the amino

acid sequence was correct or the DNA sequence was correct. Similarly, the Skilled Person could not have used the DNA sequence to make the recombinant protein, as the erroneous sequence encodes for a different protein. Therefore, the Skilled Person wanting to make recombinant hpG-CSF would not have known how to implement the 959 Application.

[196] Dr. Maloy disagrees with Dr. Van Etten. In Dr. Maloy's view, the Skilled Person would have understood that "Alu" is not a three-letter code for a standard amino acid. The Skilled Person would have considered whether this was a typographical error, would have looked to the DNA codons appearing directly below "Alu", and would immediately conclude the "Alu" should have read "Glu", as that is the amino acid corresponding to the listed DNA codon. In relation to errors in the DNA codons, Dr. Maloy opines the Skilled Person would have understood these were typographical errors and would have thought it more likely that the amino acid sequence was correct, because it is very easy to make a mistake when typing codons. Dr. Maloy opines the Skilled Person would have understood more than enough about DNA codons and amino acids not to have been led astray by the typographical errors in the sequences.

[197] In response to this evidence, Pfizer notes that Dr. Maloy conceded on cross-examination there were typographical errors in Table VII of the 959 Application. He also acknowledged the Skilled Person would be forced to assume which one of the amino acid sequence or the DNA sequence was correct (if either was), if attempting to rely on either sequence without redoing the work of cloning the gene for hpG-CSF. Pfizer submits that, since there were errors in both sequences, this would be an impossible choice.

[198] As an initial point, I have some reservations about Pfizer's position that errors of an admittedly typographical nature support a conclusion that the priority application does not disclose the same invention as an application that does not contain those errors. However, neither party has identified any jurisprudential guidance on this point. I will therefore rely on the expert evidence as to how the Skilled Person would react to the errors.

[199] Notwithstanding my general reservations about Dr. Maloy's evidence, expressed earlier in these Reasons, this is a point on which I prefer his evidence to that of Dr. Van Etten, because I find it the more logically compelling. Because the Skilled Person would know there is no amino acid called "Alu", they would conclude this entry in the amino acid sequence was a typographical error. Recognizing there were two amino acids with similar spellings (Glu and Ala), the Skilled Person would realize the mistake was intended to read "Glu", because the accompanying codon in the DNA sequence coded for "Glu".

[200] Turning to the discrepancies between the amino acid and the DNA codon (which are at different locations in the sequence than the above "Alu" error), I understand Pfizer's argument that the errors could be in either the amino acid or the codon at each of those three positions in Table VII of the 959 Application. Dr. Van Etten explains in his report that the codons at those positions code for: (a) the amino acid valine (Val) rather than the stated amino acid leucine (Leu); (b) lysine (Lys) rather than the stated amino acid glutamate (Glu); and (c) serine (Ser) rather than the stated amino acid phenylalanine (Phe). There are no particular similarities in the three-letter symbols in any of these cases.

[201] In contrast, comparing Table VII of the 959 Application with the correct entries in Table VII of the 537 Patent, it is apparent the three letter sequences for the mistyped codons are very close to the correct codon, with just one of the three nucleotides being wrong in each case. The stated DNA codon in the 959 Application and the correct codons for each of Leu, Glu and Phe are, respectively: (a) GTG and TTG; (b) AAG and GAG; and (c) TCC and TTC. I therefore find logical Dr. Maloy's opinion that the Skilled Person would conclude the mistakes were more likely in the codons.

[202] Finally, I turn to the third category of error (i.e. the positions in Table VII where the nucleotides stated for the two DNA strands are not complementary). I note Dr. Van Etten's opinion that, in the absence of the other two categories of errors, the third category would not prevent disclosure of the amino acid and DNA sequences of hpG-CSF. This is because the match between the amino acid and the codon would indicate to the Skilled Person that there were typos in the template strand (i.e. the complementary DNA strand). I therefore conclude that, if the Skilled Person was capable of resolving the other two categories of errors, as described above, the third category would not be material.

[203] While Dr. Maloy acknowledged in cross-examination that the Skilled Person would have to assume one of the amino acid sequence or the DNA sequence was correct, this does not undermine his opinion that the Skilled Person would assume the amino acid sequence to be the correct one. I disagree with Pfizer's submission that it was impossible for the Skilled Person to choose which sequence to follow. Rather, I find that the errors in Table VII would not cause a

Skilled Person to conclude from the 959 Application and the application for the 537 Patent that they are in substance directed to different inventions.

[204] As Pfizer acknowledges in its opening written submissions, the Supreme Court of Canada in *Free World Trust* described the Skilled Person as having a mind willing to understand a specification addressed to them (at para 44). Amgen relies on *Whirlpool Corp v Cameo Inc*, 2000 SCC 67 at paragraph 49 to the same effect. Taking into account this principle and the above analysis, I disagree with Pfizer's position that the Skilled Person would be stymied by the typographical errors in the 959 Application.

3. Granulocyte Colony-Stimulating Activity

[205] I therefore turn to Pfizer's second submission, that the 959 Application does not disclose any biological testing demonstrating granulocyte colony-stimulating activity. Pfizer takes this position in reliance on Dr. Van Etten's evidence. He notes that Claim 47 of the 537 Patent requires the recombinant protein to have granulocyte colony-stimulating activity, but the 959 Application only discloses what is described as the ^{3}H-thymidine uptake assay and the WEHI Assay. Dr. Van Etten states these biological tests do not demonstrate granulocyte colony-stimulating activity.

[206] In response, Amgen relies principally on the evidence of Dr. Griffin, who was asked to comment on whether the 959 Application discloses the granulocyte colony-stimulating activity of Claim 47, such that Claim 47 contains the same invention as that described in the 959 Application. Dr. Griffin opines the inventions are the same. In particular, he disagrees with Dr.

Van Etten's opinion that the 959 Application does not disclose that Amgen's recombinant protein has granulocyte colony-stimulating activity. Dr. Griffin relies on the description in the 959 Application of the results of testing in the WEHI Assay, which showed the ability of recombinant, *E. coli*-derived materials to induce differentiation in a line of mouse cells.

[207] As an initial point, I note that both experts express their opinions in the context of the granulocyte colony-stimulating activity required by Claim 47 of the 537 Patent. I am conscious of authority to the effect that, under s 28(1) of the Old Act, entitlement to a priority date is determined by reference to the application as a whole, not on a claim by claim basis (see *Fox on Patents*, § 4:7(b)). I am also conscious of the point raised by Pfizer, although in a different context, that the Asserted Claims were not present in the 737 Application as filed, but rather became part of the application during the course of its prosecution. However, neither party raised this point in the context of their submissions on the invention date, and I am satisfied that a recombinant protein having at least granulocyte colony-stimulating activity forms part of the invention of the 537 Patent—and by extension the 737 Application. As such, this activity must also be disclosed in the 959 Application in order for both to relate to the same invention.

[208] Returning to the expert evidence, there is an apparent divergence in the opinions of Drs. Van Etten and Griffin as to whether testing in the WEHI Assay is a means of demonstrating granulocyte colony-stimulating activity. In closing argument, Pfizer's counsel explained that Dr. Van Etten's evidence is based on the fact particular assays (the CFU-GM, BFU-E and CFU-GEMM assays) are used to determine colony-stimulating activity, including granulocyte colony-stimulating activity. The WEHI Assay is not one of these assays. However, Pfizer's counsel

understands Dr. Griffin's evidence to be that the WEHI Assay is regarded as a close proxy for determining whether there is granulocyte colony-stimulating activity.

[209] I agree with this characterization of the divergence in the expert evidence. Dr. Zsebo, the Amgen scientist who conducted the WEHI Assay in August 1985, provided the following evidence in her affidavit:

> 34. I recall discussing with Dr. Souza, before we had the results of the WEHI-3B D^+ assay using our recombinant protein, that induction of differentiation in the WEHI-3B D^+ assay was seen to be a "hallmark" of G-CSF activity. Similarly, I had discussed with Dr. Souza that G-CSF showed strong differentiation induction in the WEHI-3B D^+ assay and GM-CSF was known to induce activity only weakly. If our recombinant protein induced differentiation in the WEHI-3B D^+ assay, we could therefore conclude that our recombinant protein possessed granulocyte-colony stimulating activity, like natural G-CSF.

[210] The treatment of this subject in Dr. Van Etten's report is very brief. Also, in cross-examination, he was referred to portions of a paper on hematopoietic colony-stimulating factors, authored in 1984 by N. Nicola and M. Vadas of the WEHI Institute. Dr. Van Etten agreed (and agreed the Skilled Person would have understood from reading that paper) that G-CSF (in that paper, murine G-CSF) was unique among the CSF classes, was very potent to differentiating activity on myeloid leukemic cell lines, and was capable of inducing complete terminal differentiation in some lines of WEHI-3B cells.

[211] Pfizer submits that, even if one were to accept Amgen's argument that strong differentiation induction in the WEHI Assay was a hallmark of granulocyte colony stimulating-activity, the substance of the 959 Application is not essentially the same as the 537 Patent,

because it does not include the results from the CFU-GM, BFU-E, and CFU-GEMM assays (which tests were not performed until after August 23, 1985). I do not consider this a compelling argument. I appreciate that the specification of the 537 Patent discloses testing in the CFU-GM, BFU-E, and CFU-GEMM assays. However, Dr. Van Etten's opinion is based upon a requirement that the 959 Application disclose the recombinant protein having granulocyte colony-stimulating activity, not based upon a requirement to disclose testing in particular assays. In my view, the question is whether the 959 Application's disclosure related to the WEHI Assay results meets this requirement.

[212] Pfizer further argues the information contained in the 959 Application does not actually show the recombinant protein induced strong differentiation in the WEHI Assay, which was the hallmark of granulocyte colony-stimulating activity. Pfizer refers to Dr. Maloy's admission on cross-examination that the only information provided in the 959 Application is that the recombinant material was found to induce differentiation, with no quantitative or qualitative indication of those results. Dr. Maloy further admitted that determining whether there was any activity in the WEHI Assay required comparing the results to positive and negative controls, which were not reported in the 959 Application. Dr. Maloy acknowledged he had not reviewed Amgen's lab books in arriving at the opinions in his report.

[213] Dr. Griffin also acknowledged in cross-examination that he did not review Amgen's lab books. As such, his opinion as to the significance of the WEHI Assay results in the 959 Application is based only on the information in that application. The 959 Application does not set out detailed data surrounding the WEHI Assay results, and the statement of the results does

not include the word “strong” before “differentiation”. However, the application does state that colonies were classified as undifferentiated, partially differentiated or wholly differentiated; that colony cell counts were counted microscopically; and the resulting conclusion that the *E. coli* recombinant material was found to induce differentiation.

[214] Moreover, Dr. Griffin is the expert who spoke to this subject in the most detail; and, other than pointing out he had not reviewed Amgen’s lab books, his opinion thereon was otherwise unchallenged in cross-examination. Dr. Griffin’s report first reviews the prior art indicating that Drs. Metcalf, Nicola, and Welte reported their respective factors (murine G-CSF, CSF- ß, and pluripotent CSF) could induce differentiation in WEHI-3B (D+) cells. He then reviews the references to such prior art in the 959 Application itself, and he concludes, based on the results disclosed in the 959 Application, that Dr. Souza had a strong basis for finding the recombinant protein had granulocyte colony-stimulating activity, as it showed differentiation in the WEHI Assay. Pfizer has not convinced me that Dr. Griffin’s opinion should be rejected.

[215] Finally, Pfizer relies on the principle expressed in *Ratiopharm* at paragraph 122, that the Court should not presume that, just because the specification of a patent has used particular words or qualifiers, such description is accurate. Pfizer argues there was actually no basis to make the statement in the 959 Application about the WEHI Assay results. Pfizer acknowledges it bears the burden of undermining that statement.

[216] This argument takes me to Pfizer’s submissions on the evidence of Dr. Zsebo. Her affidavit contains detailed evidence surrounding the WEHI Assay that she and her research

assistant, Victoria Yuschenkoff, conducted on [REDACTED]. She states they knew their recombinant protein had granulocyte colony-stimulating activity by August 21, 1985, when they reviewed the results from the WEHI Assay, which they understood was a hallmark of such activity. However, Pfizer submits that Dr. Zsebo's cross-examination exposed problems with Amgen's reliance on the [REDACTED] WEHI Assay.

[217] First, Pfizer argues there is no intelligible record of the assay results. The relevant pages from Ms. Yuschenkoff's laboratory notebook are attached as Exhibit L to Dr. Zsebo's affidavit. On cross-examination, Dr. Zsebo struggled to make sense of some of the entries in Ms. Yuschenkoff's laboratory notebook. She believed one of the dilution levels recorded in the notebook for the samples tested in the WEHI Assay was an error. Also, she explained that data for the positive and negative controls tested in the WEHI Assay was not recorded. Indeed, the number of colonies in the negative and positive controls was not actually counted but was only visually inspected.

[218] Second, Pfizer observes Dr. Zsebo relied on a document attached to her affidavit as Exhibit M to provide her evidence. Exhibit M was her summary of Ms. Yuschenkoff's notebook pages in Exhibit L, which she created at counsel's request in the context of the Apotex Application. In examination-in-chief, Dr. Zsebo asserted Exhibit M contained exactly the same numbers as Exhibit L. However, Pfizer submits this statement proved to be untrue on cross-examination, referencing the unexplained dilution level error in Exhibit L. Pfizer also emphasizes Dr. Zsebo prepared Exhibit M for purposes of other litigation years after the August 1985 WEHI Assay was performed.

[219] I do not find Pfizer's efforts to challenge Dr. Zsebo's evidence particularly persuasive. While the contemporaneous record of the WEHI Assay results (Exhibit L) was made by Ms. Yuschenkoff, she was Dr. Zsebo's assistant, and Dr. Zsebo participated in those experiments. While Exhibit M is not a contemporaneous record, Dr. Zsebo explained that it represents a different presentation of the same data from Exhibit L, organized according to the particular HPLC fraction and dilution level being tested.

[220] I recognize there is a discrepancy between the largest dilution level reflected in Exhibits L and M. However, Pfizer has not convinced me the discrepancy is material. Dr. Zsebo explained the main point of the experiment was to demonstrate that, at high dilutions, there is very little differentiation activity and, at very concentrated samples, there is a lot of differentiation activity. She identifies the most compelling data as that shown for the samples with the smallest dilution level (i.e. the most concentrated), for which 100 per cent of the colonies were differentiated or partially differentiated. Dr. Zsebo describes the data as demonstrating a pretty substantial difference. In cross-examination, she stated she was very confident in the results reflected in Exhibit M and what they represent, and I do not find Pfizer to have undermined that evidence.

[221] With respect to the positive and negative controls, Pfizer is correct that the data for those aspects of the WEHI Assay test was not captured quantitatively or preserved. However, Dr. Zsebo explained in cross-examination that these results were visually assessed as validating that the assay had performed according to specifications. She had also elaborated upon this approach in her examination-in-chief. She explained the assay results were counted by hand under a

dissecting microscope, which could be time-consuming. The role of controls was to verify the validity of the assays through a visual assessment, i.e., the negative controls looked negative and the positive controls looked positive. Beyond that, the scientists did not have the appetite to count each one of these colonies. Rather, they went on to score the test samples.

[222] While Pfizer notes the importance of controls to the WEHI Assay results, it has not adduced expert evidence that undermines Dr. Zsebo's explanation as to how the control testing was conducted. With the benefit of her evidence, I do not find the absence of quantitative recorded control data to show there was no basis for Amgen to make the statement it did in the 959 Application about the WEHI Assay results.

[223] In conclusion, I find that the substance of the descriptions of the invention in the 959 Application and in the 737 Application are essentially the same. There is no basis to conclude the applications are in substance directed to different inventions. Amgen is therefore entitled to rely on the August 23, 1985 priority date of the 959 Application.

B. *Evidence Establishing the Invention was Achieved by August 23, 1985*

[224] Having reached this conclusion on the priority application, it is unnecessary for me to address whether Amgen's evidence establishes the subject matter of each of the Asserted Claims was invented no later than August 23, 1985. However, in case I have erred in my analysis surrounding the 959 Application, I will address this argument as well.

1. Legal Principles

[225] As noted, the invention date has been described as the date on which the inventor reduced their invention to a definite and practical shape, or the date at which the inventor can prove that they first formulated, either in writing or verbally, a description which affords the means of making that which is invented (see *Christiani* at 454, 456).

[226] Pfizer relies on Justice Snider's articulation of the applicable test in *Sanofi-Aventis* at paragraph 274:

> [274] Summarizing my understanding of the date of invention, the date of invention will be the date on which the inventor can demonstrate three things:
>
> 1. the invention is identified;
> 2. the invention has been reduced to writing[;] and
> 3. the invention is "practical" in that it will do the job that is claimed; in other words, it will have utility.

[227] I have some doubt that reduction to writing is a strict requirement. While writing is perhaps the most common means by which an inventor can demonstrate the invention's reduction to a definite and practical shape, the Supreme Court's reference in *Christiani* to a description of the invention being formulated verbally has been quoted by the Federal Court of Appeal (see *Apotex v Wellcome* (2000), 10 CPR (4^{th}) 65 (FCA) at para 31). More recently, the Federal Court in *Pfizer Canada Inc v Pharmascience Inc*, 2013 FC 120 at para 110 endorsed the following definition:

> [110] Another exception arose under the provisions of the Patent Act as it existed prior to the October 1, 1989 amendments. There the act of invention would become relevant in considering obviousness, as obviousness was to be considered as of the "date of the invention". While that date, in the absence of other evidence, was presumed to be the filing date of the application in Canada - or the priority date, if any - a patentee may have wished to establish an even earlier date; for instance, so as to make a certain intervening publication irrelevant as to the issue of obviousness. In such a circumstance, the Courts have said that the "date of the invention" is the date when the invention was reduced to a definite and practical shape by building it or by fully describing how it will be practiced and showing that it has utility […].
>
> [Emphasis added.]

[228] Regardless, this point does not appear material in the present matter, as Amgen has not identified any verbal (or other than written) formulation of the invention upon which it relies to establish the invention date.

[229] Pfizer submits that, where a claimed invention has several essential features, the invention date is the date on which the patentee can prove the invention was described or an embodiment was made that had all of the essential features (see, e.g., *Janssen-Ortho Inc v Novopharm Limited*, 2006 FC 1234 at paras 43-50). Similar to the issues it raised in connection with the 959 Application, Pfizer submits Amgen has no reliable documentary evidence that, by August 23, 1985, it demonstrated granulocyte colony-stimulating activity through the WEHI Assay or possessed the correct Claim 43 amino acid sequence.

2. Granulocyte Colony-Stimulating Activity through the WEHI Assay

[230] Pfizer’s arguments surrounding the invention date and the WEHI Assay relate to the evidence of Dr. Zsebo and the documents attached to her affidavit. Those arguments have

already been addressed in the above analysis of the 959 Application, and I adopt the same conclusion here. That is, I find Dr. Zsebo's evidence of a WEHI Assay, showing that Amgen's recombinant protein induced differentiation, demonstrated the Souza team had achieved a recombinant protein having G-CSF activity as of August 21, 1985.

3. Correct Claim 43 Amino Acid Sequence

[231] In challenging whether Amgen had the Claim 43 amino acid sequence by August 23, 1985, Pfizer raises additional arguments surrounding Amgen's documentation (i.e., other than related to the 959 Application). Pfizer takes the position that Amgen's only evidence it had reduced the correct amino acid sequence for the naturally occurring protein to writing by August 23, 1985 is the first two pages of Exhibit R to Mr. Boone's affidavit. Although the correct amino acid sequence is shown in handwriting in another document (Exhibit Q to Mr. Boone's affidavit), Mr. Boone admits he does not know when such handwriting was added to that document.

[232] Pfizer raises several issues with Amgen's reliance on Exhibit R. First, it submits Amgen must overcome the hearsay nature of this document. Mr. Boone's affidavit refers to this document as a DNA sequencing record, dated August 15, 1985, which sets out the fully correct sequence for the recombinant protein. However, while Exhibit R forms part of Mr. Boone's affidavit, and therefore part of the evidence before the Court, Pfizer takes issue with the use that can be made of that evidence. It submits Amgen is seeking to rely on Exhibit R for the truth of its contents and cannot do so without satisfying the requirements of s 30 of the *Canada Evidence Act*, RSC 1985, c C-5 [CEA]. Indeed, Exhibit R was the subject of a s 30 motion by Amgen,

argued at the conclusion of the evidentiary stage of the trial. I reserved my decision on that motion, which I advised counsel would be included in these Reasons.

(a) *Amgen's Canada Evidence Act Motion*

[233] Some background to this motion requires explanation. Exhibit R appears to be a computer printout entitled "Translation of ppocdna", setting out an amino acid sequence with accompanying DNA codons. The particular copy of that document in Exhibit R to Mr. Boone's affidavit shows what appear to be three pairs of amino acids crossed out with marker or pen. That is, a total of six amino acids appear crossed out and therefore unreadable. However, Mr. Boone was asked about this on cross-examination, and he testified the original document had been found. In that original document, he explained, these amino acids were actually highlighted, not crossed out.

[234] Pfizer's counsel then made an effort to impeach Mr. Boone, referring him to the transcript from his discovery examination, in which he described the three pairs as crossed out. He agreed that was his evidence, based on looking at the reprint of the document. He also adopted his discovery evidence to the effect that: (a) taking into account the cross-outs of the amino acids, which someone made for an unknown reason, Exhibit R does not show the final sequence; but (b) the DNA sequence still exists in Exhibit R and matches the 537 Patent.

