Federal Court Cour fédérale

Date: 20200604

Docket: T-1304-16

Citation: 2020 FC 668

Ottawa, Ontario, June 4, 2020

PRESENT: Mr. Justice McHaffie

BETWEEN:

CANADA RNA BIOCHEMICAL INC.

Applicant

and

CANADA (MINISTER OF HEALTH), AND ATTORNEY GENERAL OF CANADA

Respondents

JUDGMENT AND REASONS

I. Overview

[1] Lumbrokinase is an enzyme complex derived from earthworms. It has "fibrinolytic" properties, meaning that it enhances the breakdown of blood clots. Such products are often termed "blood thinners," although they do not actually thin the blood. Canada RNA Biochemical Inc (C-RNA) sought a natural health product (NHP) licence for its oral lumbrokinase capsules,

branded Boluoke. C-RNA emphasized Boluoke's fibrinolytic properties and sought to label it for its ability to "reduce blood viscosity" and "improve circulation."

[2] As evidence of the safety and efficacy of Boluoke, C-RNA filed information on the longstanding use of earthworms in Traditional Chinese Medicine, research and clinical studies, and the approval and safety record of Boluoke in other countries. The Natural and Non-Prescription Health Product Directorate (NNHPD) of Health Canada was concerned that the fibrinolytic properties of lumbrokinase entailed a potential risk of internal bleeding. This was of particular concern in the non-prescription context of NHPs. Health Canada found that the information and evidence filed by C-RNA did not satisfy these concerns, since it did not adequately demonstrate safety in healthy populations. Health Canada therefore refused both C-RNA's initial application and a subsequent application, and upheld that refusal on a reassessment.

[3] C-RNA argues that the refusal of its application was unreasonable. It argues that Health Canada misinterpreted the *Natural Health Products Regulations*, SOR/2003-196 [*NHP Regulations*], by reading in terms such as "healthy population" and "risk/benefit" that are not found in the regulations. C-RNA also argues that Health Canada was unreasonable in categorizing Boluoke as a "high risk" product, in doing so based on evidence of intravenous drugs when Boluoke is an oral capsule, and in adopting an overly stringent approach to the evidence that effectively treated its product as a non-NHP drug rather than an NHP. It further claims that Health Canada ignored relevant evidence and that its refusal to accept that Boluoke was safe was unreasonable.

[4] I conclude that Health Canada's refusal of C-RNA's application was reasonable. Health Canada's approach to the *NHP Regulations* is consistent with the text, context and purpose of the regulations, and it thoroughly and reasonably considered the evidence filed by C-RNA. It reached a consistent and reasoned view on the adequacy of the safety evidence, and it is not this Court's function to stand as a scientific review panel to second-guess that decision.

[5] C-RNA also argues that the refusal was procedurally unfair. It relies on numerous aspects of Health Canada's review, including non-disclosure of information and documents, the use of new guidelines that were not in place at the time of the original application, and irregularities in the reconsideration process.

[6] I also conclude that the process that led to the refusal was fair. C-RNA had notice of Health Canada's concerns and ample opportunity to address them. C-RNA was not improperly persuaded to re-submit its application, and fairness did not require that Health Canada disclose the information and internal documents C-RNA says it should have been given. There is also no indication that C-RNA was prejudiced by the application of certain guidelines instead of others, and in any case, the standard ultimately applicable was, throughout, the one set out in the *NHP Regulations*. The reconsideration process, while not "textbook" as the Minister concedes, gave C-RNA the required opportunity to be heard before reconsideration, and the final decision was made after a fair reassessment of the application by an appropriate officer. What is required is fairness, not perfection, and C-RNA was given a fair process.

[7] The application for judicial review is therefore dismissed.

II. Issues

[8] C-RNA structured its submissions to address three aspects of Health Canada's refusal to grant an NHP licence: Health Canada's interpretation of the *NHP Regulations*; the fairness of the process; and the reasonableness of Health Canada's refusal. The first and third of these go to the substantive merits of the decision, while the second is a matter of procedural fairness. I will therefore address the issues as follows:

A. Was Health Canada's decision to refuse a licence for C-RNA's Boluoke lumbrokinase product unreasonable, and in particular:

   (1) did Health Canada err in its interpretation of and approach to the *NHP Regulations*; and/or

   (2) was the refusal unreasonable in light of the information filed in support of the application?

B. Was the process leading to Health Canada's decision to refuse a licence for C-RNA's Boluoke lumbrokinase product unfair?

[9] To assess these issues, it is necessary to consider in some depth both the regulatory framework applicable to NHPs and the history of C-RNA's applications for a product licence for Boluoke. I will consider these matters before turning to C-RNA's particular arguments.

III. The Natural Health Products Regulatory Framework

A. *The Regulatory Context*

[10] Promulgated under the *Food and Drugs Act*, RSC 1985, c F-27 [*FDA*], the *NHP Regulations* created a new scheme for the approval and regulation of NHPs. As the Federal Court of Appeal has said, this scheme is "legally and operationally discrete" from the regime for the regulation of other drugs under the *Food and Drug Regulations*, CRC, c 870: *Canada (Health) v The Winning Combination Inc*, 2017 FCA 101 at para 8. I use the term "other drugs" to mean drugs that are not NHPs, since NHPs fall within the *FDA* definition of "drug": *FDA*, ss 2 ("drug"), 37(1.1)(*b*); *Mancuso v Canada (National Health and Welfare)*, 2015 FCA 227 at para 4.

[11] The intention to treat NHPs distinctly from other drugs is seen from the regulations themselves. With a few exceptions, the provisions of the *Food and Drug Regulations* do not apply to NHPs: *NHP Regulations*, ss 3, 60, 96–103.1; *Winning Combination (FCA)* at para 8.

[12] The Regulatory Impact Analysis Statement (RIAS) that accompanied the *NHP Regulations*, while not part of the regulations, is a useful tool to understand how they are intended to work: RIAS, SOR/2003-196, *Canada Gazette Part II*, Vol 137, No 13 at p 1571; *Mounted Police Association of Ontario v Canada (Attorney General)*, 2015 SCC 1 at para 113. The RIAS describes the goals that the regulations intended to accomplish:

> These Regulations are intended to provide Canadians with ready access to natural health products that are safe, effective, and of

> high quality, while respecting freedom of choice and philosophical and cultural diversity.

[13] The parties stressed different aspects of this balanced statement of purpose. The Minister highlighted the fundamental importance of safety, while C-RNA submitted that Health Canada had lost sight of its mandate of "respecting freedom of choice and philosophical and cultural diversity." Both of the principles are important to the NHP context. That said, the *NHP Regulations* and the regulatory context in which they were promulgated emphasize the importance of safety.

[14] The *NHP Regulations* arose in the wake of recommendations contained in a 1998 report from the House of Commons Standing Committee on Health: RIAS at p 1572; House of Commons, Standing Committee on Health, *Natural Health Products: A New Vision* (November 1998) (Chair: Joseph Volpe). C-RNA relies on this Report, noting that it sets out as a "guiding principle" that "NHPs are different in nature from and must not be treated strictly as either food or pharmaceutical products." I agree that this principle is reflected in the *NHP Regulations* and must be recognized in their interpretation: see, *e.g., Winning Combination (FCA)* at para 14.

[15] However, another relevant guiding principle in the Report is that "[s]afety of NHPs is of primary concern." Indeed, the Report underscores that the common objective of the Standing Committee members was that "the health of Canadians must remain as the most vital criterion underlying any regulatory analysis" [emphasis added]. Notably, while the Minister is expressly required by the *NHP Regulations* to evaluate safety and prevent injury to health, the importance of "freedom of choice and philosophical and cultural diversity" exists only as an underlying

principle rather than an identified criterion for evaluation. A review of the Standing Committee Report, the RIAS, and the *NHP Regulations* themselves confirms that while the regulations are intended to treat NHPs under a process and principles distinct from those for other drugs, they are not intended to do so at the expense of the health (broadly considered) or safety of Canadians.

[16] This is consistent with the objective of the *FDA*, the enabling statute of the *NHP Regulations*. The Supreme Court of Canada has described the *FDA*'s objective as being "to encourage bringing safe and effective medicines to market to advance the nation's health": *AstraZeneca Canada Inc v Canada (Minister of Health)*, 2006 SCC 49 at para 12. This description applies equally to the *NHP Regulations*: *Winning Combination (FCA)* at para 58.