[235] Amgen's counsel represented during the hearing of the motion that the original, highlighted document came into counsel's possession the day before the commencement of trial. Although there is no evidence to that effect, Pfizer's counsel did not dispute this representation.

However, there is no evidence as to when Amgen itself located the original document. Following the conclusion of the first week of trial (Mr. Boone having testified on Wednesday of that week), Amgen's counsel advised Pfizer's counsel the original document was in his possession and offered to make it available for Pfizer's counsel's review.

[236] These events lead to the motion, presented orally by Amgen at the conclusion of the second week of trial, seeking to have the highlighted document admitted into evidence for the truth of its contents as a business record under s 30 of the CEA. Amgen's counsel explained it has two objectives in introducing the highlighted document under s 30. First, Amgen wishes to respond to Pfizer's efforts to impeach Mr. Boone's testimony that the cross-outs in the document were actually highlighting. Second, Amgen wishes to prove what the document says, because it forms part of the invention story. However, Amgen takes the position it does not need to rely on the amino acid sequence in the highlighted Exhibit R to prove the invention date. It argues instead that Mr. Boone's evidence relies on the DNA sequence in Exhibit R to establish the invention had been recorded.

[237] Pfizer opposed the motion, arguing that the requirements of s 30 were not met, and that it was unfair for Amgen to withhold the original document until after Mr. Boone's oral testimony and then attempt to introduce it into evidence. While Pfizer raised several arguments in support of both grounds of opposition, it is not necessary for me to address most of these. In my view, the outcome of the motion turns on whether Amgen has satisfied the requirements of s 30(1) of the CEA:

Canada Evidence Act, RSC 1985, c C-5	*Loi sur la preuve au Canada*, LRC 1985, ch C-5
Business records to be admitted in evidence	**Les pièces commerciales peuvent être admises en preuve**
30 (1) Where oral evidence in respect of a matter would be admissible in a legal proceeding, a record made in the usual and ordinary course of business that contains information in respect of that matter is admissible in evidence under this section in the legal proceeding on production of the record.	**30 (1)** Lorsqu'une preuve orale concernant une chose serait admissible dans une procédure judiciaire, une pièce établie dans le cours ordinaire des affaires et qui contient des renseignements sur cette chose est, en vertu du présent article, admissible en preuve dans la procédure judiciaire sur production de la pièce.

[238] To satisfy these requirements, Amgen relies on s 30(6), which states:

Court may examine record and hear evidence	**Le tribunal peut examiner la pièce et entendre des témoins**
30 (6) For the purpose of determining whether any provision of this section applies, or for the purpose of determining the probative value, if any, to be given to information contained in any record admitted in evidence under this section, the court may, on production of any record, examine the record, admit any evidence in respect thereof given orally or by affidavit including evidence as to the circumstances in which the information contained in the record was written, recorded, stored or reproduced, and draw any reasonable inference from the form or content of the record.	**30 (6)** Aux fins de déterminer si l'une des dispositions du présent article s'applique, ou aux fins de déterminer la valeur probante, le cas échéant, qui doit être accordée aux renseignements contenus dans une pièce admise en preuve en vertu du présent article, le tribunal peut, sur production d'une pièce, examiner celle-ci, admettre toute preuve à son sujet fournie de vive voix ou par affidavit, y compris la preuve des circonstances dans lesquelles les renseignements contenus dans la pièce ont été écrits, consignés, conservés ou reproduits et tirer toute conclusion raisonnable de la forme ou du contenu de la pièce.

[239] Amgen submits the Court can draw reasonable inferences from Mr. Boone's evidence to conclude that Exhibit R is a record made in the usual and ordinary course of business. In particular, it relies on the following paragraphs from Mr. Boone's affidavit [emphasis in original]:

> 3. Counsel for Amgen has asked me to detail my work on the G-CSF project, in order to assist in responding to various allegations advanced by Pfizer Canada ULC that claims 43 to 47 of the 537 Patent are invalid. The work that led to the invention of genetically engineered G-CSF is already described in some detail in the 537 Patent itself, but my focus in this affidavit is to provide additional detail about how Dr. Souza's team developed the invention, including the motivations behind the various decisions we made, the alternatives that we considered, and the challenges presented by each step of the process. Although my work on the G-CSF project took place many years ago, it was a major event in my career, and I maintain a strong recollection of several aspects of the process. My memory is also refreshed by looking at Amgen records made during the course of the project, including lab notes, several relevant excerpts of which are identified below and attached to my affidavit as exhibits.
>
> […]
>
> 117. Attached as **Exhibit Q** is a DNA sequencing record dated [REDACTED], which is similar to the document at Exhibit P (containing the sequence with an error), but has handwritten corrections to the sequence, which matches the sequence we ultimately obtained for the PPO2 cDNA, provided at pages 22-24 of the 537 Patent. I am not certain when the handwritten corrections were made. However, I know that we had the corrected sequence by August 15, 1985, the date of the DNA sequencing record attached at **Exhibit R** (in which the sequence is fully correct).

[240] Amgen notes that, in paragraph 3 of Mr. Boone's affidavit, he explains that the G-CSF project was a major event in his career, that he maintains a strong recollection of several aspects of the project, and that he has refreshed his memory by looking at Amgen's records made during the course of the project. Such records included lab notes, several relevant excerpts of which are attached to his affidavit as exhibits. Amgen then relies on Mr. Boone's statement in paragraph 117 that he knows they had the correct sequence by August 15, 1985, the date of the DNA sequencing record attached as Exhibit R.

[241] In my view, these paragraphs do not establish that Exhibit R represents a record made in the usual and ordinary course of business. Paragraph 117, the sole reference to Exhibit R in Mr. Boone's affidavit, merely states his reliance on Exhibit R to confirm the date by which the correct sequence had been identified. It provides no evidence that Exhibit R was produced in the usual and ordinary course of business. Similarly, paragraph 3 merely states Mr. Boone relied on Amgen records, some excerpts of which are attached to his affidavit, to refresh his memory. There is nothing in paragraph 3 to the effect that Exhibit R was produced in the usual and ordinary course of business. Nor is it possible to draw inferences to that effect from either paragraph or their combination.

[242] I appreciate that Mr. Boone's affidavit establishes more broadly that he had a significant role in the G-CSF project, and I agree with Amgen's submission that the import of the referenced paragraphs is that Exhibit R was created during his involvement in this project, such that it is admissible evidence. However, this evidence does not satisfy the requirements of s 30 or otherwise make the document admissible for the truth of its contents.

[243] I therefore dismiss Amgen's CEA motion. However, as explained below, I am not convinced that Amgen's efforts to prove an invention date by August 23, 1985 fail as a result of its failure on this motion.

(b) *Remaining Evidentiary Effect of Exhibit R to Mr. Boone's Affidavit*

[244] Pfizer's position is that, if Amgen cannot rely on Exhibit R for the truth of its contents, then it has no evidence that it had either the amino acid or the DNA sequence in hand by August

23, 1985. However, Amgen takes the position it does not require admission of the original highlighted document to establish its invention date. As noted above, I agree with its submission that the version of Exhibit R attached to Mr. Boone's affidavit is still in evidence. Amgen relies on Mr. Boone's evidence given in cross-examination that, even with the three pairs of amino acids crossed out, the DNA sequence is still present in Exhibit R and matches the patent.

[245] I note that, immediately after giving this evidence in cross-examination, Mr. Boone agreed with Pfizer's counsel that the DNA sequence in Exhibit R (dated August 15, 1985) is not the full DNA sequence of the recombinant protein expressed in *E. coli*. This statement was not further explained by Mr. Boone or further pursued by Pfizer in cross-examination or argument. However, I interpret it to point out that Exhibit R sets out the DNA sequence for naturally occurring G-CSF, rather than recombinant G-CSF. The parties do not dispute that the recombinant protein necessarily has an extra amino acid, methionine [Met], at its N-terminal, as a result of its expression in *E. coli*. Exhibit R does not include that amino acid or the corresponding codon. Pfizer raises that point as an additional argument in support of its position that Exhibit R does not set out the invention of the 537 Patent. I will return to the significance of the Met shortly.

[246] Leaving that point aside for the moment, the question is whether Exhibit R can assist Amgen, when it has not been admitted for the truth of its contents. I find that it can. The test is whether the invention has been reduced to a definite and practical shape, for instance in written form. In my view, Exhibit R is evidence of the fact that the invention had been reduced to written

form before August 23, 1985, and relying on the document for that purpose does not represent a hearsay use.

[247] Of course, Amgen must still contend with the fact that six of the amino acids are, using Mr. Boone's language, crossed out in that document. Even accepting his testimony that what presents as crossing out is actually highlighting, those amino acids are obscured in the version of Exhibit R in evidence. Therefore, the amino acid sequence in Exhibit R does not particularly assist Amgen. However, as Amgen submits, Mr. Boone's evidence is that the correct DNA sequence is found in that document. As the amino acid sequence follows quite mechanically from the DNA sequence, I find Exhibit R does serve as evidence the invention had been formulated by the date of that document.

[248] In arriving at that conclusion, I have considered Pfizer's argument that the evidence provides no explanation of what Exhibit R is, who produced it, or what its purpose is. I accept that the evidence surrounding Exhibit R is light. However, Mr. Boone's affidavit does identify it as Amgen's document, made during the course of the G-CSF project in which he was significantly involved, and which recorded the DNA sequence of the invention by August 15, 1985. I consider Mr. Boone's evidence sufficient to establish those facts, and those facts sufficient to address Pfizer's position that Amgen cannot establish it had the sequence in hand by August 23, 1985.

[249] Finally, I return to Pfizer's argument that Exhibit R does not set out the full Claim 43 sequence, as it does not include the N-terminal Met or the DNA codon for that amino acid. Pfizer

notes Dr. Maloy was insistent on cross-examination that the Met is essential to the invention. Pfizer also observes Amgen might argue that adding the Met to the sequence in Exhibit R was obvious. While Pfizer accepts this point, it submits the failure to articulate the Met in Exhibit R is fatal to the invention Amgen claims, as adding the Met is the very essence of the invention.

[250] Amgen's response to this argument relies on the 959 Application, not for its status as a patent application, but as an additional document identifying whether the invention had been formulated by August 23, 1985. Example 6 of the 959 Application states that it "[…] relates to E. coli expression of an hpG-CSF polypeptide by means of a DNA sequence encoding [Met-1] hpCSF" and goes on to explain, by reference to Table IX, the requirement to include a synthetic fragment in the expression vector to add the Met and replace certain amino acids cleaved off by enzymes in an earlier experiment. Table IX in turn shows the amino acid and DNA sequence of the synthetic fragment, with Met (and its codon) in the -1 position, followed by the first three amino acids of the target polypeptide (and their codons).

[251] Amgen also refers to Court to evidence provided by Mr. Boone and Dr. Maloy, which further explains the role of the Met and the initial codon sequence in the *E. coli* expression. Mr. Boone explains that, in preparing for that expression, Amgen was forced to cut the DNA sequence at a site inside the coding region, resulting in loss of some of the initial nucleotides. It was therefore necessary to replace those nucleotides in the final plasmid. It was also necessary to insert a codon for Met as the first codon of the coding region, as Amgen understood those nucleotides were the necessary "start codon" for expression of a protein in *E. coli.* As previously noted, I do not understand there to be any dispute surrounding this point. Mr. Boone refers to the

DNA sequence encoding Met plus the initial amino acids as a “linker”, the sequence for which is shown at Table XVII of the 537 Patent. I note that Table XVII is identical to Table IX of the 959 Application.

[252] To similar effect, in cross-examination, Dr. Maloy testified that Table IX of the 959 Application identified the need to add a Met at the -1 position of the amino acid sequence to generate the full sequence of 175 amino acids.

[253] I accept the 959 Application demonstrates that, by August 23, 1985, Amgen had identified and documented the need to add the codon encoding Met, as the first of 175 codons encoding for recombinant G-CSF, to express the target protein recombinantly in *E. coli*. The remaining question is whether it is problematic for Amgen that this element of the invention appears in the 959 Application, separate from the sequence of 174 codons in Exhibit R.

[254] Pfizer argues that, to establish an invention date earlier than the Canadian filing date, the invention must be captured in one document, or potentially in documents incorporated by reference into one document. Amgen notes that Pfizer has cited no authority for this proposition. In the absence of any such authority, I find no basis to adopt such a restriction. As noted in *Lubrizol Corp v Imperial Oil Ltd* (1992), 45 CPR (3^{rd}) 449 (FCA) at 462, the essential fact to be proved is that, at the asserted date, the invention was not merely an idea that floated through the inventor’s brain but had been reduced to a definite and practical shape. While it is appropriate to scrutinize the evidence to ascertain whether it establishes this fact, I find no legal impediment to

relying on more than one document if, in the context of the evidence in a particular proceeding, those documents support a conclusion that the invention had been fully formulated.

[255] In conclusion, if Amgen were unable to rely on the 959 Application to establish August 23, 1985 as a priority date, I find the evidence establishes an invention date no later than that date. I will therefore employ August 23, 1985 as the invention date in the obviousness analysis that follows.

XII. OBVIOUSNESS – ANALYSIS

A. *Legal Principles*

[256] The parties agree the analytical framework to be employed for assessing obviousness is as explained by the Supreme Court of Canada in *Plavix* at para 67:

> (1) (a) Identify the notional "person skilled in the art";
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?
>
> […]

> It will be at the fourth step […] that the issue of "obvious to try" will arise.

B. *The Skilled Person and their Common General Knowledge*

[257] The identification of the Skilled Person has already been performed earlier in these Reasons. For ease of reference, I found that the Skilled Person is a team consisting of:

A. a molecular biologist with a PhD and several years of work experience in academia or industry;

B. a hematologist with an MD and board certification (or, alternatively, a PhD in hematology and several years of work experience in academia or industry); and

C. a protein biochemist with a PhD and several years of work experience in academia or industry.

[258] The Skilled Person's CGK means knowledge generally known by the Skilled Person at the relevant time that they bring to the various tasks assigned to them under patent law. In *Eurocopter v Bell Helicopter Textron Canada Ltée*, 2013 FCA 219 at paragraphs 64-65, CGK was described as follows:

> [64] Common general knowledge does not amount to all information in the public domain. While the common general knowledge of the skilled person certainly includes knowledge of patents, it does not include knowledge of *all* patents: *General Tire* at pp. 481 to 484. Nor does it include knowledge of all journal articles or other technical information: *British Acoustic Films Ltd. v. Nettlefold Productions* (1935), 53 R.P.C. 221 (Eng. C.A.), at p. 250, cited approvingly in *General Tire* at pp. 482-483.
>
> [65] Rather, it is well established that the common general knowledge is limited to knowledge which is generally known at the relevant time by skilled persons in the field of art or science to which the patent relates: *Sanofi* at para. 37; *Free World Trust c. Électro Santé Inc.*, 2000 SCC 66, [2000] 2 S.C.R. 1024 (S.C.C.) ("*Free World Trust*") at para. 31. Thus, accordingly, the common

> general knowledge is with respect to the subset of patents, journal articles and technical information which is generally acknowledged by skilled persons as forming part of the common general knowledge in the field to which the patent relates […]

[259] Stated similarly in *Mylan Pharmaceuticals ULC v Eli Lilly Canada Inc*, 2016 FCA 119 at paragraph 24:

> [24] The common general knowledge, in contrast, is the "knowledge generally known by persons skilled in the relevant art [skilled persons] at the relevant time": *Apotex Inc. v. Sanofi-Synthelabo Canada Inc.*, 2008 SCC 61, at para. 37, [2008] 3 S.C.R. 265. Unlike the prior art, which is a broad category encompassing all previously disclosed information in the field, a piece of information only migrates into the common general knowledge if a skilled person would become aware of it and accept it as "a good basis for further action": *General Tire & Rubber Co. v. Firestone Tyre & Rubber Co.*, [1971] F.S.R. 417, (1972) R.P.C. 457 at 483 (C.A.).

[260] I do not understand the parties to have any disagreement as to these principles. Indeed, there also appears to be very little disagreement as to the relevant CGK, to be taken into account based on the application of these principles, in conducting the obviousness analysis. In its closing written submissions, Amgen acknowledges the parties generally agree as to the background scientific knowledge the Skilled Person would have had as of August 23, 1985.

[261] Pfizer's expert, Dr. Van Etten, states the CGK includes understanding, and knowing how to implement, the standard techniques of protein biochemistry (including protein purification, protein refolding, and amino acid sequencing), molecular biology (including recombinant DNA technology), and hematology (including cell-based assays). His report provides lengthy explanations of scientific background information in these fields, which he considers to form part

of the CGK. This includes appendices that provide considerable detail in each of the following areas:

A. cloning a gene using the "probe approach", involving starting with a small portion of a protein's amino acid sequence and employing a probe to learn the protein's entire amino acid sequence using the gene as an intermediary;

B. directly expressing a recombinant protein in *E. coli*; and

C. purifying and refolding the protein so that it has biological activity and testing for that activity.

[262] Dr. Boxer similarly describes the CGK of the Skilled Person as including an understanding of the fundamentals of molecular biology and protein biochemistry, which would include the available tools and techniques of recombinant DNA technology and protein biochemistry as of August 23, 1985.

[263] Dr. Hermodson, Pfizer's expert on amino acid sequencing, provides a detailed explanation of the structure of proteins; the amino acid sequencing process; the iterative process researchers used to sequence proteins; and his opinion on useful results in amino acid sequencing. He opines that this information would have been included in the CGK of the skilled protein biochemist. I understand Dr. Hermodson's use of the term "skilled protein biochemist" to be a reference to the Skilled Person but particularly to the member(s) of the Skilled Person "team" to whom Example 1 of the 537 Patent is directed. As previously noted, Example 1 sets out the process Amgen used to partially sequence the target protein, which falls within Dr. Hermodson's expertise and is the focus of his evidence.

[264] Turning to Amgen's experts, Dr. Maloy refers to Dr. Van Etten's report, in particular his appendices, as including extensive detail on various laboratory tools and techniques that had

been disclosed in the art prior to August 1985. Dr. Maloy generally agrees that the individual tools and techniques Dr. Van Etten describes would have been available to the Skilled Person. However, Dr. Maloy states they might not have been part of the CGK.

[265] To somewhat similar effect, Dr. Griffin disagrees all of the publications Dr. Van Etten cited would form part of the CGK in the field to which the patent relates. He explains that, in 1985-1986, scientific research did not take place using online tools. Rather, information came from attending conferences, from reading journals to which individuals subscribed or that were housed in libraries, or from articles circulated or discussed among colleagues in the field. Therefore, one could not be sure that information in publications became part of the CGK in the field until well after the date of publication, and then only if it made a significant impact in the field. Dr. Griffin opines that textbooks available at the time would have formed part of the CGK.

[266] Dr. Speicher, Amgen's expert on amino acid sequencing, describes the Skilled Person's CGK as consisting of: the general approaches to protein purification and partial amino acid sequencing in 1985; the operation of automated Edman degradation amino acid sequencers; and some ability to make "calls" of partial amino acid sequences when provided a sufficient amount of a sufficiently pure experimental protein that produced strong and straightforward signals.

[267] These opinions from Amgen's experts obviously do not represent unqualified endorsements of the opinions of Pfizer's experts as to the relevant CGK. However, as previously noted, Amgen describes the parties as being in general agreement as to the background scientific knowledge the Skilled Person would have had as of August 23, 2985. In so stating, Amgen

references the evidence of Drs. Maloy and Griffin set out above. Amgen does identify one particular technique, the use of inosine probes, that it disputes had become routine by August 23, 1985. I will address that particular point later in these Reasons. Otherwise, neither Amgen nor its experts have identified any particular tools, techniques, or publications as not having entered the CGK by that date. I accept Pfizer's experts' description of the CGK.

[268] Having said that, at this stage of the analysis, I am of course not reaching any conclusions on whether the CGK is sufficient to bridge the gap between the state of the art and the inventive concept of the Asserted Claims. I am conscious Amgen and its experts take significant issue with the opinions of Pfizer's experts on that question, which will be addressed later in my analysis.

C. *Inventive Concept*

[269] Step 2 of the *Plavix* obviousness test requires identification of the inventive concept of the claim in question or, if that cannot readily be done, construction of the claim. The Federal Court of Appeal recently provided the guidance on this step of the test in *Ciba Specialty Chemicals Water Treatments Limited v SNF Inc*, 2017 FCA 225 [*Ciba*] at paragraphs 72-77 [emphasis added]:

> [72] The next issue is the identification of the inventive concept. We can find some guidance as to how to approach the inventive concept in *Pozzoli*. At paragraph 17 of the Court of Appeal's reasons, Lord Jacob quoted from his reasons in the Court of Appeal's decision in *Unilever v. Chefaro*, [1994] R.P.C. 567 (*Unilever*) at page 580:
>
> > It is the inventive concept of the claim in question which must be considered, not some generalised concept to be derived from the specification as a

> whole. Different claims can, and generally will, have different inventive concepts. The first stage of identification of the concept is likely to be a question of construction: what does the claim mean? It might be thought there is no second stage - the concept is what the claim covers and that is that. But that is too wooden and not what courts, applying *Windsurfing* stage one, have done. It is too wooden because if one merely construes the claim one does not distinguish between portions which matter and portions which, although limitations on the ambit of the claim, do not. One is trying to identify the essence of the claim in this exercise.