[17] While the regimes for NHPs and other drugs are "legally and operationally discrete," they do not exist in isolation from each other. The borderline between NHPs and other drugs is drawn by the definition of "natural health product" in subsection 1(1) of the *NHP Regulations*, and by subsection 2(2), which states that a substance is not an NHP if the *Food and Drug Regulations* require it to be sold by prescription. Prior to 2012, such prescription drugs were listed on Schedule F to the *Food and Drug Regulations*; they are now listed on the Prescription Drug List: *Food and Drug Regulations*, s A.01.010 ("prescription drug", "Prescription Drug List"); *FDA*, s 29.1. The RIAS for the *NHP Regulations* at page 1577 notes that subsection 2(2) "clearly distinguishes prescription drugs from NHPs" and states:

> This clarifies the original policy intent of the NHP Regulations to regulate substances that are safe for over-the-counter use. It was not the intent of the Regulations to take substances off Schedule F

> or to regulate substances that require a prescription or have a narrow margin of safety.

[18] In deciding whether a drug should be on the Prescription Drug List, the Minister is to consider the need for practitioner supervision, and whether the "level of uncertainty" respecting the drug justifies such supervision: *Food and Drug Regulations*, s C.01.040.3. Thus, if a substance that is sold for treatment, mitigation or prevention of a health condition (*i.e.*, a drug) presents issues or uncertainties that suggest it should be used under medical supervision, then it may be considered for inclusion on the Prescription Drug List, which would take it outside the *NHP Regulations*: *FDA*, s 2 ("drug"); *Food and Drug Regulations*, s C.01.040.3; *NHP Regulations*, s 2(2). This is one of the issues that arose in Health Canada's review of Boluoke.

[19] This context provides the backdrop for the particular provisions in the *NHP Regulations* at issue in this matter, namely sections 5(*g*) and 7. These sections are found in Part 1 of the *NHP Regulations*, which deals with product licences.

B. *The Regulatory Provisions at Issue*

[20] NHPs can only be sold in Canada under a product licence: *NHP Regulations*, s 4. Section 5 of the *NHP Regulations* sets out what must be filed as part of an application for a product licence, including information regarding the "safety and efficacy" of the NHP. At the time of C-RNA's application for a product licence, subsection 5(*g*) read as follows:

Licence Application	**Demande**
5 An application for a product licence shall be submitted to the Minister and shall contain the following information and documents:	**5** La demande de licence de mise en marché est présentée au ministre et comporte les renseignements et documents suivants :
[…]	[…]
(g) information that supports the safety and efficacy of the natural health product when it is used in accordance with the recommended conditions of use;	**g)** les renseignements montrant l'innocuité et l'efficacité du produit lorsqu'il est utilisé selon les conditions d'utilisation recommandées;
[Emphasis added.]	[Je souligne.]

[21] In 2018, an amendment to the English version of subsection 5(*g*) changed the word "supports" to "demonstrates," such that the provision now reads "information that demonstrates the safety and efficacy of the natural health product…" While information that "demonstrates" safety and efficacy might at first blush suggest a higher standard than information that simply "supports" it, a closer reading shows that the terms are synonymous in this context and that the amendment was simply a clarification rather than a substantive change.

[22] Significantly, other provisions in the regulations—both before and after the amendment—refer to an applicant or licensee having to provide information "demonstrating" that the NHP is safe and efficacious: *NHP Regulations*, ss 11(2)(*c*), 16, 17(1)(*b*), 17(2)(*a*). This includes section 11, dealing with applications to amend a product licence, which must include "information demonstrating that the natural health product is safe and efficacious after the change": *NHP Regulations*, s 11(2)(*c*). It would be incongruous if a different standard of safety

and efficacy information was required when a licence application is first filed than when it is amended. This is particularly so since the French version, which was not amended, uses the same verb "*montrer*" in each section: *NHP Regulations*, ss 5(*g*), 11(2)(*c*).

[23] The RIAS for the amending regulation confirms that the amendment was designed to address one of many identified discrepancies between French and English versions of various regulations: RIAS, *Regulations Amending Certain Department of Health Regulations (Miscellaneous Program)*, SOR/2018-69, *Canada Gazette Part II*, Vol 152, No 8, p 775 at p 779. I also refer for completeness to the principle that amendments are not deemed to involve a change in the law: *Interpretation Act*, RSC 1985, c I-21, ss 45(2)–(3).

[24] I therefore read the word "supports" in subsection 5(*g*) as it read prior to 2018 as being synonymous with the word "demonstrates." The meaning of the provision as a whole, and in particular whether it creates a test the applicant must meet, is discussed further below.