[73] This passage anticipates the Supreme Court's teaching on patent construction in *Whirlpool Corp. v. Camco Inc.*, 2000 SCC 67 at paragraph 45, [2000] 2 S.C.R. 1067, where it said:

> The key to purposive construction is therefore the identification by the court, with the assistance of the skilled reader, of the particular words or phrases in the claims that describe what the inventor considered to be the "essential" elements of his invention.

[74] The reminder in *Unilever* that it is inventive concept of the claim which is in issue, "not some generalised concept to be derived from the specification as a whole," is very apt: *Unilever* at page 569. Part of the difficulty in the search for the inventive concept is the use made, or to be made, of the disclosure portion of the specification of the patent. In *Connor Medsystems Inc v. Angiotech Pharmaceuticals Inc.* [2008] UKHL 49, [2008] R.P.C. 28 (*Connor*), Lord Hoffman wrote at paragraph 19 that "[t]he patentee is entitled to have the question of obviousness determined by reference to his claim and not to some vague paraphrase based upon the extent of his disclosure in the description."

[75] This emphasis on the claims is consistent with section 28.3 of the Act which stipulates that it is "the subject-matter defined by a claim" which must not be obvious.

[76] Lord Jacob was alive to the possibility that difficulties in the identification of the inventive concept could lead to "unnecessary satellite debate". His counsel was that "if a disagreement about the inventive concept of a claim starts getting

> too involved, the sensible way to proceed is to forget it and simply to work on the features of the claim": *Pozzoli* at paragraph 19. Lord Hoffman wrote, once again in *Connor* at paragraph 20, that the inventive concept "is a distraction almost as soon as there is an argument as to what it is."
>
> [77] There may be cases in which the inventive concept can be grasped without difficulty but it appears to me that because "inventive concept" remains undefined, the search for it has brought considerable confusion into the law of obviousness. That uncertainty can be reduced by simply avoiding the inventive concept altogether and pursuing the alternate course of construing the claim. Until such time as the Supreme Court is able to develop a workable definition of the inventive concept, that appears to me to be a more useful use of the parties' and the Federal Court's time than arguing about a distraction or engaging in an unnecessary satellite debate.

[270] Consistent with the reasoning in *Ciba*, Dr. Van Etten opines the inventive concept of each of the Asserted Claims is no different than the Skilled Person's understanding of those claims (i.e. his claim construction). He therefore adopts his claim construction opinions (canvassed earlier in these Reasons) for purposes of this step in the *Plavix* analysis. Pfizer argues the obviousness analyses of Amgen's experts are deficient in part because they do not opine on the inventive concept of the Asserted Claims. However, Amgen notes that Dr. Maloy provided claim construction opinions and, relying on *Ciba*, submits that this suffices for purposes of identifying the inventive concept of the claims (see also *Tearlab Corporation v I-MED Pharma Inc*, 2019 FCA 179 at paras 75-78).

[271] In response to this submission, Pfizer refers the Court to *Eli Lilly Canada Inc v Apotex Inc*, 2018 FC 736 [*Eli Lilly*] at paragraphs 97 to 98. Pfizer submits that, in *Eli Lilly*, Justice Manson departed from the reasoning in *Ciba* and refocused on the inventive concept as explained in *Plavix.* I disagree with Pfizer's characterization of *Eli Lilly*. Rather, Justice Manson

expressly found that, when read purposely in light of *Plavix* and *Novopharm SCC, Ciba* does not qualify the approach to determining obviousness (at para 98).

[272] Pfizer also submits Dr. Maloy's claim construction cannot serve as an opinion on the inventive concept of the Asserted Claims, because he performed that analysis as of 2007 (the publication date), not as of 1985 (the priority date, when obviousness is assessed). I do not see how this distinction assists Pfizer in the present case. Dr. Van Etten also performed his claim construction analysis as of 2007 and yet adopted those constructions for purposes of the inventive concept. Moreover, Pfizer has not identified any difference in the constructions that would apply as of the different dates, such as would undermine reliance on Dr. Maloy's constructions.

[273] Regardless, I agree with Amgen's position that the differences between the parties' respective positions on claim construction are inconsequential for purposes of the obviousness analysis. I have previously considered this point when construing the Asserted Claims earlier in these Reasons. As the differences in the parties' proposed constructions are immaterial, I adopt the claim constructions set out in Appendix "A" to these Reasons as the inventive concepts of the Asserted Claims.

[274] In so concluding, I am conscious that Justice Hughes held the inventive concept of Claim 43 is a recombinantly produced polypeptide having an amino acid sequence beginning with a Met followed by some or all of the amino acid sequence of the Welte protein possessing some or all of its biological properties (Apotex Decision at para 96). However, I have previously

concluded there is good reason not to adopt automatically the claim construction from the Apotex Decision. That conclusion applies to the inventive concept as well (see also *Allergan* at para 50).

[275] I do note that Justice Hughes' construction of Claim 43 included a reference to the biological properties of the polypeptide. Related thereto, Pfizer points out in its closing submissions what it describes as an inconsistency in Amgen's position. As stated earlier in these Reasons, Amgen's counsel confirmed during trial that it is not asserting that Claim 43 includes as an essential element a polypeptide having biological activity. However, in its closing written argument, Amgen submits that: (a) showing activity in common with the natural G-CSF was essential to the inventor's understanding that the invention of Claims 43-47 had been achieved (i.e. a recombinant version of the protein had been successfully made); and (b) determining or soundly predicting that recombinant G-CSF showed the activity of naturally occurring G-CSF was additionally essential to Claim 47.

[276] Amgen's submissions do not present any inconsistency in relation to Claim 47, which the parties agree includes a requirement for biological activity, i.e. granulocyte colony-stimulating activity. However, in relation to the other claims, the expert evidence does not support a conclusion that they include such a requirement. To the extent Amgen is simply identifying an argument related to the experiments necessary to achieve its invention, relevant to the assessment whether the differences between the state of the art and inventive concept were obvious, that question is of course addressed later in these Reasons.

D. *State of the Art*

[277] The next step in the *Plavix* obviousness framework is to identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed. This analysis first requires identification of the prior art relevant to the 537 Patent as of August 23, 1985.

[278] Dr. Van Etten's report attaches as Exhibit "H-1" a list of prior art documents, provided to him by Pfizer's counsel, which he opines are representative of the state of the art on the subject matter of the 537 Patent as of August 23, 1985. He opines these documents would have been found by a reasonably diligent search as of that date, as they are not obscure—almost all of them are articles in scientific journals or chapters in scientific books available at university libraries. He notes the list is representative of the state of the art, but not comprehensive, as many other journal articles and books on recombinant DNA technology were published by the mid 1980s. However, Dr. Van Etten considers this list of documents to fairly reflect the state of the art and to strike a reasonable balance, by providing the state of the art relevant to the 537 Patent without listing the thousands of publications that would have been found by a comprehensive search.

[279] Amgen has not identified any particular documents on this list that should not be included in the prior art. Nor has it argued in favour of including any other documents. Rather, Amgen acknowledges the state of the art included Welte 1985, Maniatis 1982, and a wealth of published literature with individual examples of recombinant technology projects. As Amgen correctly notes, where the parties diverge is on the question as to how well the state of the art prepared the

Skilled Person to successfully undertake trying to make a recombinant version of G-CSF. In my view, the parties' arguments on that question are best considered not in identifying the state of the art, but in the last step of the *Plavix* analysis, assessing whether the differences between the state of the art and the inventive concept of the claims would have been obvious to the Skilled Person.

[280] I adopt Dr. Van Etten's list of prior art documents as representing the state of the art for purposes of the obviousness analysis. The analysis in this case will focus in detail upon only a small number of prior art documents (such as Welte 1985 and Maniatis 1982). I therefore need not include the full list here. Where significant, I will indicate below any prior art document that has not previously been identified as such.

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

[281] As Pfizer correctly notes, Dr. Van Etten was the only expert who expressly opined on the differences between the state of the art and the inventive concept of the Asserted Claims. For the final step of the *Plavix* analysis related to Claim 43, Dr. Van Etten identifies Welte 1985 to be the key piece of prior art and concludes the only differences between the recombinant protein (which is the inventive concept of Claim 43) and the natural protein identified in Welte 1985 are: (i) identifying the amino acid sequence for naturally occurring hpG-CSF; and (ii) adding an N-terminal methionine residue to that sequence to enable recombinant expression in *E. coli*.

[282] I interpret Amgen's submissions as adopting largely the same position. It emphasizes that no one knew the DNA and amino acid sequences of naturally occurring hpG-CSF, no one had

expressed recombinant hpG-CSF, and no one had published a protocol for expressing recombinant hpG-CSF, before the Souza team at Amgen did so. I adopt Dr. Van Etten's articulation of the differences between the state of the art and the inventive concept of Claim 43.

[283] I note that Justice Hughes concluded the difference between the inventive concept of Claim 43 and Welte 1985 was the amino sequence of a polypeptide beginning with a Met that has some or all of the sequences of Welte's factor (i.e. protein) and some or all of its biological properties (see Apotex Decision at para 97). Other than the biological properties (which does not form part of the present construction of Claim 43), this articulation of the gap is largely consistent with the articulation I have adopted above.

[284] Before leaving Claim 43, I note that the only gap at issue in the next step of the *Plavix* obviousness test is the identification of the amino acid sequence of naturally occurring hpG-CSF. I do not understand Amgen to be arguing that the other gap, the addition of the N-terminal Met, was not obvious. As Pfizer submits, Dr. Maloy acknowledges an N-terminal Met is required for expression of a recombinant protein in *E. coli*.

[285] Turning to Claims 44 to 46, Pfizer takes the position that there is no additional gap between the state of the art and those claims. Dr. Van Etten opined Claims 44 to 46 add to Claim 43 only known, general DNA tools (recombinant DNA, expression vector, and transformed host cell) needed to make the recombinant protein of Claim 43. I agree with this analysis (and do not understand Amgen to be arguing otherwise).

[286] Finally, Pfizer submits the additional differences between the state of the art and the inventive concept of Claim 47 are: (a) the general process steps of growing a host cell and then expressing and purifying the recombinant protein of Claim 43; and (b) the purified protein having granulocyte colony-stimulating activity. These additional differences are supported by Dr. Van Etten's report and are consistent with the construction of Claim 47. To similar effect, Amgen submits that determining or soundly predicting that recombinant hpG-CSF showed the activity of naturally occurring hpG-CSF was additionally essential to Claim 47. The parties' submissions are consistent with the construction of Claim 47. I adopt Pfizer's articulation of the additional differences between the state of the art and the inventive concept of Claim 47.

F. *Whether Differences would be Obvious to the Skilled Person*

1. Legal Principles - Obvious to Try Test

[287] The last step of the *Plavix* obviousness test asks whether, viewed without any knowledge of the alleged invention as claimed, the differences identified above constitute steps that would have been obvious to the Skilled Person, or whether they require any degree of invention. It is at this step the issue of "obvious to try" may arise. In considering when the obvious to try test is appropriate, *Plavix* explains as follows (at para 68):

> [68] In areas of endeavour where advances are often won by experimentation, an "obvious to try" test might be appropriate. In such areas, there may be numerous interrelated variables with which to experiment. For example, some inventions in the pharmaceutical industry might warrant an "obvious to try" test since there may be many chemically similar structures that can elicit different biological responses and offer the potential for significant therapeutic advances.

[288] While Pfizer's submissions include a brief obviousness argument without recourse to the obvious to try test, most of the submissions by both parties employ that test. In my view, applying the above guidance from *Plavix,* that test is well suited to the obviousness analysis in this particular case. *Plavix* provides the following framework for application of the test [defined terms added]:

> [69] If an "obvious to try" test is warranted, the following factors should be taken into consideration at the fourth step of the obviousness inquiry. As with anticipation, this list is not exhaustive. The factors will apply in accordance with the evidence in each case.
>
> 1. Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art? [the Self-Evident Factor]
>
> 2. What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine? [the Extent of Effort Factor]
>
> 3. Is there a motive provided in the prior art to find the solution the patent addresses? [the Motive Factor]
>
> [70] Another important factor may arise from considering the actual course of conduct which culminated in the making of the invention. It is true that obviousness is largely concerned with how a skilled worker would have acted in the light of the prior art. But this is no reason to exclude evidence of the history of the invention, particularly where the knowledge of those involved in finding the invention is no lower than what would be expected of the skilled person.
>
> [71] For example, if the inventor and his or her team reached the invention quickly, easily, directly and relatively inexpensively, in light of the prior art and common general knowledge, that may be evidence supporting a finding of obviousness, unless the level at which they worked and their knowledge base was above what should be attributed to the skilled person. Their course of conduct would suggest that a skilled person, using his/her common general

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

[289] As Amgen notes, the course of conduct of the inventor is only indirectly relevant to the obvious to try test, to the extent it permits an inference as to how the Skilled Person would have acted. In *Bristol-Myers Squibb Canada Co v Teva Canada Ltd*, 2017 FCA 76 at paragraph 44, the Court of Appeal described the inventor's course of conduct as essentially an elaboration upon the Extent of Effort Factor from *Plavix*.

[290] Ultimately, the threshold Pfizer must meet is set out in paragraph 66 of *Plavix* :

> [66] For a finding that an invention was "obvious to try", there must be evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough.

2. Motive Factor

[291] Turning to the obvious to try factors, the Motive Factor can be addressed relatively quickly, as the parties' submissions on this factor are brief.

[292] Pfizer submits this factor is entirely in its favour, as the parties' experts agree that, as a result of Welte 1985, there was specific motivation in 1985 to make a recombinant G-CSF. Pfizer refers in particular to Dr. Maloy's general agreement with Drs. Van Etten and Boxer that there would have been a strong motivation to make a recombinant G-CSF in August 1985.

[293] Consistent with the evidence in the present case, Justice Hughes made the following finding on this point at paragraph 103 of the Apotex Decision:

> [103] Welte had already identified the critical protein, isolated it, purified it, and characterized it in several respects, albeit not the amino acid sequence. Welte concluded his paper by suggesting that the 5637 cell line is a valuable source for large-scale production and for isolating and cloning of the relevant gene. I have no doubt that this was motivational for leading edge scientific labs such as Amgen to undertake the task.

[294] Amgen acknowledges that the Skilled Person would have recognized the utility of cloning and recombinantly expressing the gene for the protein identified by Welte 1985 and that this factor weighs in favour of a finding of obviousness. However, Amgen emphasizes this is only one factor of a list of non-exhaustive factors and that it is not determinative. It argues that, if the presence of a vague motivation to succeed were all that was necessary to make a new therapeutic drug product obvious, then none of them would be inventive. Amgen notes that in *Laboratoires Servier v Apotex Inc*, 2008 FC 825 [*Laboratoires 2008*] at para 258, aff'd 2009 FCA 222 at para 34, the invention was found to be not obvious despite the acknowledged presence of motivation, at least in a general sense, to reach the invention.

[295] I agree with Amgen that the Motive Factor is only one factor and is not determinative. However, I also consider there to be a distinction between, on the one hand, what Amgen describes as a vague motivation to succeed or a motivation in a general sense and, on the other hand, a motivation to achieve a very specific product. The motivation in the present case falls into the latter category. I agree with Pfizer this particular factor is entirely in its favour.

3. Self-Evident Factor

[296] This factor asks whether it is more or less self-evident that what is being tried ought to work, including considering whether there are a finite number of identified predictable solutions known to the Skilled Person. On this factor, the parties' positions, and the evidence of their respective experts, diverge significantly.

(a) *Pfizer's Experts*

[297] Pfizer submits it would have been more or less self-evident to the Skilled Person that the recombinant protein could be made (Claims 43-46) and purified to demonstrate granulocyte colony-stimulating activity (Claim 47). Pfizer relies on Dr. Van Etten's evidence that recombinant DNA technology emerged in the mid 1970s as a new field of molecular biology which, among other things, allowed scientists to manipulate DNA *in vitro*. By 1985, the technology had been used on numerous occasions to make large amounts of proteins which, like G-CSF, were available only in small amounts from natural sources. Dr. Van Etten states that recombinant protein expression was perhaps the most commonplace, practical application of recombinant DNA technology.

[298] Dr. Van Etten refers to Maniatis 1982 as a leading and comprehensive guide to recombinant DNA technology. He agrees with statements in that manual that it details almost every laboratory task involved in molecular cloning and that the protocols therein had all been thoroughly tested and used successfully in the authors' laboratories. Quoting from Kevin Struhl, "Cloning cookbook for the laboratory" (1985), 316 *Nature* 222 at 222, Dr. Van Etten describes the following as matching his recollections of Maniatis 1982:

> Ten years ago, molecular cloning was an art that was practised only in a few Californian laboratories. Now, with everyone and his brother involved in recombinant DNA manipulations, the field has exploded into a vast and complex technology that is far beyond the ability of an individual to learn and remember completely. Furthermore, because these techniques have become invaluable in almost all fields of biological science, it is frequently the case that those who want to use them are not trained as molecular biologists. In short, there is a great need for a cookbook, which contains a reasonably complete collection of recipes that are easy to follow and up to date.
>
> Three years ago Cold Spring Harbor Laboratory published such a collection, *Molecular Cloning: A Laboratory Manual* by Maniatis, Fritsch and Sambrook. This book is omnipresent in molecular biology laboratories and is utilized to the point where it is frequently referred to as "The Bible". Although experts usually use shortened versions of the procedures, the methods are clearly described and they do work.

[299] Dr. Van Etten explains that by 1985, recombinant DNA technology had spread beyond cutting-edge academic institutions and biotechnology companies and become a tool of virtually every contemporary laboratory in any field of biology or biochemistry. He also opines that Amgen's success in producing the recombinant protein was not surprising, as there were only a limited number of ways to use recombinant DNA technology to express the protein.

[300] Pfizer's expert, Dr. Boxer, also expressed an opinion on obviousness, focusing in particular on the portion of the process following isolation of the gene encoding the naturally occurring protein. He opines it was self-evident that a recombinant form of the protein, with an additional N-terminal Met, could be made in *E. coli*, and the Skilled Person would have anticipated being able to do so by direct expression. Dr. Boxer explains direct expression of mammalian proteins in *E. coli* was standard practice by August 23, 1985. He also opines that, as of August 23, 1985, there was a finite number of ways for making large quantities of hpG-CSF, of which direct expression would be the most direct and preferred.

[301] Dr. Hermodson also speaks to obviousness, but I read his opinion as focusing principally upon the Extent of Effort Factor in the obvious to try analysis, relying significantly on Amgen's course of conduct as demonstrated by Example 1 of the 537 Patent. I will consider that aspect of his opinion later in these Reasons. However, Dr. Hermodson was also asked to review Welte 1985 and to comment on what researchers working with proteins would have done with the information in that publication. That opinion is potentially relevant to obviousness and will be considered shortly in connection with the parties' arguments surrounding the "blinding" of experts.

(b) *Amgen's Experts*

[302] Dr. Maloy opines the prior art could not have assured the Skilled Person in August 1985 it was more-or-less self-evident that protein purification followed by N-terminal amino acid sequencing ought to work to determine the amino acid sequence of G-CSF. Nor did the prior art teach any method for producing and isolating biologically active recombinant G-CSF that a

Skilled Person could have confidently expected ought to work. Instead, Dr. Maloy opines the prior art taught that proteins reportedly purified to homogeneity still frequently had contaminants that prevented adequate amino acid sequencing, and that developing a process to make properly folded recombinant protein was a significant challenge for which there was no one-size-fits-all solution.

[303] Dr. Maloy concludes the Skilled Person would have known there were a multitude of tools and techniques available for attempting to clone and recombinantly express the gene of the protein identified by Welte 1985; but, without the benefit of hindsight from knowledge of the 537 Patent, the Skilled Person would not have been able to identify a path that was obviously going to work.

[304] Dr. Speicher opines the amino acid sequences obtained by the Souza team were determined using the application of substantial specialized skill, judgment, and creativity and were beyond the capabilities of the Skilled Person as of August 23, 1985. He states it would not have been more or less self-evident to the Skilled Person that any accurate N-terminal amino acid sequence information could be obtained for a purified protein of unknown sequence. Also, it would not have been more or less self-evident that, even if a partial sequence could be obtained, such a sequence would correspond to the N-terminus of the protein (and biological activity) that the researchers were attempting to identify or that it would be sufficiently long, unambiguous or useful for a cloning project.

[305] These opinions by Dr. Speicher are expressed as his conclusions reached in discharging the second mandate in his report. That mandate was to review Amgen's protein purification and protein sequencing work described in Example 1 of the 537 Patent and to opine whether that work was capable of being successfully carried out by the Skilled Person as of August 23, 1985, or rather whether it would have required ingenuity, inventiveness or creativity that the Skilled Person did not possess. Like some of Dr. Hermodson's conclusions, I view Dr. Speicher's opinion as better considered under the Extent of Effort Factor.

[306] Dr. Griffin does not express an opinion on obviousness.

(c) *Blinding of Experts*

[307] In support of its position that the Court should prefer the opinions of its experts over those of Amgen, Pfizer emphasizes that, unlike Amgen's experts, its experts were "blinded", i.e., they provided portions of their opinions without having first reviewed the 537 Patent. In response, Amgen submits the blinding of Pfizer's experts was an exercise in futility. Amgen notes jurisprudence from this Court to the effect that blinding is not a guarantee of reliability and is not a sufficient reason to prefer the evidence of one expert witness over another (see, e.g. *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2018 FC 259 [*Hospira FC*] at para 203, rev'd on other grounds 2020 FCA 30 [*Hospira FCA*]).

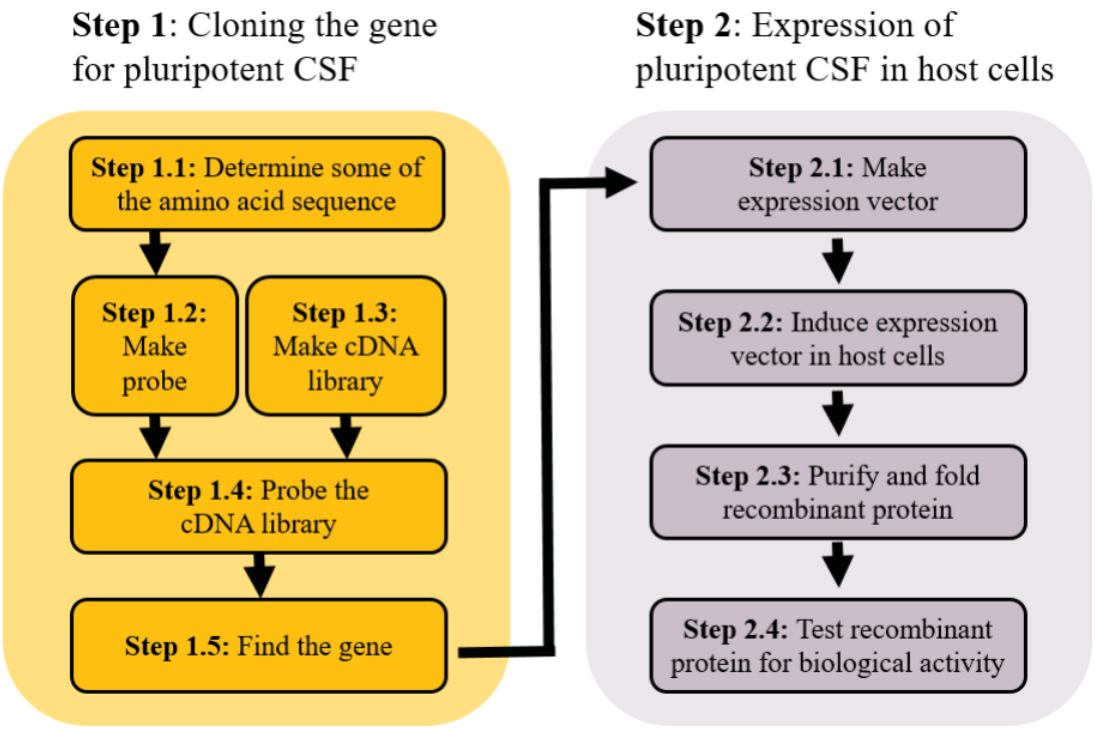
[308] Amgen also argues the blinding of Dr. Van Etten was of little value, because he was already familiar with Amgen's product NEUPOGEN and had read an article published by Dr. Souza in 1986, which described the invention of recombinant G-CSF. Moreover, Amgen argues

the effect of blinding was that Dr. Van Etten gave opinions in relation to his blinded mandates from the perspective of a scientist at the relevant time, rather than from the perspective of the Skilled Person.

[309] I accept the proposition that blinding is not a guarantee of reliability. Whether it is a sufficient reason to prefer the evidence of one expert over another depends on the details of the evidence in a particular case. As Justice Brown expressed in *Gilead Sciences, Inc v Canada (Health)*, 2016 FC 857 at paragraph 59, the effect of blinding is a question of relevance, reliability, and weight. It is not a doctrinal matter.

[310] I also agree with Amgen that blinding can create a structural impediment to experts employing the required tools to formulate their opinions. The second mandate addressed in Dr. Van Etten's report is potentially subject to this concern. After Dr. Van Etten read and summarized Welte 1985, Pfizer's counsel asked him if *scientists* at the time would have thought there was any research that naturally flowed from Welte 1985 and, if so, to explain what that next research project would be.

[311] Dr. Van Etten responded that the next project would be to test the potential for the purified protein from Welte 1985 in the management of clinical diseases involving hematopoietic derangement or failure. This would involve making a recombinant version of the protein using recombinant DNA technology. Dr. Van Etten then explains the steps involved in this process, summarized graphically in the following figure:



[312] In cross-examination, Amgen's counsel elicited Dr. Van Etten's confirmation that he was performing this mandate from the perspective of a scientist, not from that of the Skilled Person. This approach was of course unavoidable, if Dr. Van Etten was to perform this mandate on a blinded basis, as he had not yet read the 537 Patent from which the characteristics of the Skilled Person could be derived. However, the potential concern identified by Amgen is that Dr. Van Etten was not taking into account the particular characteristics of the Skilled Person, including the lack of inventiveness, in arriving at his opinion.

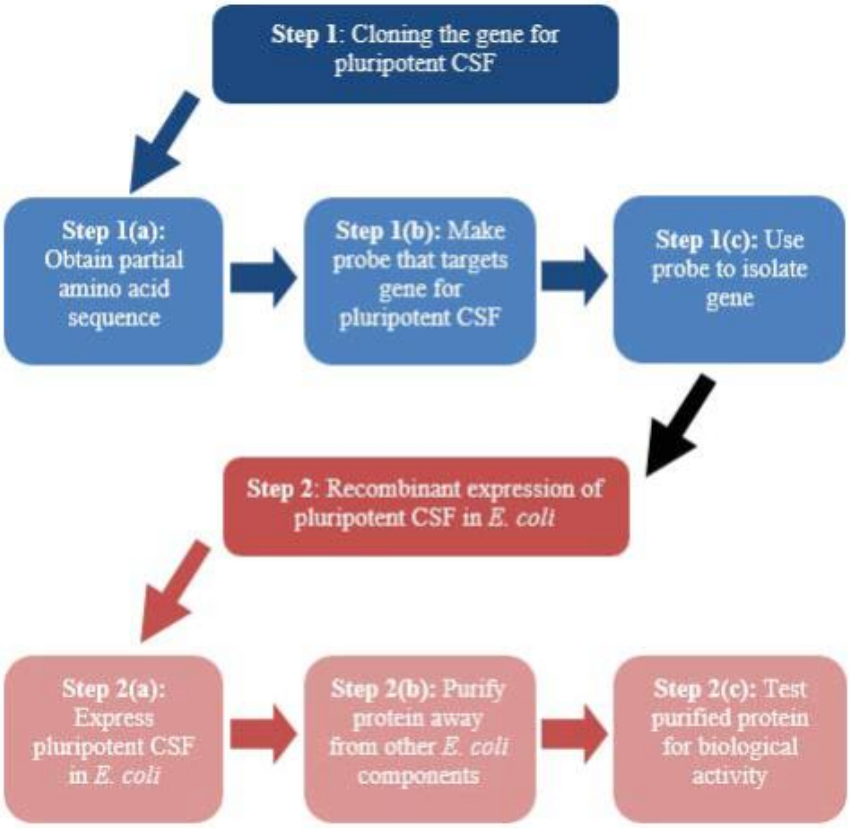
[313] In re-direct examination, Dr. Van Etten confirmed he would arrive at the same opinion if performing the same mandate from the perspective of the Skilled Person. In my view, this answer does not particularly assist Pfizer, if the point of its methodology was to employ binding

to argue for increased reliability, as Dr. Van Etten was certainly well versed in the 537 Patent by the time he was asked this question in re-direct.

[314] However, I find more compelling Pfizer's point that each of its experts independently set out the same roadmap for what the Skilled Person would have taken from Welte 1985, all while blinded to the 537 Patent.

[315] For example, Dr. Hermodson was asked to review Welte 1985 and to comment on what researchers working with proteins would have done with the information in that publication. He opines the next logical step for those working in the area would be to take the protein isolated in Welte 1985 and produce it recombinantly (i.e. in large amounts). Dr. Hermodson states the standard steps to do this would be to: (a) obtain a partial amino acid sequence; (b) make oligonucleotide probes; (c) clone the gene for the protein; and (d) express the protein in a host cell. While less detailed and omitting the final steps (purifying and refolding the recombinant protein and testing it for biological activity), I agree with Pfizer that Dr. Hermodson's opinion identifies the same path as that of Dr. Van Etten. However, I also note that, like Dr. Van Etten, Dr. Hermodson was not providing his blinded opinion from the perspective of a Skilled Person.

[316] Similarly, Dr. Boxer states the next research project following Welte 1985 would have been to produce the protein using recombinant DNA technology, in order to undertake clinical testing. He then explains the steps by which the Skilled Person would have cloned the gene for the protein and expressed the protein by recombinant means. Dr. Boxer provides the following illustration of these steps:



[317] Again, I agree with Pfizer that Dr. Boxer's opinion of the research path that would follow from Welte 1985 is consistent with Dr. Van Etten's opinion. Moreover, unlike the other two Pfizer experts, Dr. Boxer did provide his blinded opinion from the perspective of a Skilled Person. This was possible, even though Dr. Boxer was not at this stage provided with a copy of the 537 Patent, because Pfizer's counsel provided him with the characteristics of the Skilled Person, both as to subject matter expertise (consistent with Dr. Van Etten's opinion) and lack of inventiveness and asked him to employ this perspective.

[318] This approach demonstrates a potential means of avoiding the concern about blinding creating a structural impediment to experts employing the required tools to formulate their

opinions. If one expert provides an opinion defining the Skilled Person after reviewing the relevant patent, that definition can be provided to another expert, who can then give a blinded opinion from the perspective of the Skilled Person without having read the patent or the other experts' opinions.

[319] In the present case, Pfizer convincingly asserts that the reliability of its expert opinions is enhanced by the fact that three blinded experts independently arrived at consistent opinions. It can also respond to some extent to the argument that the opinions do not take into account the particular characteristics of the Skilled Person. As Dr. Boxer's opinion had the benefit of the Skilled person's perspective, and his opinion is consistent with those of Pfizer's other experts, Pfizer can credibly argue that Skilled Person perspective would not have altered Dr. Van Etten's and Hermodson's blinded opinion.

[320] While this only takes Pfizer so far, as logically it cannot be concluded with certainty that the Van Etten and Hermodson opinions would have been unchanged by the Skilled Person's perspective, it does assist Pfizer to some extent in responding to Amgen's challenge to the validity of its blinding methodology. I would not consider this methodology to be a sufficient reason to prefer Pfizer's experts over those of Amgen. However, blinding is a factor favourable to the reliability of Pfizer's expert opinions on the work that would flow from Welte 1985 and, as that work is consistent with the steps actually taken by the Amgen team in pursuit of the alleged invention, these opinions support Pfizer's position that the invention was obvious to try.

[321] In support of its position that the Court should prefer its experts, Pfizer also presents arguments contrasting the parties' respective experts' analytical methodologies. Pfizer submits that only its experts followed the *Plavix* framework in analysing obviousness; and that Amgen's experts, rather than following that framework, merely identified technical issues in the process leading to the invention that they say the Skilled Person would have found, or anticipated finding, challenging. I agree that Pfizer's experts' analyses are structured around the *Plavix* framework more expressly than those of Amgen's experts. However, I am not convinced that this is a basis to prefer the opinions of Pfizer's experts. Rather, I read it as a function of the fact Amgen's experts' reports are written as responses to the obviousness opinions expressed in the Pfizer reports.

(d) *Analysis*

[322] As noted in *Hospira FCA*, while being "more or less self-evident to try to obtain the invention" is a requirement for obviousness to try, being "more or less self-evident that what is being tried ought to work" is not a requirement but merely a factor to be considered (at para 90). Much of the following analysis, in considering that factor, engages with Amgen's evidence and arguments surrounding challenges the Skilled Person would anticipate, and that the Amgen team actually encountered, in pursuit of the invention. However, it remains Pfizer's burden to prove the Skilled Person would be able to overcome these challenges, individually and collectively, to achieve the invention.

(i) Obtaining Adequate Amino Acid Sequence Information

[323] Amgen acknowledges the Skilled Person, having read Welte 1985, could have identified various methods available to attempt cloning and recombinant expression of the target protein. However, it submits the Skilled Person could not have had any more than a *hope* they *might* succeed if they employed these methods. The first way in which Amgen submits the attempt could have gone wrong is the potential for failure in obtaining adequate amino acid sequence information. Amgen relies principally on the evidence of Dr. Maloy, and testimony of Dr. Hermodson in cross-examination, to support its position that the cloning and recombinant expression project was susceptible to failure, because of difficulty obtaining an adequate and accurate partial amino acid sequence from the naturally occurring protein.

[324] Amgen notes Dr. Maloy's evidence that Dr. Welte's purification process was reported to have produced a highly pure protein preparation, and yet, it did not enable adequate sequencing in Amgen's first runs. Dr. Maloy concludes therefrom that it was entirely possible that the reworked purification process devised by Dr. Souza would also have been inadequate to enable effective sequencing.

[325] Dr. Hermodson confirmed on cross-examination that one of the risks facing the skilled protein biochemist was making a miscall or no call at all when sequencing a protein, because of the presence of high background noise in the chromatograms. Dr. Hermodson also agreed chromatograms sometimes become difficult to read in later cycles because of high background noise, contributed to by factors such as contaminants in an impure protein sample or the inefficiency of the Edman degradation process itself. He testified the skilled biochemist's ability

to correctly call a sufficient contiguous stretch of amino acids in 1984/1985 depended on a number of fundamental criteria, including getting a sufficient amount of a pure enough protein.

[326] Amgen also relies on Dr. Hermodson's agreement on cross-examination that the skilled protein biochemist, starting with an experimental protein that had never been subjected to amino acid sequencing, would not know in advance that they would succeed in obtaining a useful sequence for designing a probe. They would hope for success, but success would not be self-evident until the work was undertaken. However, I also note Dr. Hermodson's statement, during this same series of questions, that the assumption is that getting probe sequences from the protein will in fact give you the wherewithal to clone the gene.

[327] I do not find the evidence on which Amgen relies to particularly assist it. This evidence identifies there is some risk of failure that the Skilled Person would face in pursuing the invention or deciding whether to pursue it. However, as Justice Locke held in *Leo Pharma* at para 105:

> [105] Leo asserts that the person skilled in the art also does not take risks. However, it has not been able to produce any authority in support of this assertion. While I accept that the skilled person has some conservative qualities, I am unaware of any authority indicating that risk aversion is one of them. I do not accept that the skilled person avoids risk.

[328] In other words, the evidence upon which Amgen relies establishes the Skilled Person could *possibly* fail, that success was not certain. However, that is not the question contemplated by the Self-Evident Factor currently under consideration. That question does not ask whether

success is certain. As explained by the Federal Court of Appeal in *Bristol-Myers Squibb Canada Co v Teva Canada Limited*, 2017 FCA 76 at paragraph 62 [emphasis added]:

> [62] As a result, I am of the view that a categorical approach to obviousness, such as that advocated by BMS, is inappropriate. The elaboration of a hard and fast rule that obviousness cannot be shown unless all the elements of the inventive concept can be predicted with a high degree of certainty is the antithesis of the approach to obviousness that the Supreme Court favoured in *Plavix 1*. Not every case requires recourse to the "obvious to try" test and not every recourse to the "obvious to try" test must follow in the furrow of the preceding application of that test.

[329] Similarly, in *Laboratoires Servier v Apotex Inc*, 2019 FC 616 at paragraph 269, Justice Roy held:

> [269] […] There is no need to have certainty that the "try" in the obvious to try will be successful. It is rather that [*sic*] is more or less self-evident that the "try" ought to work in view of the common general knowledge and the prior art; a mere possibility will not suffice but an amount of uncertainty is allowed in the obvious-to-try analysis. It would not be obvious to try if certainty was required.

[330] The evidence from Dr. Hermodson's cross-examination upon which Amgen relies must be read in the context of his statement that the assumption is that getting probe sequences from the protein will in fact give you the wherewithal to clone the gene. I interpret Dr. Hermodson's opinion to be that, while success cannot be predicted with certainty, the Skilled Person would assume their efforts to obtain an adequate amino acid sequence, design a probe, and clone the gene would be successful. This opinion appears consistent with the evidence (addressed further under the Extent of Effort Factor below) surrounding commodification of amino acid sequencing

work at core facilities in the early-to-mid 1980s. In my view, the evidence relevant to amino acid sequencing favours Pfizer under the Self-Evident Factor.

(ii) Screening cDNA Library

[331] Still related to the process of cloning the gene, Amgen submits that, even with a lengthy and unambiguous partial amino acid sequence in hand, there was a significant risk of failure in screening a cDNA library. As Dr. Van Etten acknowledged in his report, there was a practical limit on the number of probes that could be used to screen a cDNA library (i.e., 128). A probe could be designed to avoid areas of the amino acid sequence having high degeneracy, but the degeneracy of the amino acid sequence was ultimately up to nature, not within the control of the experimenter, and could not be known in advance. Amgen notes Dr. Van Etten acknowledged in cross-examination that the Skilled Person would have to make a decision as to how to approach that problem.

[332] The solution to this problem adopted by the Souza team was to use inosine probes. In Appendix "A" to his report (entitled "The Probe Approach"), Dr. Van Etten describes this technique as using inosine to act as a "universal" base. In this method, the probe is constructed using one or more codons that employ an inosine base in the "wobble" or final position, where the nucleotide could vary. The inosine base therefore exponentially reduces the number of probes required. For example, there are four possible codons encoding the amino acid alanine: the first two positions are GC and the third position can be A, C, G, or T. By replacing the third position with an inosine (I), the number of probes can be reduced from four to one.

[333] Dr. Van Etten explains this method had been published in two journal articles by Dr. K. Matsubara and colleagues in March and April of 1985. These articles are part of the list of prior art referenced earlier in these Reasons. Dr. Matsubara showed that a probe could be made using inosine to reduce the number of probes needed, and the probe would still bind tightly to the DNA target. Noting Amgen's use of this method, Dr. Van Etten opines as follows:

> It did not take any amount of creativity or ingenuity to put three inosines in a probe as of August 23, 1985. Dr. Matsubara's articles showed that the inosine approach could be successful, even when five inosines were used in a probe. The Matsubara articles were widely read at the time.

[334] Amgen submits this opinion is given with the benefit of hindsight; and, in opining the Skilled Person would have seen from the prior art that the inosine technique "could be successful", Dr. Van Etten employed the wrong standard. Dr. Maloy acknowledges this technique had been disclosed in the prior art shortly before August 1985 and, if the Skilled Person became aware of it, its potential utility would have been apparent. However, Dr. Maloy does not agree the technique had already become routine by August 1985 or that the Skilled Person would have used it expecting success based on two publications from a single group or researchers.

[335] Amgen also notes Dr. Van Etten's observation that inosine (I) was known to form a base pair with A, C, T and only perhaps with G. Amgen submits the uncertainty as to how inosine behaved opposite a G nucleotide militates against a conclusion that it would have been self-evident to the Skilled Person the inosine method ought to work.

[336] In response to these arguments, Pfizer notes Dr. Maloy's confirmation on cross-examination that the *Proceedings of the National Academy of Sciences* (in which one of the Matsubara articles was published) is a leading and widely read publication. Also, when another publication in *Nature* was put to him in cross-examination, Dr. Maloy agreed it showed another group of researchers using inosine probes in or about the summer of 1985.

[337] The use of inosine probes was clearly part of the prior art by August 1985, and I agree with Pfizer's submission that the evidence supports Dr. Van Etten's opinion that such use cannot be characterized as inventive. I also consider the evidence canvassed above to support Dr. Van Etten's inclusion of that technique as part of the CGK surrounding the probe approach by that time.

[338] These findings alone do not necessarily translate into a conclusion that it would have been self-evident to the Skilled Person that the inosine technique would solve the problem of degeneracy and the resulting concern about the practical limit on the number of probes that could be used to screen a cDNA library. However, Dr. Van Etten opines the Skilled Person would have expected the "probe approach" to work for hpG-CSF. He notes that, by August 23, 1985, there were at least nine examples of the probe approach being used to clone genes for mammalian proteins that were low abundance, extracellular proteins involved in cell signalling, like hpG-CSF. I read that opinion as focusing not solely upon the inosine technique, but also relating to the broader probe approach explained in Appendix "A" to his report.

[339] Appendix "A" explains that a molecular biologist designing a probe had two ways to deal with degeneracy: the mixed probe approach and the unique probe approach. Dr. Van Etten explains that, employing the mixed probe approach, if the available amino acid sequence for the protein of interest did not contain a stretch of amino acids encoded by 128 or fewer DNA sequences, scientists had three options as of August 23, 1985: using more amino acid sequencing to find a better stretch of amino acids, using inosine, or switching to the unique probe approach. That is, the use of inosine was not the only means of addressing the practical limit of 128 probes.

[340] Further, when confronted in cross-examination with that practical limit, Dr. Van Etten also explained that one obvious way to overcome the limit is to prepare multiple independent batches of probes, i.e. screening multiple cDNA libraries, each with no more than 128 probes. Pfizer characterizes this solution as the "brute force approach" and observes Amgen was considering this possibility. Mr. Boone's affidavit explains Dr. Souza was concerned the inosine technique would not be effective (because of the uncertainty as to how inosine would behave opposite a G nucleotide), which meant Amgen would be faced with making more than 1500 probes to try to locate the target cDNA.