[25] The "recommended conditions of use" referred to in subsection 5(*g)* are defined in the regulations as meaning its recommended use or purpose, dosage form, route of administration, dose, duration of use and risk information: *NHP Regulations*, s 1(1) ("recommended conditions of use"). Subsection 5(*f*) requires a product licence application to include the recommended conditions of use for the NHP.

[26] The other provision of particular relevance to C-RNA's arguments is section 7 of the *NHP Regulations*, which reads as follows:

Issuance and Amendment	**Délivrance et modification**
7 The Minister shall issue or amend a product licence if	**7** Le ministre délivre ou modifie la licence de mise en marché si les conditions suivantes sont réunies :
(a) the applicant submits an application to the Minister that is in accordance with section 5 or subsection 11(2), as the case may be;	**a)** le demandeur présente au ministre une demande conforme à l'article 5 ou au paragraphe 11(2), selon le cas;
(b) the applicant submits to the Minister all additional information or samples requested under section 15;	**b)** le demandeur fournit au ministre les renseignements complémentaires ou les échantillons demandés en vertu de l'article 15;
(c) the applicant does not make a false or misleading statement in the application; and	**c)** le demandeur ne fait pas de déclaration fausse ou trompeuse dans sa demande;
(d) the issuance or amendment of the licence, as the case may be, is not likely to result in injury to the health of a purchaser or consumer.	**d)** la délivrance ou la modification de la licence ne risque pas de causer un préjudice à la santé de l'acheteur ou du consommateur.
[Emphasis added.]	[Je souligne.]

[27] For a product licence to be issued, subsection 7(*a*) requires the application to be "in accordance with section 5." To be "in accordance with section 5," the application must, among other things, contain the information demonstrating safety and efficacy required by subsection 5(*g*). Health Canada treats subsection 7(*a*) as including a substantive requirement to demonstrate safety and effectiveness. This can be seen in Health Canada's Safety and Efficacy Class Review Assessment Report (SEAR), used in the assessment of NHP product applications.

The SEAR form used by Health Canada includes check boxes relating to a potential refusal of an application, including "Insufficient information to support the **safety** of the product (7a)" and "Insufficient information to support the **efficacy** of the product (7a)" [emphasis in original]. The SEAR form also contains other boxes related to subsections 7(*b*), (*c*) and (*d*). C-RNA's application was refused pursuant to subsection 7(*a*) based on it containing insufficient information to support the safety of Boluoke.

[28] C-RNA submits that subsections 5(*g*) and 7(*a*) do not create a substantive standard but only an administrative requirement to file information of safety and efficacy. The substantive requirement for safety, C-RNA argues, is found in subsection 7(*d*), which requires that approval of the NHP is "not likely to result in injury to the health of a purchaser or consumer." In support of this proposition, it relies on the decision of Justice Russell in *Winning Combination Inc v Canada (Health)*, 2016 FC 381, which was reversed in part by *Winning Combination (FCA)*.

[29] I do not believe that Justice Russell went so far as to conclude that subsection 5(*g*) was a purely administrative requirement: *Winning Combination (FC)* at paras 137–142. In this regard, I agree with the Minister that C-RNA's reliance on paragraphs 42 to 46 of the decision is misplaced, as those paragraphs simply summarize the applicant's arguments. In any case, to the extent that Justice Russell's decision might be read in this way, it was overtaken by the Court of Appeal's conclusion that in exercising their discretion under section 7 of the *NHP Regulations*, the Minister "must be satisfied that the product is safe and effective, albeit to different standards than in the assessment of new drugs" [emphasis added]: *Winning Combination (FCA)* at para 58. In my view, this statement and the structure of the *NHP Regulations* both indicate that to be

satisfied under subsection 7(*a*) that an application complies with section 5, the Minister must be satisfied not just that the applicant has filed information on safety and effectiveness, but that the information demonstrates that the NHP is safe and effective when used in accordance with the recommended conditions of use. This accords with the Minister's approach as seen in the SEAR and in its refusal of C-RNA's application.

[30] I also do not agree that in showing safety, an applicant need only show that the NHP is not "likely to result in injury to the health of a purchaser or consumer," the standard set out in subsection 7(*d*). The *NHP Regulations* use the term "safe when used in accordance with the recommended conditions of use" and the term "likely to result in injury to health" to mean two different things. This can be seen from the appearance of the two terms in different provisions that empower the Minister to stop sales of NHPs, with different procedural requirements. If the Minister has grounds to believe an NHP is no longer "safe," they may stop sales, but only after requesting further information and providing the licensee an opportunity to respond: *NHP Regulations*, ss 16, 17(1)(*a*)–(*b*). However, if the Minister has grounds to believe an NHP may cause "injury to health," they must suspend the product licence (thereby stopping sales) *without* giving the licensee an opportunity to be heard: *NHP Regulations*, s 19; see also s 4(3)(*a*).