[341] In my view, the evidence supports a conclusion that it would have been self-evident to the Skilled Person that an available variation of the probe approach would be effective. As Justice Manson explained in *Eli Lilly* at paragraph 120:

> [120] As Justice Hughes stated in *Shire Biochem Inc v Canada (Health)*, 2008 FC 538 at paragraph 80, "the existence of a number of possible routes to solve a problem does not mean that the route taken was not obvious." This statement was endorsed by Justice Barnes in *Janssen Inc v Teva Canada Limited*, 2015 FC 184 [*Janssen*] at paragraph 113. Justice Barnes also endorsed the

> notion that "a route may be an obvious one to try even if it is not possible to be sure that taking it will produce success, or sufficient success to make it commercially worthwhile" (*Janssen* at para 113, citing *Brugger v Medic-Aid Ltd*, [1996] RPC 635 at p 661).

[342] I appreciate the Skilled Person would expect certain potential challenges, and there was no one, guaranteed solution to such challenges. Amgen's counsel elicited from Dr. Van Etten in cross-examination that, among his nine examples of the probe approach, there were a number of variations in the target proteins, including their respective abundance, and the particular strategy the respective scientists applied to the probe approach. Dr. Van Etten also agreed there are a number of different variations of the probe approach, as different proteins can present different challenges and require such variations based in part upon the amino acid sequence that is obtained. However, *Plavix* teaches that the existence of a finite number of identified predictable solutions known to the Skilled Person favours a finding that the alleged invention was obvious to try.

(iii) Addressing Glycosylation

[343] Amgen next raises the point that, in advance of undertaking the G-CSF project, the Skilled Person would not have known whether post-translational modification of the recombinant protein would be important. Cellular machinery operates to modify a protein after its initial expression in a cell (i.e. a post-translational modification). These modifications may be important to the correct functioning of the protein. Moreover, different post-translational modifications may occur when a protein is expressed in *E. coli* versus a mammalian cell. Most relevant to this action is that mammalian cells often glycosylate (i.e. attach a string of sugar molecules) to proteins, while *E. coli* cells do not. Both parties acknowledged examples prior to

August 1985 in which a lack of glycosylation prevented a protein expressed recombinantly in *E. coli* from having the same biological activity as its naturally occurring counterpart.

[344] Amgen describes the "cautionary tale" of a protein called erythropoietin [EPO] that suffered from this problem. Dr. Van Etten acknowledges EPO is a hematopoietic growth factor for which glycosylation was found to be important for *in vivo* activity (meaning activity within a living organism). In other words, without glycosylation, recombinant EPO did not have the desired biological activity of naturally occurring EPO.

[345] Amgen observes that the reports of Drs. Van Etten and Dr. Boxer address this risk the Skilled Person would face by citing experiments in Welte 1985 that concluded glycosylation may not be a major structural feature of the protein identified by SKI. Amgen submits that, while these experiments were informative, they were limited to a single type of glycosylation (namely N-linked glycosylation, meaning O-linked glycosylation was still possible), and that the conclusion in Welte 1985 was equivocal.

[346] Dr. Maloy explained that the experiment Dr. Welte performed involved exposing the protein sample to neuraminidase, which targets N-linked glycosylation (associated with asparagine residues) but does not reliably remove O-linked glycosylation (associated with serine and threonine residues). Based thereon, Dr. Maloy opines the Skilled Person would have needed to express the recombinant protein in *E. coli* and test for activity before they could have been confident that the protein's activity was not dependent on a post-translational modification such

as glycosylation. Amgen submits Dr. Boxer agreed with Dr. Maloy's statement on cross-examination.

[347] I do not find these submissions particularly persuasive. While I appreciate Welte 1985 does not definitively state that glycosylation is not a major structural feature of the protein, the effect of the conclusion in Welte 1985 is one of encouragement, addressing and placating the risk represented by the glycosylation concern. Moreover, Dr. Van Etten identified many successful precedents where lack of glycosylation in a protein expressed in *E. coli* had no impact on biological activity of the recombinant protein. Dr. Boxer gives similar evidence.

[348] I also find compelling Pfizer's argument the Skilled Person would have been aware of alternative approaches to protein expression other than direct expression in *E. coli*. Even if it turned out the recombinant protein expressed in *E. coli* did not have biological activity because of the lack of glycosylation, the Skilled Person would try the next logical option: expressing the protein in mammalian cells. Dr. Boxer explains that, as of August 23, 1985, there was a finite number of ways to make large quantities of the recombinant protein, almost all of which was done either in *E. coli* or in a mammalian cell line. The most direct and preferred method for G-CSF would have been direct expression in *E. coli*, particularly given the encouragement from Welte 1985 that glycosylation might not be a major feature of the protein.

[349] Overall, I find the Skilled Person would conclude it was self-evident that what was being tried ought to work, despite possible concerns about post-translational modifications involving glycosylation.

(iv) Adding an N-Terminal Methionine

[350] The parties agree a recombinant protein expressed in *E. coli* necessarily differs from the naturally occurring counterpart produced in mammalian cells. As previously noted, expression in *E. coli* requires the addition of a methionine residue at the N-terminal position. While there was no "cautionary tale" in August 1985 that demonstrated issues arising from the addition of an N-terminal methionine (as there was for glycosylation), it was still a change to the composition of the protein, which created a potential for different behaviour. Dr. Maloy opined the effect of adding the Met could not be known until the activity of the recombinant protein was experimentally tested in a biological assay.

[351] In response, Pfizer refers to the following paragraph from Dr. Boxer's report:

> In any event, the skilled person would not have expected the addition of the N-terminal methionine to affect the biological activities of the [Claim 43] Polypeptide. In general, the ends of proteins were often unstructured and adding an amino acid to the end of the linear chain would not have been expected to interfere with the folding of the protein. Consistently, in the above list of the at least seven human cell-signaling proteins that had been directly expressed in *E. coli* before August 23, 1985, all had, at least when first translated, an N-terminal methionine and all had at least some biological activity.

[352] Pfizer further submits that Dr. Maloy did not counter this opinion. I agree with this submission, as the full paragraph on this point in Dr. Maloy's report, which Amgen cites in support of its position, reads as follows [emphasis added]:

> **Unknown Effect of N-terminal Methionine**. As Dr. Van Etten and Dr. Boxer again correctly acknowledge, an N-terminal methionine is required for expression of a recombinant protein in *E. coli*. While I would generally agree that there were many other

> recombinant proteins seemingly unaffected by the addition of an N-terminal methionine, the recombinant protein is not identical to the naturally occurring protein, and there was always a potential for it to behave differently. When dealing with a new protein, whether or not the methionine would be a problem could not be predicted until the activity of the recombinant protein was experimentally tested in a biological assay.

[353] Moreover, as with Amgen's glycosylation argument, in the event the N-terminal Met did prove to have a material effect, it was available for the Skilled Person to perform the expression in mammalian cells. The evidence again supports a conclusion it would have been more or less self evident to the Skilled Person that what was being tried ought to work.

(v) Solubilizing and Refolding Proteins from Inclusion Bodies

[354] Amgen submits the Skilled Person would have been aware, in 1985, of the significant risk that a recombinant protein expressed in *E. coli* would be dysfunctional because it was expressed as an inclusion body (*i.e.*, an insoluble mass of tangled proteins). Amgen describes Dr. Maloy's evidence as opining that inclusion bodies were a common and potentially unresolvable issue. It also relies on Dr. Van Etten's evidence in cross-examination, acknowledging that many proteins expressed in *E. coli* are expressed in inclusion bodies, and that Maniatis 1982 did not teach a solution.

[355] While Amgen acknowledges published examples in which inclusion bodies were overcome (meaning the protein was successfully detangled from the insoluble clump and refolded in the form required for biological activity), it argues those examples were not entirely comparable to G-CSF in terms of number of cysteines (amino acids between which disulphide bonds form), the organisms in which the genes were expressed, and the mode of protein

expression. The Skilled Person would also have understood there were unpublished failures in which inclusion bodies were not successfully overcome. Dr. Boxer acknowledged on cross-examination that disulfide bond formation might be an obstacle to successful refolding. He also agreed no two publications cited in his report demonstrated an identical approach to making recombinant protein.

[356] Pfizer does not dispute inclusion bodies were a known problem that often arose, but it notes Dr. Van Etten and Dr. Boxer identified known solutions to address the issue. Based thereon, Dr. Boxer opines it would have been routine work as of August 23, 1985, to convert an unfolded recombinant form of G-CSF from *E. coli* into a biologically-active, properly-folded protein. He states protein biochemists were well acquainted with using detergents and other solubilizing agents to solubilize proteins and with removing the agent to allow for spontaneous refolding, and that there were published means of doing so. Dr. Boxer acknowledges this may have taken more than one attempt, employing different methods (as further identified in his cross-examination), but he characterizes this process as ordinary work of molecular biologists and protein biochemists working with recombinant proteins.

[357] I again find the weight of the expert evidence to favour Pfizer. While Dr. Van Etten acknowledged in cross-examination that Maniatis 1982 did not teach a solution to address inclusion bodies, he explained such strategies could be found in other relevant literature in the field. Amgen's cross-examination of Dr. Boxer served to highlight the nature of the problem of inclusion bodies, the fact that there are a number of solutions, and that no one solution will work for all proteins. However, Dr. Boxer testified that, although proteins are different, and the details

in approaching them can be different, the general form is always the same, and the number of approaches is finite. As previously observed, the existence of a number of possible routes to solve a problem does not mean the route taken was not obvious (see *Eli Lilly* at para 120). In my view, Dr. Boxer's opinion was not undermined in cross-examination.

[358] In contrast, Pfizer's cross-examination of Dr. Maloy's opinion successfully undermined a portion of the support for his opinion that inclusion bodies were a potentially unresolvable issue. He refers to a 2008 study reporting a successful purification rate from inclusion bodies of only 26%. However, on cross-examination, Dr. Maloy conceded the paper describing the study stated proteins that were insoluble were generally abandoned, rather than trying to find effective refolding conditions. As such, it is a mischaracterization of this paper to suggest the authors had a 26% success rate in efforts to purify proteins from inclusion bodies. I have previously expressed my intention to treat Dr. Maloy's evidence with caution and have little difficulty preferring the opinion of Dr. Boxer on this issue.

(vi) Tracing Errors

[359] Finally, Amgen submits that successfully cloning and recombinantly expressing functional G-CSF did not just require a single successful experiment. Rather, it involved many steps, all of which needed to be performed successfully. Even if the risk of error at any individual step could have been considered slight in isolation, the risk compounds when the project is evaluated as a whole. If an error occurred, it may have been difficult to trace and fatal to the entire endeavor.

[360] Pfizer responds that work is not inventive simply because it is free of errors. I agree. The possibility of error, and the possibility that such error is not or cannot be properly identified, contributes to the risk that the project will not succeed. However, the jurisprudential guidance on the role of risk in the obvious to try analysis (canvassed earlier in these Reasons) remains applicable. The Skilled Person is not risk averse and would not be discouraged from attempting the G-CSF project by known potential problems with identifiable solutions.

(e) *Authorities on the Self-Evident Factor*

[361] Before leaving the first factor of the obvious to try analysis, I must also consider the authorities which Amgen refers as illustrating what qualifies as an experiment that is "self-evident ought to work". First, Amgen relies on *Plavix* itself, where the invention was a particular molecular configuration of an existing drug (an isomer) that was more useful than an equal mix of the two possible isomers (the racemate). The Court found that several methods to separate the two isomers were known to the skilled person, but it was not self-evident to try them, even though the skilled person would have known a single isomer might have different properties than the racemate (at para 85).

[362] Similarly, in *Laboratoires 2008*, the invention was a chemical modification of an existing drug that improved upon its function. The Court held the invention was not obvious, even though it was the result of combining disclosures already made in the prior art, and even though the prior art suggested that what was being tried might work (at para 256). Among the factors noted by the Court was that small changes in structure can have unpredictable pharmacological effects (at para 255).

[363] In *Pfizer Canada Inc v Apotex Inc*, 2017 FC 774, aff'd 2019 FCA 16, the inventive concept was a crystalline salt of a known drug. The Court found the invention was not obvious, even though salt formulations of drugs were known to have different and useful properties as compared to the pure active ingredient, and even though techniques to screen for salts and crystals were known. The critical factor was that it could not be predicted in advance which salt forms would be stable and have useful qualities. There was only a mere possibility or hope of success, rather than an expectation that what was being tried ought to work (at paras 26, 28, 298 and 300).

[364] Finally, in *Apotex Inc v Shire LLC*, 2018 FC 637, the invention involved the chemical modification of a known drug into a prodrug, which was metabolized and released as the active drug at a stable rate. Apotex argued the chemical modification at issue was one of a limited number of options that the skilled person would have recognized might work, and could have reached through routine screening tests. The Court found that, even if the testing itself may have been routine, it was not obvious to try because there was no way of knowing what the properties of the modified chemical would be before testing. The Court also agreed that Apotex's argument had improperly glossed over the uncertainty present at each step of the project (at paras 6-7, 134-145).

[365] Each of these decisions turned on the particular issues and evidence before the Court. However, more generally, I agree with Pfizer's submissions that these cases all involve compounds or combinations that had not previously been made or isolated, and whose properties were therefore not known. In contrast, the reason for undertaking the G-CSF project was to make

a recombinant version of the natural protein reported in Welte 1985 with its known properties. None of these authorities convinces me to alter any of the above analysis of the Self-Evident Factor of the obvious to try test.

(f) *Conclusion on the Self-Evident Factor*

[366] I conclude the Skilled Person would find self-evident that the steps leading to the Claim 43 polypeptide ought to work, which favours a finding that Claim 43 was obvious to try.

4. Extent of Effort Factor

[367] The Extent of Effort Factor asks what is the extent, nature and amount of effort required to achieve the invention, including whether only routine trials, or rather prolonged and arduous experimentation, are carried out. As previously noted, the inventor's actual course of conduct can also be relevant in considering this factor. As with the Self-Evident Factor, the parties' positions and the evidence of their respective experts on this factor diverge significantly.

(a) *Pfizer's Experts*

[368] Dr. Van Etten opines the experimentation required to bridge the gap between Welte 1985 and the inventive concept of Claim 43 would be in the nature of routine trials, i.e. the sort of work detailed in the appendices to his report. He recognizes it would take some time in the laboratory to clone the gene and express the protein in *E. coli*, but he finds nothing about the particular protein at issue that would have suggested to the Skilled Person that the project would be difficult.

[369] Focusing in particular upon the amino acid sequencing work described in Example 1 of the 537 Patent, Dr. Hermodson opines Example 1 does not describe any amino acid sequencing work outside the abilities of an ordinary skilled protein biochemist in 1985. Through successive runs, Amgen used the same iterative process for amino acid sequencing used by skilled protein biochemists at the time. Dr. Hermodson provides the following summary of this opinion:

> First, the hpG-CSF protein was produced in sufficiently large amounts by the 5637 cells that the skilled protein biochemist would have expected to be able to sequence it using ordinary methods;
>
> Second, Amgen's handful of purifications and sequence runs was an iterative, steadily-improving process that was typical at the time. Amgen worked through the standard steps that a protein biochemist would use when working through the iterative process of sequencing;
>
> Third, Amgen did not take any technical steps that were out of the ordinary. Amgen just sequenced the N terminus of the purified protein. None of the adjustments made by Amgen (i.e., increasing sample amount, increasing sample purity, using polybrene, and using a reducing agent) included creativity or ingenuity;
>
> Fourth, there is nothing to indicate that Amgen's amino acid sequencing work took more than the usual amount of time;
>
> Finally, the amino acid sequencing work described in the 537 Patent was no different than what many other labs were doing to produce recombinant proteins at that time. In 1985, every major research university and many commercial labs had the facilities and expertise to complete this project on their own.

[370] Pfizer’s third expert, Dr. Boxer, opines that as of August 23, 1985, it was standard laboratory work for the Skilled Person to carry out the necessary steps to directly express hpG-CSF in *E. coli*, namely making the expression vector, transforming it in *E. coli*, and inducing expression of the recombinant protein. This work would not have been prolonged or arduous.

[371] Dr. Boxer explains that, to make the expression vector, it would have been standard practice to insert the gene for hpG-CSF into an expression vector for direct expression. The techniques for doing so were described in laboratory manuals like Maniatis 1982. The tools needed to apply the techniques described in Maniatis 1982 (including restriction enzymes and synthetic linker DNA) could generally be purchased from suppliers as of August 23, 1985. Maniatis 1982 also provides details on commercially-available expression vectors. Similarly, the techniques for transforming *E. coli* cells with an expression vector and inducing direct expression of the recombinant protein were described in Maniatis 1982.

(b) *Amgen's Experts*

[372] Dr. Maloy disagrees the work conducted by the Souza team in pursuit of the G-CSF project was routine. As previously noted under the previous factor, Dr. Maloy opines that inclusion bodies represent a significant and potentially insurmountable hurdle. He asserts there was no routine way to purify biologically active recombinant G-CSF. While Welte 1985 and other publications would have served as points of reference for this task, they do not teach a routine, one-size-fits-all approach. Rather, each recombinant protein is a different challenge, and some are simply incapable of biological activity.

[373] Dr. Maloy's report focuses significantly on the Souza team's actual course of conduct, in relation to the same categories of challenges canvassed in the above analysis of the Self-Evident Factor. I will return to these challenges and Dr. Maloy's evidence below in analysing arguments surrounding the inventor's course of conduct.

[374] Dr. Speicher also expresses an obviousness opinion based on his review of Amgen's work as described in Example 1 of the 537 Patent. He concludes the amino acid sequences obtained by the Souza team were beyond the capabilities of the Skilled Person as of August 23, 1985. He also disagrees with the opinions of Drs. Hermodson and Van Etten that the amino acid sequencing work described in the patent was straightforward or routine. Dr. Speicher concludes those opinions ignore the many challenges faced by the Skilled Person and rely on references reporting on the work of extraordinarily skilled protein biochemists whose skills far exceeded the abilities of the Skilled Person. He identifies a number of factors, relevant to understanding the realistic capabilities of the Skilled Person in August 1985 to obtain a useful amino acid sequence from an experimental protein sample, which contribute to his opinion.

(c) *Analysis*

[375] Each party's submissions, advocating that its experts' opinions be preferred, focus significantly on Amgen's actual course of conduct and the challenges that Amgen argues militate against a finding that the relevant work was routine. As in my analysis of the Self-Evident Factor, I will consider each of these challenges individually, although only addressing evidence and arguments that were not addressed under the Self-Evident Factor.

(i) Purifying the Natural Protein for Sequencing

[376] Amgen notes the Souza team was provided with samples of the protein preparation that had been purified to "apparent homogeneity" by Dr. Welte and his colleagues at SKI. Amgen's protein biochemist, Dr. Por Lai, had lengthy post-doctoral experience in amino acid sequencing;

however, he was unable, after three unsuccessful sequencing attempts using the SKI samples, to obtain any useful sequencing information to enable the design of oligonucleotide probes.

[377] In the Amino Acid Reports prepared by Dr. Lai, and in the 537 Patent, the main obstacle cited was that the SKI samples were contaminated, probably with chemical residues from the purification process, and required further purification. Although Welte 1985 indicated the SKI protein had been purified to "apparent homogeneity", Dr. Hermodson agreed there were limitations in assessing purity of a protein preparation through the silver staining technique used by SKI, as this technique can fail to detect non-protein contaminants. Indeed, after reviewing the chromatograms from the second run using the SKI samples, Dr. Hermodson observed they showed very high background noise, which was consistent with contamination.

[378] After a third unsuccessful run, Amgen addressed the problem with the purity of the SKI protein samples by obtaining samples of the 5637 cell line from Dr. Welte, and a subclone (1A6) from that line, and reworking the cell culturing and purification methods that Dr. Welte had used. Amgen relies on the laboratory notebook of Joan Fare as describing the experiments that she carried out to optimize the cell culturing steps. Dr. Speicher opined that the specific purification modifications employed by Amgen were far from routine, beyond the capabilities of the Skilled Person, and demonstrated exceptional skill and judgment.

[379] Dr. Lu testified as to his direct involvement in the fourth and fifth amino acid sequencing efforts performed on the protein sample prepared in-house at Amgen. He carried out the HPLC step of the fifth sequencing effort, including the operation of the detector. Dr. Lu testified Amgen

was fortunate to have carried out the fifth amino acid run, because one of the amino acids within the stretch selected by Dr. Souza and Mr. Boone (residues 23-30) to design the oligonucleotide probes had been miscalled in the fourth run. Therefore, Amgen argues the remaining steps in the project may have ultimately led to failure had the same stretch of amino acids been selected from the fourth run to design probes.

[380] Pfizer disputes Amgen's assertion that the SKI samples were not pure. It relies on statements in Welte 1985 and subsequent publications, authored by Dr. Souza, Dr. Zsebo, Mr. Boone, and others, in the journals *Science* and *Immunobiology* in 1986, which describe Dr. Welte's protein as having been purified to homogeneity or near homogeneity. Pfizer also notes that Amgen has provided no evidence of contamination. While Example 1 of the 537 Patent states that the SKI samples were contaminated, Amgen has not called any witness who actually handled those samples. Pfizer further relies on Dr. Griffin's Declarations in the USPTO proceeding, stating there was no contamination of Dr. Welte's protein. Finally, it notes a lack of information about the SKI samples—even if the SKI samples were contaminated when received by the Souza team, there is no evidence when or how that contamination occurred.

[381] I do not find these arguments by Pfizer persuasive. I read Dr. Griffin's opinion in the Declarations, that Dr. Welte's protein was pure, to be based on the results of the silver staining technique disclosed in Welte 1985. As Amgen notes, Pfizer's expert Dr. Hermodson identified the limitations in that technique and observed the chromatograms from the second run using the SKI samples to show high background noise, consistent with contamination. That opinion

detracts from the weight that can be afforded either to the Declarations or to the statements about purity made in Welte 1985 and Dr. Welte's later publications.

[382] However, Pfizer also argues there is no evidence that Amgen's purification process was inventive or materially different than that of Dr. Welte or that it was ultimately material to the success of the G-CSF project. I find these submissions (below) more compelling.

[383] Mr. Boone's evidence is that Amgen significantly reworked Dr. Welte's purification process. However, as noted earlier in these Reasons, I am treating Mr. Boone's subjective characterizations of Amgen's work with some caution. Regardless, I consider the significance of these changes in the purification protocol to be a subject more suited to expert evidence.

[384] Focusing on the differences between the Welte and Souza purification processes, Amgen notes first a change in the conditioned medium chosen to culture the cells. Dr. Souza's team chose to use Iscove's IMDM rather than RPMI 1640, a choice that Dr. Maloy opined was particularly non-obvious. However, Dr. Maloy supports this conclusion by noting neither he nor Dr. Van Etten could identify what made the medium chosen by Dr. Souza preferable. Dr. Van Etten's report states that each of Iscove's IMDM and RPMI 1640 was a well-known medium that could be purchased ready-made from vendors for growing cells. I agree with Pfizer's submission there is no evidence the choice of medium was material to the success of the purification efforts or the G-CSF project.

[385] Other than the change in conditioned medium, the other change Dr. Maloy considered particularly non-obvious was the use of membrane filtration (also referred to in the evidence as ultrafiltration), instead of using an ammonium sulfate precipitate, as part of the purification protocol. Dr. Maloy states that, although membrane filtration was a known approach, using an ammonium sulfate precipitate (that Welte 1985 reported using) was "…*the* standard first step for purifying a protein from a supernatant," [emphasis in original].

[386] However, on cross-examination, Dr. Maloy was referred to a book by Robert Scopes, published in 1982 and entitled *Protein Purification* [Scopes 1982], with which he was familiar. In a chapter related to protein purification, there is reference to use of ammonium sulfate, which Dr. Maloy confirmed was Dr. Welte's process, and a minimum protein concentration limit for the use of that process. Dr. Maloy confirmed from reviewing Welte 1985 that the concentration of Dr. Welte's protein was $1/10^{th}$ of that minimum limit.

[387] Dr. Maloy was then referred to a passage from Scopes 1982 that explained the most important methods for concentrating dilute protein solutions involved simply removing water. This could be done by a variety of procedures based on the semi-permeable membrane or gel filtration principle, in which proteins cannot pass through a membrane or surface that water and small molecules can. Scopes 1982 states the most commonly employed system is ultrafiltration, in which water is forced through a membrane, leaving the more concentrated protein solutions behind.

[388] I note Dr. Maloy did not adopt the opinion expressed in Scopes 1982. Indeed, he was not asked to do so. Nor did he resile from his own opinion. At most, Pfizer's cross-examination identifies information in a textbook from the relevant time, known to Dr. Maloy, which appears inconsistent with his opinion. However, I also note Dr. Maloy offered no explanation, either in his report or in cross-examination, for his opinion that use of ammonium sulfate precipitate was the standard first step.

[389] Dr. Van Etten opined that both membrane filtration and ammonium sulfate precipitation were typical ways to concentrate proteins. Given the size of the protein identified in Welte 1985, Dr. Van Etten opined that Amgen's decision to use a membrane that concentrated proteins of that size was logical. Like Dr. Maloy, Dr. Van Etten does not offer support for his opinion that both approaches were typical. However, given the caution I have previously expressed surrounding Dr. Maloy's evidence, I prefer the opinion of Dr. Van Etten.

[390] Another change the Souza team made from the Welte 1985 protocol was to use a C4 column or matrix, instead of C18, for its HPLC. However, Dr. Van Etten describes this as a minor adjustment and actually represents the use of a more standard approach, as matrices with shorter carbon chains were generally thought to be better when purifying proteins.

[391] Dr. Speicher's opinion related to Amgen's purification process differs significantly from that of Dr. Van Etten. Dr. Speicher opines the Souza team displayed exceptional skill and judgment, beyond the capabilities of the Skilled Person, in selecting the precise modifications to the Welte protocol. However, he provides little support for that opinion. Indeed, he does not

point to any particular difference between the protocols leading to improved protein material. Rather, he bases his opinion on the sequencing results from the sample purified in-house at Amgen (Runs #4 and #5), which were better than Runs #1 and #2 with the SKI sample. I ascribe little weight to this opinion.

[392] Dr. Speicher also opines Amgen's optimization and scale-up efforts, producing a significantly larger quantity of natural protein, were far from routine. To produce 30L of conditioned medium and subsequently purify a low abundance protein, he says, requires skill and judgement. Again, there is little support for this assertion, and I afford it little weight.

[393] Finally, I find compelling an argument Pfizer advances arising from the 1986 *Science* article by Dr. Souza, Dr. Zsebo, Mr. Boone, Dr. Welte and others. That article describes in a footnote Amgen's in-house process for growth of cells in the conditioned medium and purification of the natural G-CSF. It states the protein was purified as described in Welte 1985, except for the modification of the final step mentioned in the text (apparently referring to the text of Welte 1985). Pfizer submits the modification of the final step refers to the change from the C18 column to the C4 column (a subject I have addressed above). While Pfizer does not cite evidence in support of that particular submission, I find persuasive that the authors of the *Science* article, including Dr. Souza and other key members of his team, describe their own purification process as following the Welte 1985 protocol with just one unspecified change. This article supports Pfizer's position that Amgen did not regard its purification work as inventive.

[394] I am satisfied that the Skilled Person would not require, nor did Amgen require, inventive solutions to the potential purification problem.

(ii) Partially Sequencing the Natural G-CSF Protein

[395] Amgen's closing submissions do not rely significantly on Dr. Speicher' opinions in support of its argument that the extent of work the Skilled Person would need to embark on, and that Amgen completed, was long and arduous. However, I will consider his evidence here, as Dr. Speicher expresses strong opinions relevant to the Extent of Effort Factor, in the context of the sequencing of the naturally occurring protein.

[396] In support of his opinion that Amgen's sequencing work was not routine, he identifies particular decisions (such as using polybrene and the reducing agent ß-mercaptoethanol, vacuum drying the sample, and re-dissolving the sample in formic acid before sequencing) as requiring the exercise of judgment, skill and ingenuity. In contrast, Dr. Hermodson describes the use of polybrene and a reducing agent as among the techniques the Skilled Person would apply as part of the iterative process of amino acid sequencing. I do not understand Amgen's evidence or argument to be that any of these techniques were themselves inventive. Rather, they are identified as examples in support of Dr. Speicher's opinion and Amgen's position that the skill or judgment to select these techniques was beyond the capabilities of the Skilled Person in 1985.

[397] As previously noted, Dr. Speicher identifies a number of points contributing to his opinion that the sequencing work described in Example 1 was not straightforward or routine and exceeded the abilities of the Skilled Person. He notes the mid-1980s was a period of rapid

advancements in N-terminal sequencing, and something that may have become routine by 1988 or 1990 was not necessarily routine in 1985. He refers to the top tier of protein biochemists, representing about 20% of protein biochemists at that time, having extraordinary skill that was far superior to the capabilities of the Skilled Person working in a commercial or academic laboratory. Dr. Speicher identifies leaders in the field, such as Dr. M. Hunkapiller and Dr. L. Hood, who were, in his view, at least several years ahead of even this extraordinarily skilled group and ranked in the top 1% of protein biochemists in 1985.

[398] Dr. Speicher also states that, due to rapid advances in the field and its often highly competitive nature, protein biochemists who published the results of their research had a strong tendency to overstate analytical capabilities by focusing on exceptional rather than routine results. Usually only the most outstanding, exceptional results from these extraordinary labs were published in the literature, which in no way reflected routine results.

[399] Further, Dr. Speicher contrasts the abilities of protein biochemists to sequence standard proteins, such as myoglobin, with their lesser abilities to determine the amino acid sequence of the vast majority of experimental samples. He explains the significant difference between calling a sequence for a known standard (i.e. simply confirming the expected signal is present), and interpreting data from an unknown protein sample, particularly when the signal-to-background (i.e. the strength of amino acid signals compared to background signals) was not high, a situation which Amgen faced in 1985.

[400] Dr. Speicher also opines that, in the mid-1980s, laboratories with extraordinary skill could usually obtain substantial sequence data from a protein standard (such as myoglobin) starting with hundreds of picomoles and sometimes starting with less than 100 picomoles of a protein sample. He characterizes these as exceptional results by extraordinary laboratories, which were the results most typically published and cited in the mid-1980s. These same laboratories, with lower frequency, could occasionally obtain extended sequence runs (in excess of 40 amino acid residues) starting with less than 500 picomoles of an experimental protein, but this was not routine, even for the protein biochemist of extraordinary skill.

[401] These opinions are significantly at odds with those of Drs. Van Etten and Hermodson. As an initial point, I will address the parties' respective evidence and argument related to the quantity of protein needed to achieve successful resequencing results. Dr. Speicher's opinion is set out immediately above. In contrast, Dr. Hermodson's report states that, in 1985, with a properly optimized sequencer, the yield on 100 pmol of a protein sample would typically give rise to 40 to 50 amino acids of identifiable sequence.

[402] However, on cross-examination, Dr. Hermodson was unable to support his opinion by reference to the publications that his report cited as support. Indeed, when referred to data related to the sequencing of a number of proteins, contained in a publication authored by leading scientists Hunkapiller and Hood attached to Dr. Hermodson's report, he acknowledged the data indicated that, with a couple of exceptions, between 250 and 850 pmol was required to result in over 40 amino acids being called. Another publication demonstrated at least 500 pmol being required to identify more than 30 residues of an experimental protein.

[403] Dr. Speicher states the only objective assessments of the amino acid sequencing capabilities of the Skilled Person, of which he is aware, were from a series of Edman sequencing studies reported by the Association of Biomolecular Resource Facilities [ABRF] in the late-1980s to mid-1990s. He explains this organization provided realistic "unknown" test samples to any interested protein sequencing lab and conducted analysis of returned results in a double blind manner. The results of these studies demonstrated that, even three to five years after 1985, extended amino acid sequences were not typically achieved by Skilled Persons working at commercial or academic laboratories, when starting with < 100 pmol amounts of a highly purified, "ideal" unknown protein.

[404] In my view, both his cross-examination and the ABRF data undermine Dr. Hermodson's opinion as to the results that could typically be obtained with 100 pmol of a protein sample. I therefore prefer Dr. Speicher's opinion that hundreds of pmol of an experimental protein were typically required to obtain sequence runs in excess of 40 amino acid residues. I appreciate Dr. Speicher also qualifies this opinion as related to the capabilities of laboratories of extraordinarily skill, and I will return to this point later in my analysis.

[405] However, I have difficulty finding this conclusion particularly assists Amgen. Dr. Hermodson's report sets out his calculations of the quantity of protein employed by Amgen in each of sequencing Runs 1, 2, 4 and 5. These amounts are, respectively, 140-200 pmol, 260-320 pmol, 400-450 pmol, and 620-700 pmol. Each successive run, with an increased quantity of protein sample, resulted in an increased number of correct amino acids called, culminating with the calls from Run 5 that were used to move forward with the G-CSF project.

[406] These results are consistent with Dr. Hermodson's opinion that there is a positive correlation between the amount of protein sequenced and the number of residues correctly identified, which is exactly what the skilled protein biochemist would expect. Moreover, the amount of protein sequenced in Run 5 is in the upper hundreds of pmol, consistent with the required amounts identified in Dr. Speicher's opinion. In my view, Amgen's successful challenge to Dr. Hermodson's evidence surrounding capabilities at the 100 pmol level does not undermine his opinion that the Skilled Person could expect the results Amgen actually achieved.

[407] I now turn to Dr. Speicher's opinion to the effect that only laboratories of extraordinary skill could achieve these results. As Pfizer submits, this opinion appears inconsistent with the evidence that, in the early-to-mid 1980s, core facilities conducted amino acid sequencing work as a core technical service for other scientists. Dr. Hermodson explains that he managed such a facility at Purdue University in the relevant period. Dr. Speicher also describes such core facilities as the subjects of the ABRF studies discussed in this report.

[408] Dr. Hermodson also notes he has never applied for a patent for amino acid sequencing work. He explains that his published work involved strategies for sequencing a whole protein, not generating probe sequences in the core facility he managed. To similar effect, Dr. Speicher estimates he is named as a co-author on fewer than 5% of the academic papers for which he contributed the sequencing work. Generally, he is included as a co-author only for projects for which, in his words, he made a "substantive creative contribution". I agree with Pfizer's submission this evidence is consistent with the conclusion that 95% of the time, Dr. Speicher was involved in amino acid sequencing work that qualified as routine.

[409] In my view, this distinction between work that involved a creative contribution and work that did not is key to understanding Dr. Speicher's evidence. In his report, he adopts an interpretation of the Skilled Person that excludes individuals in the top 10-20% in ability. He therefore concludes that the prior art published by extraordinary individuals does not inform what was routine and within the capabilities of the Skilled Person. In adopting this interpretation, Dr. Speicher relies on the following definition of the Skilled Person, set out in a footnote to his report:

> The skilled person is an individual or team of people with the ordinary level of skill in the relevant area(s) at the applicable time. As explained to me, the skilled person is "neither first nor last in their class but somewhere in the middle." This hypothetical person has no scintilla of inventiveness or imagination but possesses the common general knowledge in the relevant area(s).

[410] Dr. Speicher adopts the approach described above based on instructions from counsel that the Skilled Person is "neither first nor last in their class but somewhere in the middle." This characteristic often ascribed to the Skilled Person was the subject of the recent decision by the Federal Court of Appeal in *Hospira FCA* at paras 77-80:

> [77] I see no reviewable error in the Judge's analysis of the notional "person skilled in the art": see Reasons at paras. 58-80. Though the appellants take issue with many aspects of the Judge's analysis on this issue, I see nothing that rises to the level of an error of law or a palpable and overriding error of fact or of mixed fact and law.
>
> [78] However, I do have a comment on the statement by the Judge that the PSA is "neither first nor last in her class but somewhere in the middle": see Reasons at paras. 69 and 74, citing *Merck-Frosst-Schering Pharma GP v. Canada (Health)*, 2010 FC 933, 385 F.T.R. 1, at para. 69, and *Amgen Canada Inc. v. Apotex Inc.*, 2015 FC 1261, 138 C.P.R. (4th) 383, at para. 45, aff'd on other grounds 2016 FCA 196, 141 C.P.R. (4th) 245.

> [79] I agree with the Judge's reference to the well-known statement by this Court in *Beloit Canada Ltd. v. Valmet Oy*, [1986] F.C.J. No. 87, 8 C.P.R. (3d) 289 at 294 (F.C.A.) that the classical touchstone for obviousness is the technician skilled in the art but having no scintilla of inventiveness or imagination; a paragon of deduction and dexterity, wholly devoid of intuition; a triumph of the left hemisphere over the right.
>
> [80] The statement that the PSA is neither first nor last in her class is reasonable to indicate that the PSA has certain qualities of a competent technician (deduction and dexterity), but lacks others (inventiveness and imagination). However, the statement is problematic if it is read to suggest that those at the top of their class are inventive while those at the bottom are not. In fact, the quality of inventiveness is not tied to class rank. Rather, it concerns the ability to look at a problem in a way that would not be obvious to others in their field. An inventive person may be at the bottom of the class, and a person at the top of the class may not be inventive. The same may be said of experts. Highly specialized practitioners may be leaders in their field, but may not be inventive. Conversely, inventiveness may manifest in persons with limited expertise.

[411] Pfizer submits Dr. Speicher's approach to the legal construct of the Skilled Person falls afoul of this guidance from *Hospira FCA.* I agree with this submission. As I read *Hospira FCA*, the Court of Appeal is emphasizing that the obviousness analysis focuses on whether inventiveness or ingenuity was required to arrive at the invention. That analysis employs the construct of the Skilled Person, who is without such inventiveness, to answer that question. However, as the Court of Appeal notes, the Skilled Person is a "paragon of deduction and dexterity" [my emphasis]. It is not that the Skilled Person has a mediocre skill level, but rather that they lack inventiveness and imagination.

[412] In the real world, a person at the top of their class or field may or may not actually be inventive. Therefore, in the Extent of Effort Factor and the obviousness analysis generally, one

does not automatically exclude from the analysis the work or publications of leaders in the field. What matters is how that work or those publications inform the question whether the skilled person could have bridged the obviousness gap (without applying inventiveness, which the skilled person does not possess). In my view, the error in Dr. Speicher's approach is that it is too mechanical, as it rejects as irrelevant the work of leaders in the field, not because of an analysis that supports a conclusion that work demonstrated inventiveness, but because of who was responsible for the work.

[413] In conclusion on this point, taking into account the above analysis, the opinions of the parties' respective experts, and the evidence of the actual course of conduct of Dr. Souza's team involved in the amino acid sequencing work, I find that work skilled but routine, militating in favour of a finding that the invention was obvious to try.

(iii) Designing Probes

[414] Amgen also submits its use of the inosine probes to screen the cDNA library was not routine, particularly given the uncertainty as to how inosine would behave opposite a G nucleotide. I appreciate that, as this technique entered the prior art only in 1985, it was arguably less routine than other steps taken by Amgen in connection with the G-CSF project. However, I have previously addressed arguments surrounding the role of inosine probes in the context of the Self-Evident Factor and have not found that role to favour Amgen in the obvious to try analysis.

[415] In the context of Amgen's actual course of conduct, it explains that Dr. Souza and Mr. Boone designed experiments (referred to as N-myc experiments) to examine the uncertainty

surrounding inosine's interaction with G nucleotides. The results of these experiments revealed a potential concern—that inosine actually repels G nucleotides rather than binding to them. Despite those results, Amgen proceeded with the inosine strategy, which turned out to be successful. However, Amgen emphasizes that, if the Souza team had chosen to screen against the lower strand of complementary cDNA strands, it would have encountered more G nucleotides, possibly preventing identification of the G-CSF gene.

[416] Pfizer responds by reference to Mr. Boone's evidence on cross-examination. He confirmed that the results of the N-myc experiments indicated a 1.6% chance of the "worst-case scenario" occurring—that is, where three inosines within a probe matched with three G nucleotides in the target gene, likely preventing the probe from binding. In contrast, 42% of the time, there would be no match with a G at all, and therefore no issue. Further, Pfizer emphasizes Amgen could have simply repeated the process using the upper strand, if Amgen had gotten unlucky on the lower strand and the probes did not bind as a result.

[417] While this evidence does not suggest that the Skilled Person could disregard the uncertainties associated with the inosine technique, nor does it result in a departure from my earlier analysis. Using inosine probes was not long and arduous work, and the role of inosine probes in arriving at Amgen's invention does not support a finding that the invention was not obvious to try.

(iv) Sequencing the G-CSF Gene

[418] The next step in the G-CSF project was to sequence the cDNA identified as a match by screening the cDNA library with the probes discussed above. Amgen again submits that, while this step in the project involved established lab techniques, it carried a risk of error, as evidenced by what actually occurred. Relying on Mr. Boone's affidavit, Amgen explains that the first time Dr. Souza and Mr. Boone sequenced the cDNA, they failed to obtain the full and correct cDNA sequence of the target protein. After troubleshooting, they discovered a small region of DNA had not been correctly mapped. This error occurred because sequencing technology available in 1985 was not capable of sequencing the cDNA from start to finish. Amgen had to break the cDNA into fragments, sequence the fragments, and then piece the sequence fragments back together. A small piece of the sequence was missing after the first attempt, and Dr. Souza and Mr. Boone needed to be attentive to realize the error. Because the error was detected, Dr. Souza and Mr. Boone were able to correctly determine the entire DNA sequence.

[419] In my view, this submission does not assist Amgen. As it notes, this step in the project involved established lab techniques, supporting a conclusion the work was routine. The error described by Amgen's witnesses was successfully identified and solved with *skill*, not *creativity*.

(v) Solubilizing and Refolding Proteins from Inclusion Bodies

[420] After creating the expression plasmids into which the DNA sequence was inserted (preceded by a linker that included a Met—the start codon for expression of proteins in *E. coli*), the plasmids were introduced into *E. coli* cells, thus transforming them. The *E. coli* cells then expressed the protein encoded by the DNA. However, rather than secreting the protein outside of

the cells into the medium (as 5637 cells had done when producing the protein natively), the *E. coli* cells clumped the protein into insoluble inclusion bodies within the cells. Amgen submits that this created another difficult challenge.