[31] The Minister's ability to stop sales if no longer satisfied that the product is "safe when used in accordance with the recommended conditions of use" confirms that this is a substantive requirement that must be established by a licensee. The different procedural requirements arising when concerns about "safety" and "injury to health" arise confirms that they represent different substantive standards. An applicant must therefore show not only that their product is not likely

to cause "injury to health" (subsection 7(*d*)), but that it is "safe when used under the recommended conditions of use" (subsections 5(*g*) and 7(*a*)). While a product that is safe when used under the recommended conditions of use will presumably not cause injury to health, I do not believe that this renders subsection 7(*d*) redundant. Notably, safety is set out jointly with efficacy in subsection 5(*g*), an issue addressed further below in discussing the "risk-benefit" analysis. However, subsection 7(*d*) confirms that if a product is "likely to cause injury," no licence can be granted, regardless of the efficacy of the product.

[32] As a final note in reviewing the provisions, subsection 7(*b*) refers to section 15 of the *NHP Regulations*. That section says that where the information and documents submitted with a licence application under section 5 are "insufficient to enable the Minister to determine whether the product licence should be issued," the Minister may request that the applicant provide such additional information as is "necessary to make the determination." The NNHPD's practice is to send such requests in the form of an Information Request Notice (IRN).

C. *The Minister's Guidelines*

[33] Over time, the NNHPD has published a number of guidance documents to assist industry, the public, and its own decision-makers in understanding and applying the *NHP Regulations*. Such guidelines have long been recognized as being appropriate, helpful, and even persuasive. They do not, however, have force of law and cannot amend, limit or qualify statutory or regulatory provisions: *Maple Lodge Farms Ltd v Canada*, [1982] 2 SCR 2 at pp 3–4, 6–7, aff'g [1981] 1 FC 500 (CA) at pp 513–514; *Canada (Information Commissioner) v Canada (Minister*

of Citizenship and Immigration), 2002 FCA 270 at para 37. At issue in this matter are guidelines issued in 2006 and 2012.

(1) The 2006 Guideline

[34] In 2006, the NNHPD (then known as the Natural Health Products Directorate) issued a guidance document entitled *Evidence for Safety and Efficacy of Finished Natural Health Products (Version 2.0)*. This 2006 Guideline included an epigraph noting the role of the directorate, using language that parallels that of the RIAS, as referenced in paragraph [12] above:

> "Our role is to ensure that Canadians have ready access to natural health products that are safe, effective and of high quality while respecting freedom of choice and philosophical and cultural diversity." – *Natural Health Products Directorate*

[35] The 2006 Guideline states that evaluation of an NHP for safety and efficacy "includes an assessment of its recommended conditions of use, its appropriateness for self-care and the existing totality of evidence related to the NHP." It goes on to provide further detail on what is meant by "recommended conditions of use," "self-care" and "totality of evidence." The 2006 Guideline also sets out an approach in which the "health claims" of a product are divided into two categories: traditional use claims and non-traditional use claims. A "health claim" is a statement about the expected benefit to the consumer of taking an NHP, such as "maintains healthy gums" or "reduces blood cholesterol."

[36] Traditional use claims are those based on the knowledge, skills, theories, beliefs and experiences indigenous to different cultures. Such traditional use claims must be introduced with qualifiers identifying the traditional use, such as "In Traditional Chinese Medicine used to…"

Non-traditional use claims do not use such qualifiers, and are established based on scientific evidence such as clinical trials. The 2006 Guideline identified types of evidence that might be used to support traditional use claims and non-traditional use claims. Other types of NHPs, including homeopathic medicines, are addressed under other guidelines.

[37] I note that the Minister initially objected to C-RNA filing the 2006 Guideline on this application, since it was not part of the Certified Tribunal Record. It was accepted for filing by Direction of Prothonotary Aalto acting as Case Management Judge, subject to arguments on its admissibility. No such arguments were made before me. The Minister, appropriately in my view, focused their submissions on responding to C-RNA's arguments regarding the guideline.