[421] Amgen explains it designed several different matrices to solubilize and refold the recombinant protein collected from the *E. coli* cells, carrying out a number of different experiments. These experiments included employing combinations of the detergent lauric acid (to untangle the inclusion bodies), the oxidizing agent copper sulfate (to encourage disulfide bond formation), and both reducing and non-reducing conditions. The recombinant protein treated with lauric acid and copper sulfate, under non-reducing conditions, migrated rapidly and sharply as a single band on the gel, suggesting that the target protein had been correctly folded.

[422] I have previously considered arguments surrounding the challenge presented by inclusion bodies in my analysis under the Self-Evident Factor. The above submissions by Amgen surrounding the Souza team's particular methodologies to address that challenge do not support a conclusion that Amgen's work was other than routine. There is no basis to conclude such work was inventive or that it was particularly arduous. While Dr. Boxer identified many different refolding methodologies from which the Skilled Person would have to choose, he testified these could all be tried in two to three days. Indeed, as Pfizer submits, although Mr. Boone sought to characterize folding as a difficult challenge for Amgen to overcome in August 1985, he confirmed on cross-examination that Amgen's refolding experiments were performed in roughly one day.

(vi) Testing for Biological Activity

[423] Finally, Amgen submits that, after similarly treated inclusion bodies were sent to Dr. Lai for separation into fractions with HPLC, the biological activity of the fractions was tested in two *in vitro* assays, one of which (the WEHI Assay) demonstrated that the recombinant protein possessed granulocyte colony-stimulating activity.

[424] I have previously noted Amgen's submission that showing activity in common with the natural G-CSF was essential to confirming a recombinant version of the natural protein had been successfully made. However, Amgen has not presented any substantive arguments that the testing to show this activity was inventive or even particularly challenging.

(d) *Conclusion on the Extent of Effort Factor*

[425] Similar to the Self-Evident Factor, I find the balance of evidence favours Pfizer's position on the Extent of Effort Factor. That is, the extent, nature, and amount of effort required to achieve the Claim 43 polypeptide would have been within the Skilled Person's capabilities as of August 1985. Any potential challenges they would encounter could be addressed with *skill* and did not require *inventiveness*.

[426] In conclusion, the Extent of Effort Factor favours a finding that the inventive concept of Claim 43 was obvious to try. I also note this finding is consistent with the conclusion of Justice Hughes demonstrated by paragraphs 98 and 101 of the Apotex Decision:

> [98] Amgen stresses the difficulty and inherent risk of failure in the processes it undertook. I repeat a part of its Counsel's brief at trial on this point:

(a) The process from going to a prior art protein preparation to a functional recombinant polypeptide was inherently unpredictable. The PSA did not know that what was to be tried was going to work until experiments were performed and obtained the result.

(b) There was a variety of available techniques confronting the PSA that might be employed to try to successfully complete a recombinant cloning program. These various techniques ranged in their level of activity.

(c) There was no guidance for which methods or techniques could be applied with an expectation of success. A skilled person would have been required to select from the multitude of available techniques, methods, etc. to design a program that they hoped would work.

> (i) A skilled person would recognize that techniques that had been successful for previous researchers could not be expected to be successful for them.
>
> 26. There was a genuine possibility that the program might have been cut short, due to failure, at any number of steps along the way. The failure (or success) of many important aspects of any project are dictated by nature and are simply not amenable to any level of prediction (much less constituting a reasonable prospect of success) in advance.
>
> […]

[101] There was a high degree of skill required and risk involved in what Amgen undertook. The steps were routine in the sense that they were carried out by skilled persons operating with the science as it was known at the time. This amounts to what is termed *"skilled work"* on the Robot Curve previously reproduced, and not to the *"creative work"* necessary to deserve patent protection. This point is well made by Mustill L. J. (as he then was) in *Genentech Inc.'s Patent* [1989] RPC 147 (CA) at page 281, lines 11 to 17:

> The project was the most difficult to have been tackled at the time, but the possible routes and the destination were known, even if nobody could foresee just what obstacles might be found on the way. This does not, of course, prove directly that the invention was obvious, and the facts must be examined at a later stage. But equally, it cannot, in my judgment, be assumed that inventiveness must have been involved somewhere, just because a wager on success could have been placed at long odds.

G. *Conclusion on Obviousness*

[427] The above analysis focuses on Claim 43 of the 537 Patent, as that claim was the focus of the parties' respective submissions. Based thereon, I am satisfied on a balance of probabilities that it was more or less self-evident to try to obtain the Claim 43 polypeptide. This was not a situation with a mere possibility that something might turn up. I conclude Claim 43 is invalid for obviousness.

[428] As I understand the submissions, Amgen's position that Claims 44 to 46 were not obvious turn on the same arguments that I have already considered in relation to Claim 43. That is, the gap between the state of the art and the inventive concepts of Claim 44-46 is the same as for Claim 43. As Pfizer submits, claims 44 to 46 add known DNA tools needed to accomplish this. There is no evidence that any of these claims add anything inventive.

[429] The inventive concept of Claim 47, however, has additional differences from the prior art: (a) the general process of growing a host cell and then expressing and purifying the recombinant protein of Claim 43; and (b) the purified protein having granulocyte colony-

stimulating activity. Dr. Van Etten opined that the general process of growing the host cell and purifying the expressed recombinant protein added nothing inventive, and I do not understand Amgen to be arguing otherwise. He also opines that the Skilled Person would have expected the purified recombinant protein would have the biological activities of the natural protein, because it would have essentially the same structure, and there were many successful precedents.

[430] Again, I do not understand Amgen to argue there was anything inventive about Claim 47 other than the arguments related to Claims 43. I have previously noted Amgen's submission that determining that recombinant G-CSF showed the activity of naturally occurring G-CSF was essential to Claim 47. However, as also noted above, Amgen has not advanced any substantive arguments that the testing to show this activity was inventive or even particularly challenging.

[431] I therefore find all of the Asserted Claims invalid for obviousness.

VIII. SECTION 53 - MATERIAL MISREPRESENTATION

[432] Although I have concluded the Asserted Claims are invalid, it remains necessary to address Pfizer's allegations under s 53 of the Old Act (and, in the next section of these Reasons, its allegations of insufficiency), as such allegations could potentially result in the whole of the 537 Patent being void or invalid.

[433] Section 53 of the Old Act provides as follows:

53. (1) A patent is void if any material allegation in the petition of the applicant in respect of the patent is untrue, or if the	**53. (1)** Le brevet est nul si la pétition du demandeur, relative à ce brevet, contient quelque allégation importante qui n'est pas

specification and drawings contain more or less than is necessary for obtaining the end for which they purport to be made, and the omission or addition is wilfully made for the purpose of misleading.	conforme â la vérité, ou si le mémoire descriptif et les dessins contiennent plus ou moins qu'il n'est nécessaire pour démontrer ce qu'ils sont censés démontrer, et si l'omission ou l'addition est volontairement faite pour induire en erreur.
(2) Where it appears to a court that the omission or addition referred to in subsection (1) was an involuntary error and it is proved that the patentee is entitled to the remainder of his patent, the court shall render a judgment in accordance with the facts, and shall determine the costs, and the patent shall be held valid for that part of the invention described to which the patentee is so found to be entitled.	**(2)** S'il apparaît au tribunal que pareille omission ou addition est le résultat d'une erreur involontaire, et s'il est prouvé que le breveté a droit au reste de son brevet, le tribunal rend jugement selon les faits. et statue sur les frais. Le brevet est réputé valide quant à la partie de l'invention décrite à laquelle le breveté est reconnu avoir droit.
(3) Two office copies of the judgment rendered under subsection (1) shall be furnished to the Patent Office by the patentee, one of which shall be registered and remain of record in the Office and the other attached to the patent and made a part of it by a reference thereto.	**(3)** Le breveté transmet au Bureau des brevets deux copies authentiques de ce jugement. Une copie en est enregistrée et conservée dans les archives du Bureau, et l'autre est jointe au brevet et y est incorporée au moyen d'un renvoi.

[434] As Pfizer articulates the operation of s 53(1), it has two branches: (a) untrue statements in the petition; and (b) misleading statements in the specification. Under the second branch, upon which Pfizer relies, a patent is void if: (a) the specification contains a material addition or omission that is untrue; and (b) the false statements were willfully made with the intent to mislead. The relevant date for applying s 53 is the date the patent issued, although untrue allegations made prior to issue that are not corrected as of the issue date may be included (see *Corlac Inc v Weatherford Canada Inc*, 2011 FCA 228 [*Corlac FCA*] at paras 119).

[435] The false and misleading statements allegedly contained in the 537 Patent are references to the recombinant protein being "pluripotent". It is not disputed that the protein does not have a

pluripotent effect—i.e., it is not capable of stimulating growth of multiple lineages of mature blood cells from progenitor cells. As noted in the Background section of these Reasons, the subject protein stimulates only the growth of granulocytes. In a 1987 publication entitled "Activities of Four Purified Growth Factors on Highly Enriched Human Hematopoietic Progenitor Cells", A. Strife and others reported the subject protein shows no direct pluripotent hematopoietic growth activity. Indeed, Amgen changed its naming convention, and began referring to the protein publicly as "G-CSF" (rather than "hpG-CSF") by mid-1986 (including in a paper authored by Dr. Zsebo and others). Pfizer therefore argues Amgen was aware the protein stimulated only the growth of granulocytes even before it applied for the 537 Patent in Canada in August 1986.

[436] Amgen responds that, to succeed in this allegation, Pfizer must show not only that the 537 Patent contains a misstatement, but also that the misstatement is "material" and that it was "wilfully made for the purpose of misleading" (see *Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 at para 94). It submits Pfizer's allegation fails to satisfy each of these requirements.

[437] First, Amgen denies the 537 Patent contains misstatements. It argues that the references to "pluripotent" upon which Pfizer relies throughout the 537 Patent, most of which are simply the letter "p" in the acronym for the protein (hpG-CSF), represents the adoption of the naming convention employed by Dr. Welte for the naturally occurring protein in Welte 1985. It was Dr. Welte who first used the term "pluripotent" to refer to the protein, and the Souza team continued that usage, because the subject of the 537 Patent was a recombinantly produced version of the same protein.

[438] Second, Amgen argues that, even if the references to "pluripotent" can be characterized as misstatements, they were not material. Amgen notes the materiality of an alleged misstatement is ultimately a fact-specific determination, which assesses whether it is material to the "public"; that is, "whether the misstatement made a difference to the issuance of the patent—the rights contained therein" (see *Weatherford Canada Inc v Corlac Inc*, 2010 FC 602 at para 333, rev'd on other grounds, *Corlac FCA*; see also *Corlac FCA* at para 128).

[439] Amgen submits Pfizer led no evidence to meet its burden to show how the impugned references had or could have had any impact on the public. Rather, the evidence of the parties' experts focused on, and agreed that, the Skilled Person reading the patent on its issue date (July 31, 2007) would not have been mislead, i.e. they would not have believed the subject protein was pluripotent, but rather would have known it had granulocyte-stimulating activity. Amgen asserts the disclosure of the 537 Patent would not have prevented the public from using the invention as described.

[440] Finally, Amgen submits the evidence does not establish intention on its part to mislead. It disputes in particular that the use of the term "G-CSF" in Dr. Zsebo's 1986 paper supports Pfizer's allegation. Amgen notes that the paper also refers to the protein as "pluripotent CSF" and that it employs the G-CSF naming convention because it focuses on granulocyte colony-stimulating activity.

[441] In arriving at a decision on this issue, I am guided significantly by the expert evidence. Pfizer relies on Dr. Van Etten's evidence which, while framed as a sufficiency analysis (and

therefore is perhaps more directly relevant to the issue addressed next in these Reasons), still informs Pfizer's position on the s 53 analysis. He opines that the inventive concept of the 537 Patent as a whole (perhaps more accurately described, in the language of a sufficiency analysis, as the nature of the invention) is the production of a recombinant pluripotent granulocyte colony-stimulating factor, i.e., a recombinant protein that stimulates the growth of CFU-GM, BFU-E, and CFU-GEM(M) progenitor cells. In expressing this opinion, Dr. Van Etten relies on the patent's use of the term "pluripotent" in the Title, Background, Summary, and Examples sections of the patent, as well as in some of its claims.

[442] Having arrived at this opinion as to the invention of the 537 Patent, Dr. Van Etten concludes that the 537 Patent does not contain sufficient information to teach a Skilled Person to produce pluripotent granulocyte colony-stimulating factor, because the factor identified in the patent is not, in fact, pluripotent.

[443] Dr. Griffin disagrees that pluripotency was a requirement of what is described in the 537 Patent overall or as part of any of the Asserted Claims. He notes Welte 1985 disclosed experimental results indicating activity against multiple types of progenitor cells. Such activity was not a new discovery by Dr. Souza. Rather, the comparable experiments described in the 537 Patent were simply intended to confirm Dr. Souza's recombinant protein possessed the same biological activity as Dr. Welte's naturally occurring protein.

[444] Dr. Griffin opines the Skilled Person in 2007 would read the 537 Patent understanding it had been written in and the invention achieved in 1985. In 1985, there was no consensus on what

hematopoietic factors should be called. Different laboratories referred to the same hematopoietic factor using different terms. The Metcalf laboratory at WEHI coined the name "G-CSF", which it used to describe a murine factor. Nicola, also in the Metcalf laboratory, used the name "CSF-ß" for an analog human factor. Dr. Welte then used the name "pluripotent CSF" to describe the same human factor. Recognizing the identity between CSF- ß and pluripotent CSF, Dr. Souza coined the name, "pluripotent G-CSF" to refer to what he reported was the same factor. As such, there was no particular naming convention for that protein.

[445] Also, in both 1985 and 2007, the term "pluripotent" was used to describe the capacity of a stem or progenitor cell to differentiate into more than one type of mature blood cell. Before 1985, the term "pluripotent" had not generally been used to refer to hematopoetic colony stimulating factors (i.e. the proteins which acted on cells and caused them to behave in certain ways) but, rather, to the cells themselves. To the best of Dr. Griffin's knowledge, Dr. Welte was the first to use the term "pluripotent" in that manner, i.e. to convey that the factor had activity in multiple colony assays.

[446] Overall, Dr. Griffin opines the Skilled Person reading the 537 Patent, when it was issued on July 31, 2007, would have understood the above history as part of their CGK. They would most likely have understood Dr. Souza's use of the term "pluripotent" in the 537 Patent as describing that his protein was a manufactured, recombinant version of the naturally occurring protein named "pluripotent" by Dr. Welte.

[447] I find Dr. Griffin's analysis of this issue more compelling than that of Dr. Van Etten. As I have previously noted, these are both forthright and credible experts. However, Dr. Van Etten bases his opinion on this issue on the occurrences of the term "pluripotent" in the 537 Patent, while Dr. Griffin considers what the significance of those occurrences would have been to the Skilled Person reading the patent in 2007. I find Dr. Griffin's opinion to be better supported and, based thereon, I agree with Amgen that Pfizer has not satisfied the requirements of s 53 of the Old Act. I will therefore dismiss this allegation of invalidity.

[448] I note Pfizer submits Amgen is wrong in law to argue that it is saved from the s 53 allegation by the fact that the Skilled Person knew by 2007 that the misstatements in the 537 Patent were wrong. For clarity, my decision to reject this ground of invalidity turns not upon that argument by Amgen, but rather upon my acceptance of its expert evidence as to how the Skilled Person would interpret the patent (i.e. as not requiring a recombinant protein with pluripotent activity).

[449] Amgen devoted some written argument to the cost consequences that Pfizer should suffer if it is unsuccessful on this s 53 allegation. However, as discussed later in these Reasons, the parties have come to an agreement on costs. I will therefore refrain from addressing Amgen's submissions on this point.

XIV. INSUFFICIENCY

[450] As an initial point, I note Amgen submits that Pfizer has not properly pleaded insufficiency, as its pleading alleges insufficiency in relation to the Asserted Claims, not in

relation to the 537 Patent as a whole. I do find Pfizer's insufficiency pleading to be inelegant at best. However, on balance, I am persuaded by Pfizer's response that Amgen had the benefit of Dr. Van Etten's report, and therefore notice of the insufficiency arguments Pfizer was advancing, well in advance of trial and in advance of the preparation of its own responding expert reports. I find Amgen was not prejudiced, and I will address the insufficiency allegation on its merits.

[451] Pfizer's allegation that the 537 Patent is invalid for insufficient disclosure turns on the same technical issue and the same evidence as its s 53 allegation. That is, Pfizer asserts that (1) the nature of the invention is production of recombinant *pluripotent* granulocyte colony-stimulating factor and (2) the disclosure in the patent is not sufficient to practice this invention, because it does not contain the information necessary to allow the Skilled Person to produce a protein that is pluripotent.

[452] While my analysis of the evidence remains as set out above in considering the s 53 allegation, it remains necessary to consider whether the result of that evidence differs when applied to the principles applicable to an insufficiency allegation.

[453] As Pfizer submits, sufficiency of disclosure is a fundamental principle underlying the patent system. The *quid pro quo* of the patent bargain is that, in exchange for exclusive rights to a new and useful invention, the invention must be sufficiently disclosed so that society can benefit from its knowledge (see *Novopharm SCC* at paras 31-32). Sufficient disclosure in the specification of a patent is a precondition for granting the patent, and insufficient disclosure invalidates the entire patent (see *Novopharm SCC* at para 34).

[454] In *Novopharm SCC*, the Supreme Court set out a two-step analysis for determining whether a patent's disclosure is sufficient. The first step is to define the nature of the invention in the patent (see *Novopharm SCC* at para 53). The entire patent must be considered in making this determination, not just a particular claim, as a patent is issued for one invention (see *Novopharm SCC* at paras 55-60). The second step is to determine whether the disclosure is sufficient to enable the skilled person to practice the invention, i.e. to produce the invention using only the instructions contained in the disclosure (see *Novopharm SCC* at paras 70-71). None of these principles are controversial between the parties.

[455] However, the parties disagree on the timing as of which the above analysis is to be conducted. Pfizer submits both steps of the analysis are to be conducted as of the filing date. Amgen agrees the second step is to be conducted as of the filing date but argues the relevant date for the first step is the issue date.

[456] In support of its position, Pfizer references the Court of Appeal decision before *Novopharm SCC* (see *Pfizer Canada Inc v Novopharm Ltd*, 2010 FCA 242 [*Novopharm FCA*] at para 79 [emphasis added]):

> [79] As to the appellant's arguments regarding certain of the Judge's comments, which the appellant labels "extraneous", I have no difficulty agreeing with the Pfizer that these comments do not lead to a reviewable error. Pfizer correctly points out that the Judge was required to determine whether the disclosure was sufficient as of the date of filing. As a result, anything which occurred subsequent thereto is of no relevance. Nevertheless, in my view, the Judge's comments, although misguided in the circumstances, do not form the basis of a reviewable error. As the relevant invention is the compound found in Claim 7, the disclosure is sufficient.

[457] Amgen relies on *Idenix Pharmaceuticals, Inc v Gilead Pharmasset LLC*, 2017 FCA 161 [*Idenix*], in which the Federal Court of Appeal cited *Novopharm SCC* for the requirements of sufficient disclosure and considered whether the trial judge properly determined the nature of the invention. The Court of Appeal endorsed the trial judge's reference to *Free World Trust*, requiring patents to be read as a Skilled Person would have understood them at the date of issue (at paras 23-24).

[458] I read the reference in *Novopharm FCA* to the date of filing as relating to the second step of the sufficiency analysis as articulated by Pfizer, i.e. whether the disclosure is sufficient to enable the Skilled Person to practice the invention. I agree with Amgen that, as confirmed by *Idenix,* the first step of defining the nature of the invention is to be performed from the perspective of the Skilled Person as of the issue date.

[459] This conclusion supports a finding that my above analysis of the evidence related to the s 53 issue therefore applies to the first step of the sufficiency analysis as well. That is, it supports reliance on Dr. Griffin's opinion that the Skilled Person, reading the 537 Patent in 2007, would have understood Dr. Souza's use of the term "pluripotent" in the 537 Patent as describing that his protein was a manufactured, recombinant version of the naturally occurring protein named "pluripotent" by Dr. Welte. However, in the context of the sufficiency analysis, Pfizer raises an additional argument that I must consider in assessing the reliability of Dr. Griffin's opinion for this purpose.

[460] Pfizer argues Dr. Van Etten was the only expert to opine on how the Skilled Person would have understood the 537 Patent as a whole. Pfizer submits that Dr. Griffin failed to assess the nature of the invention by looking at the patent as a whole, including all of the claims, not just the Asserted Claims. As Pfizer correctly notes, *Novopharm SCC* explains that the entire specification of the patent, including the claims, must be considered in determining the nature of the invention and whether the disclosure was sufficient (at para 50).

[461] As expressed, Dr. Griffin's opinion is not limited to the Asserted Claims. His report asserts that pluripotency is not a requirement of what is described "in the 537 Patent overall" or as part of any of Claims 43 to 47. However, in cross-examination, Dr. Griffin acknowledged that, while he read all the claims, he did not spend a lot of time on those other than the Asserted Claims, because he understood the Asserted Claims to be the relevant part of this exercise. This acknowledgment is troubling, as it raises concern about the reliability of Dr. Griffin's opinion as to how the Skilled Person would interpret the 537 Patent as a whole. However, as explained below, I am ultimately not convinced this concern undermines his opinion.

[462] In arriving at his own conclusion, that pluripotency forms part of the inventive concept of the patent, Dr. Van Etten opines that all but two of the first 37 claims of the patent directly or indirectly require the protein to have pluripotent activity. He then provides examples of such claims. While they refer to biological activity, the only references in those claims to "pluripotent" are in the name of the protein. As noted in my earlier analysis, Dr. Van Etten bases his opinion on the occurrences of the term "pluripotent" in the 537 Patent. I found Dr. Griffin's opinion more compelling, because it analysed how the Skilled Person would have interpreted the

use of that term in the patent. As the use of the term in Claims 1-37 is comparable to its use elsewhere in the patent, there is no basis to conclude his opinion would have been different if he had considered in detail the claims other than the Asserted Claims. While Pfizer has identified a deficiency in Dr. Griffin's analytical methodology on this issue, in my view his opinion remains more compelling than that of Dr. Van Etten.

[463] Adopting Dr. Griffin's opinion in the first step of the sufficiency analysis, it is clear that Pfizer's argument under the second step cannot succeed. As there is no requirement that the 537 Patent teach the Skilled Person how to make a protein that stimulates growth in multiple cell lineages, its disclosure is sufficient. I will therefore dismiss this allegation of invalidity.

XV. PRIOR USE

[464] As I have found the Asserted Claims invalid for obviousness, Amgen's allegations of infringement of the 537 Patent will be dismissed. It is therefore unnecessary for me to consider Pfizer's argument that it is protected from a finding of infringement by the defence of prior use. However, I will briefly address this issue, so that the parties will nevertheless have the benefit of my analysis thereof.

[465] For an articulation of the rationale underlying the defence of prior use, Pfizer relies on the following passage from *Libbey-Owens-Ford Glass Co v Ford Motor Co* (1969), 57 CPR 155 at 185-186 (Ex Ct):

> […] The grant of an exclusive right to an invention for a limited period rewards a person, who has made the invention and has disclosed it to the public in the prescribed manner, for the benefit

> which thereby accrues to other members of the public. However, a member of the public who makes or acquires the invention, or some part of it, by himself before it becomes available to the public has, to that extent, no benefit to derive from the publication, yet, without a provision such as section 58, he would be restrained from practicing what he had learned and done by himself before the publication by the person to be rewarded for the information. […]

[466] While the above passage references s 58, the statutory incarnation of the defence upon which Pfizer relied (at least initially) in this action is set out in s 56 of the Old Act as follows:

***Patent Act,* RSC 1985, c P-4, as it read immediately before October 1, 1989**	***Loi sur les brevets*, LRC 1985, ch P-4, telle que parue avant le 1 octobre 1989**
56. Every person who, before the issuing of a patent, has purchased, constructed or acquired any invention for which a patent is afterwards obtained under this Act has the right to use and sell to others the specific article, machine, manufacture or composition of matter patented and so purchased, constructed or acquired before the issue of the patent therefor, without being liable to the patentee or his legal representatives for so doing, but the patent shall not, with respect to other persons, be held invalid by reason of that purchase, construction or acquisition or use of the invention by the person first mentioned, or by those to whom he has sold it, unless it was purchased, constructed, acquired or used for a longer period than two years before the application for a patent therefor, in consequence whereof the invention became public and available for public use.	**56.** Toute personne qui, avant la délivrance d'un brevet, a acheté, exécuté ou acquis une invention pour laquelle un brevet est subséquemment obtenu sous l'autorité de la présente loi, a le droit d'utiliser et de vendre à d'autres l'article, la machine, l'objet manufacturé ou la composition de matières, spécifique, breveté et ainsi acheté, exécuté ou acquis avant la délivrance du brevet s'y rapportant, sans encourir de ce chef aucune responsabilité envers le breveté ou ses représentants légaux. Toutefois, à l'égard des tiers le brevet ne peut être considéré comme invalide du fait de cet achat, de cette exécution ou acquisition ou utilisation de l'invention par la personne en premier lieu mentionnée ou par des personnes auxquelles elle l'a vendue, à moins que cette invention n'ait été achetée, exécutée, acquise ou utilisée durant une période de plus de deux ans avant la demande d'un brevet portant sur cette invention, en conséquence de quoi l'invention est devenue publique et disponible pour l'usage du public.

[467] Factually, Pfizer relies principally on the evidence of Dr. Valinger (including that the MCB was created on or about April 6, 2004) to support its argument that its filgrastim drug, NIVESTYM, will be made from a MCB established before July 31, 2007, the date when Amgen's monopoly in respect of the 537 Patent began.

[468] Amgen raises a number of arguments in support of its position that Pfizer cannot benefit from this defence. However, I need address only Amgen's principal argument that, based on statutory amendments to the Old Act including relevant transitional provisions, the prior use defence is not available to Pfizer. Amgen submits the effect of these provisions is that prior use immunity only applies to acquisitions, purchases, or construction that took place prior to January 1, 1994 or, at latest, October 1, 1996. Pfizer has admitted the MCB was not constructed before January 1, 1994. The following sets out Amgen's submissions in support of its statutory interpretation argument.

[469] Amgen acknowledges the Old Act version of s 56 required the acquisition of the invented subject matter "before the issuing of a patent" (in this case, July 31, 2007). This version of s 56 was amended effective October 1, 1989, requiring the acquisition of the invented subject matter "before an application for a patent becomes open to the inspection of the public" (see RSC 1985, c 33 (3rd Supp), s 22).

[470] Then, effective January 1, 1994, s 56 was amended again, under the *North American Free Trade Agreement Implementation Act,* SC 1993, c 44, s 194, to provide as follows:

***North American Free Trade Agreement Implementation Act*, SC 1993, c 44**	***Loi de mise en oeuvre de l'Accord de libre-échange nord-américain*, LC 1993, ch 44**
194. Section 56 of the said Act is repealed and the following substituted therefor:	**194. L'article 56 de la même loi est abrogé et remplacé par ce qui suit :**
56 (1) Every person who, before the claim date of a claim in a patent has purchased, constructed or acquired the subject matter defined by the claim, has the right to use and sell to others the specific article, machine, manufacture or composition of matter patented and so purchased, constructed or acquired without being liable to the patentee or the legal representatives of the patentee for so doing.	**56. (1)** Quiconque, avant la date de depot d'une demande de brevet ou, si elle est antérieure, la date de priorité de la demande, achète, exécute ou acquiert une invention éventuellement brevetée peut utiliser et vendre l'article, la machine, l'objet manufacturé ou la composition de matières brevetés ainsi achetés, exécutés ou acquis avant cette date sans encourir de responsabilité envers le breveté ou ses représentants 1égaux.
[…]	[…]
(4) Section 56 of the *Patent Act*, as it read immediately before October 1, 1989, applies in respect of a purchase, construction or acquisition made before the day on which subsection (1) came into force of an invention for which a patent is issued before October 1, 1989 or is issued after October 1, 1989 on the basis of an application filed before October 1, 1989.	**(4)** L'article 56 de la *Loi sur les brevets*, dans sa version ant6rieure au 1er octobre 1989, s'applique à l'achat, l'exécution ou l'acquisition, antérieurs à la date d'entrée en vigueur du paragraphe (1), d'une invention pour laquelle un brevet est délivré avant le 1er octobre 1989, ou après cette date mais relativement à une demande déposé avant cette date.
[…]	[…]

[471] When Amgen commenced this action, and Pfizer commenced its counterclaim alleging invalidity, respectively in April and May 2018, the general transition provisions in s 78.2 of the *Patent Act*, RSC 1985, c P-4, provided as follows:

***Patent Act*, RSC 1985, c P-4**	***Loi sur les brevets*, LRC 1985, ch P-4**
Patents issued before October 1, 1989	**Régime applicable aux brevets délivrés avant le 1er octobre 1989**
78.2 (1) Subject to subsection (3), any matter arising on or after October 1, 1989 in respect of a patent issued before that date shall be dealt	**78.2 (1)** Sous réserve du paragraphe (3), la présente loi dans sa version du 30 septembre 1989, à l'exception de l'article 46, s'applique

with and disposed of in accordance with sections 38.1 and 45 and with the provisions of this Act, other than section 46, as they read immediately before October 1, 1989.

Patents issued on or after October 1, 1989 on the basis of previously filed applications

(2) Subject to subsection (3), any matter arising on or after October 1, 1989 in respect of a patent issued on or after that date on the basis of an application filed before that date shall be dealt with and disposed of in accordance with sections 38.1, 45, 46 and 48.1 to 48.5 and with the provisions of this Act, other than section 46, as they read immediately before October 1, 1989.

Application

(3) The provisions of this Act that apply as provided in subsections (1) and (2) shall be read subject to any amendments to this Act, other than the amendments that came into force on October 1, 1989 or October 1, 1996.

aux affaires survenant, le 1er octobre 1989 ou par la suite, relativement aux brevets délivrés avant le 1er octobre 1989. Ces affaires sont également régies par les articles 38.1 et 45.

Régime applicable aux brevets délivrés le 1er octobre 1989 ou par la suite sur demande antérieure à cette date

(2) Sous réserve du paragraphe (3), la présente loi dans sa version du 30 septembre 1989, à l'exception de l'article 46, s'applique aux affaires survenant, le 1er octobre 1989 ou par la suite, relativement aux brevets délivrés ce jour ou par la suite au titre de demandes déposées avant le 1er octobre 1989. Ces affaires sont également régies par les articles 38.1, 45, 46 et 48.1 à 48.5.

Les modifications, sauf certaines, sont prises en compte

(3) Les dispositions visées aux paragraphes (1) et (2) s'appliquent compte tenu des modifications apportées à la présente loi sauf celles de ces modifications entrées en vigueur le 1er octobre 1989 et le 1er octobre 1996.

[472] Pursuant to the combination of ss 78.2(2) and (3), the Old Act was deemed to apply to patents filed under the Old Act but issued subsequently (which includes 537 Patent). However, the Old Act was read subject to any amendments that have subsequently come into force, unless those amendments came into force on October 1, 1989 or October 1, 1996. Thus, the transition provision unwound only those amendments to the Old Act that came into force on October 1, 1989 and October 1, 1996. When the parties commenced their respective claims, therefore, the version of s 56(1) reproduced above, that came into force on January 1, 1994 (and also had its own transition provision in s 56(4)), remained in effect and applicable to a patent such as the 537 Patent.

[473] Therefore, that version of s 56 was in force from January 1, 1994 through to the commencement of this proceeding, including in 2004 (when Pfizer's evidence indicates the MCB was created). Under that s 56(1), Pfizer needed to acquire the invented subject matter before the priority date, which in this case is August 23, 1985, in order to fall under the prior use exception. This obviously does not assist Pfizer. Pursuant to the transitional s 56(4), the exception could also apply where the invented subject matter was acquired before s 56(1) came into force (January 1, 1994). Again, submits Amgen, the creation of the MCB in 2004 does not qualify.

[474] Effective December 13, 2018, the *Patent Act* was amended again by the *Budget Implementation Act, 2018, No. 2*, SC 2018, c 27 [BIA]. As part of the amendments, both the specific transition provision at section 56(4) and the general transition provision at section 78.2 were repealed and replaced. The new transition provisions, in s 78.53 of the *Patent Act* (created by s 208 of the BIA) and s 203 of the BIA, read as follows:

Budget Implementation Act, 2018, No. 2, SC 2018, c 27	***Loi sur les brevets*, LRC 1985, ch P-4, telle que parue le 1 mai 2018**
Section 56 of Patent Act	**Article 56 de la Loi sur les brevets**
203 (1) Section 56 of the Patent Act, as enacted by section 194 of this Act, applies only in respect of an action or proceeding in respect of a patent issued on the basis of an application whose filing date is on or after October 1, 1989 that is commenced on or after October 29, 2018.	203 (1) L'article 56 de la Loi sur les brevets, édicté par l'article 194 de la présente loi, ne s'applique qu'à l'égard des actions et procédures relatives aux brevets délivrés au titre de demandes déposées à compter du 1er octobre 1989 qui sont entamées le 29 octobre 2018 ou après cette date.
Section 56 — previous version	**Article 56 — version antérieure**
(2) Section 56 of the Patent Act, as it read immediately before the coming into force of section 194 of this Act, applies in respect of	**(2)** L'article 56 de la Loi sur les brevets, dans sa version antérieure à l'entrée en vigueur de l'article 194 de la présente loi, s'applique à

any action or proceeding that is in respect of a patent issued on the basis of an application whose filing date is on or after October 1, 1989 and that is commenced before October 29, 2018.

[…]

208 Section 140 of the Act is amended by replacing the section 78.53 that it enacts with the following:

Patents — filing date before October 1, 1989

78.53 (1) Subject to subsection 78.55(2), any matter arising on or after the coming-into-force date, in respect of a patent granted on the basis of an application whose filing date is before October 1, 1989, shall be dealt with and disposed of in accordance with

(a) the provisions of this Act, other than the definitions claim date, filing date and request for priority in section 2, sections 10, 27 to 28.4, 34.1 to 36, 38.2 and 55, paragraphs 55.11(1)(a) and (b) and section 56; and

(b) sections 10 and 55 and subsections 61(1) and (3), as they read immediately before October 1, 1989.

Special case

(2) Section 56 of the Patent Act, as it read immediately before October 1, 1989, applies in respect of a purchase, construction or acquisition made before October 1, 1996 of an invention for which a patent is issued on the basis of an application filed before October 1, 1989.

l'égard des actions et procédures relatives aux brevets délivrés au titre de demandes déposées à compter du 1er décembre 1989 qui sont entamées avant le 29 octobre 2018.

[…]

208 L'article 140 de la même loi est modifié par remplacement de l'article 78.53 qui y est édicté par ce qui suit :

Brevets — date de dépôt antérieure au 1er octobre 1989

78.53 (1) Sous réserve du paragraphe 78.55(2), toute question soulevée à compter de la date d'entrée en vigueur relativement à un brevet accordé au titre d'une demande dont la date de dépôt est antérieure au 1er octobre 1989 est régie, à la fois :

a) par les dispositions de la présente loi, à l'exception des définitions de date de dépôt et demande de priorité à l'article 2, des articles 10, 27 à 28.4, 34.1 à 36, 38.2 et 55, des alinéas 55.11(1)a) et b) et de l'article 56;

b) par les articles 10 et 55 et les paragraphes 61(1) et (3), dans leur version antérieure au 1er octobre 1989.

Cas spéciaux

(2) L'article 56 de la Loi sur les brevets, dans sa version antérieure au 1er octobre 1989, s'applique à l'achat, l'exécution ou l'acquisition, antérieurs au 1er octobre 1996, d'une invention pour laquelle un brevet est délivré relativement à une demande déposée avant le 1er octobre 1989.

[475] To summarize the effect of these newest transition provisions:

A. Pursuant to s 203(1) of the BIA, a new version of s 56 enacted by the BIA does not apply in any way to Old Act patents (i.e., patents like the 537 Patent having a filing date before October 1, 1989);

B. Pursuant to s 203(2) of the BIA, the version of section 56 that was in force from January 1, 1994 until December 13, 2018 applies to patents issued based on applications filed on or after October 1, 1989 (which does not include the 537 Patent), if the action in respect of the patent was commenced before October 29, 2018; and

C. Pursuant to s 78.53(2) of the *Patent Act* (s 208 of the BIA), for an invention for which a patent is issued based on an application filed before October 1, 1989 (such as the 537 Patent), the Old Act version of s 56 applies in respect of infringing products purchased, constructed or acquired before October 1, 1996.

[476] I note Amgen's comment, made in its opening written submissions, that there is perhaps some uncertainty as to whether s 78.53(2) applies other than to matters arising on or after the "coming-into force date" referenced in s 78.53(1). Section 78.53(1) expressly applies only to such matters and is subject to s 78.53(2), but 78.53(2) does not itself contain such a qualification. I understand Amgen's point to be that it is unclear whether s 78.53(2) applies to matters (such as the present matter) arising before the coming into force date.

[477] However, I do not need to resolve this uncertainty, as I agree with Amgen that s 78.53 serves only to extend the window of opportunity, formerly provided by s 56(4), for a party to avail itself of the prior use defence. Under s 56(4), the defence applied to purchases, constructions and acquisitions before January 1, 1994, and s 78.53(2) extends this date to October 1, 1996. Amgen does not offer any explanation for this change, calling it perplexing, but submits the change is irrelevant to this case, given the evidence that the MCB was not constructed until 2004.

[478] Pfizer does not take issue with any of Amgen's presentation of the legislative history of s 56. However, it does dispute that the effect of the amendments and transitional provisions is to deprive it of access to the prior use defence. In advance of trial, Pfizer indicated an intention to rely on s 56 of the Old Act to invoke this defence. However, in closing submissions, it asserted an entitlement to rely on the common law defence of prior use, of which s 56 is a statutory formulation. Pfizer argues that the most recent transitional provisions result in a gap, in that neither 78.53(1) or (2) applies to this case, and that recourse to the common law is available fill that gap.

[479] Pfizer argues that s 78.53(1) does not apply, because the present matter arose before the "coming into force date" referenced in that section. In Pfizer's submission, this matter arose either on the July 31, 2007 issue date, when Amgen had the legal right to enforce its monopoly, or when Amgen issued its Statement of Claim on April 20, 2018. Pfizer identifies the coming into force date of s 78.53, as amended by the BIA, to be October 29, 2019. Regardless, even if s 78.53(1) applied, its application would be subject to s 78.53(2).

[480] Turning to s 78.53(2), Pfizer argues it does not apply, because the prior use at issue occurred after October 1, 1996 and therefore is not captured by this provision. This submission is correct, in the sense that the effect of s 78.53(2) is that Pfizer does not receive the benefit of the statutory prior use defence. However, in my view, this limitation in s 78.53(2) does not leave a legislative gap that could potentially be filled by the common law. Rather, Parliament has spoken and has prescribed the particular parameters, including relevant timing, under which the prior use defence can be invoked. The fact that Pfizer's circumstances do not fall within these parameters

does not mean that those circumstances were not contemplated or addressed by the legislation. It means that Parliament intended that the prior use defence is not available in such circumstances.

[481] In conclusion, Pfizer would not be entitled to avail itself of the prior use defence to protect itself against an infringement action on the fact of this case. Of course, nothing turns on this conclusion, given my earlier finding that the Asserted Claims are invalid for obviousness.

XVI. COSTS

[482] At the trial of this action, the parties agreed to address costs through post-trial written submissions. I have received and reviewed those submissions, contained in correspondence from Amgen's counsel dated March 9, 2020, which advise the parties have agreed to a specified lump sum for costs for the trial in this matter, to be paid upon the expiry of all appeals (or the expiration of the appeal period, if no appeal is made) from my decision.

[483] The parties agree that, if at least one of the Asserted Claims of the 537 Patent is valid and Pfizer would infringe at least one valid Asserted Claim, Pfizer will pay a specified lump sum to Amgen. If none of the Asserted Claims are valid or if Pfizer would not infringe any valid Asserted Claim, Amgen will pay Pfizer a specified lump sum.

[484] I see no reason not to adopt the agreement achieved by the parties. Given my decision that none of the Asserted Claims are valid, Pfizer is entitled to costs from Amgen in the amount of the lump sum the parties have agreed. Perhaps for reasons of confidentiality, the parties' correspondence does not set out that amount. My Judgment will therefore be silent on that

amount, referencing only that the amount has been agreed by the parties. In the event the parties subsequently require an Order setting out any details of the agreed costs disposition, they may file a motion seeking such relief.

JUDGMENT IN T-741-18

THIS COURT'S JUDGMENT is that:

1. The Plaintiffs' action is dismissed.

2. Pursuant to subsection 60(1) of the *Patent Act*, RSC 1985, c P-4 and subsection 6(3) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133, Claims 43-47 of Canadian Patent No. 1,341,537 are declared invalid.

3. The Defendant's counterclaim is otherwise dismissed.

4. Upon the expiry of all appeals (or the expiration of the appeal period, if no appeal is made) from this Judgment, Amgen shall pay Pfizer costs of this action in the amount of the lump sum the parties have agreed. In the event the parties subsequently require an Order setting out any details of the agreed costs disposition, they may file a motion seeking such relief.

"Richard F. Southcott"
Judge

Appendix "A"

CLAIM	CONSTRUCTION
43	Claim 43 pertains to a polypeptide with the specified sequence of 175 amino acids.
44	Claim 44 pertains to a recombinant DNA molecule that instructs cellular machinery to synthesize a specified sequence of 175 amino acids, namely the Claim 43 polypeptide. The DNA molecule can have variations in its sequence because the genetic code is degenerate, meaning that most of the amino acids are encoded by more than one codon (*i.e.*, a triplet of deoxyribonucleotides in the DNA). "Recombinant" means sections of DNA from different sources, joined together in a laboratory.
45	Claim 45 pertains to an expression vector, which is a recombinant DNA molecule that can drive synthesis of a specified sequence of 175 amino acids, namely the Claim 43 polypeptide, when inside an appropriate host cell. The DNA molecule can have variations in its sequence for the same reasons as in Claim 44.
46	Claim 46 pertains to a living cell that contains the expression vector of Claim 45, introduced using genetic engineering techniques in such a way that the cell can express the Claim 43 polypeptide.
47	Claim 47 pertains to a process for making the Claim 43 polypeptide that has granulocyte colony-stimulating activity. The process involves inserting the expression vector of Claim 43 into a living cell, reproducing that cell, and purifying the polypeptide away from other host cell proteins.

FEDERAL COURT

SOLICITORS OF RECORD

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