(2) The 2012 Guidelines

[38] In 2012, as part of an announced new approach to NHPs, the 2006 Guideline was replaced by two separate guidance documents. These two documents addressed concepts similar to the two categories of health claims described in the 2006 Guideline. "Traditional medicines" were addressed in a new guideline titled *Pathway for Licensing Natural Health Products used as Traditional Medicines*. Products that made "modern health claims" were addressed in a new guideline titled *Pathway for Licensing Natural Health Products Making Modern Health Claims*. C-RNA's 2013 application for a product licence was made as a "non-traditional" application. The *Pathway for Licensing Natural Health Products Making Modern Health Claims* document is therefore the guideline of relevance, and I will refer to it as the "2012 Guideline."

[39] The 2012 Guideline states that its policy objective is to "provide reasonable assurance that NHPs offered for sale in Canada are safe and effective when used under their recommended conditions of use." It describes a risk-based approach to assessing safety and efficacy, in which the type and amount of evidence to be filed in support of an application varies depending on the proposed health claims of the product and its overall risk profile.

[40] The approach described in the 2012 Guideline includes a categorization of products into low, medium and high levels of risk. The "high level of risk" category applies to NHPs with the narrowest safety margin and effective dose range, and those used for treatment, cure, and prevention of serious diseases, including those listed in Schedule A (now Schedule A.1) to the *FDA*. The introduction of these categories, and in particular the assignment of Boluoke to the high-level risk category, is the source of some of C-RNA's arguments. The 2012 Guideline provides guidance on the nature of evidence that can be filed to show the safety and efficacy of the product, including a table setting out evidence that will be accepted as meeting minimum criteria for evidence for each risk category.

IV. C-RNA's Application for an NHP Product Licence for Boluoke

[41] C-RNA filed two applications for NHP product licences for Boluoke, one in 2006 and a second in 2013 after the first was refused. C-RNA seeks judicial review only of the refusal of its second application. This is appropriate, as the 2006 application was rejected many years ago and that rejection was not challenged, C-RNA choosing to file its 2013 application instead. I consider the 2006 application relevant to the procedural fairness issues raised by C-RNA, and its argument that the second application should have been considered pursuant to the 2006

Guideline. I will therefore briefly summarize the process leading to its refusal. However, the substantive decision under review is the 2015 refusal of the second application, as reconsidered and affirmed in 2016.

A. *The First Application*

[42] C-RNA's first product licence application for Boluoke was filed in March 2006. The application sought approval of Boluoke as a "traditional claim" NHP to "reduce blood viscosity" and "improve circulation." The application included information regarding the manufacturing process, and an evidence summary identifying various scientific studies and providing narrative overviews of the product and the science. It also attached copies of materials regarding the use of earthworms in food and traditional medicine, and proposed labelling for Boluoke.

[43] The NNHPD issued an IRN to C-RNA in April 2009 that classified Boluoke as a "Non-Traditional" NHP. While not set out in the IRN, it appears that the classification of Boluoke as "Non-Traditional" was because it was not just earthworms, which had been used in Traditional Chinese Medicine, but an extraction using non-traditional methods of the enzyme complex contained in earthworms. The IRN stated that the evidence C-RNA had filed was not considered adequate to support safety and efficacy, noting in part that animal or *in vitro* evidence was provided as the sole source of safety or efficacy evidence. C-RNA was asked to provide further evidence to support the safety and efficacy of lumbrokinase according to the recommended conditions of use, and reference was made to the criteria in the 2006 Guideline for assessing evidence.

[44] C-RNA's response to the 2009 IRN was not to file further evidence but to say that it "did not see the deficiencies you pointed out" and to summarize the information already provided. C-RNA stated its belief that it "provided as complete a submission as can be expected from any natural health product applicant," and asked that if the NNHPD still believed the submission insufficient, that it "please be very specific as to what kind of evidence you still require."

[45] NNHPD issued another IRN in August 2011. It noted that the NNHPD had identified potential health risks associated with the use of three natural fibrinolytic enzymes, nattokinase, lumbrokinase and serratiopepsidase. Included in its discussion of this concern is the following passage referring to intravenous fibrinolytic agents, which C-RNA takes significant issue with:

> Evidence of fibrinolytic activity in humans is limited, however, the existing evidence demonstrates adverse effects and/or expresses concern of the safety of fibrinolytic enzymes in humans (Hsia et al. 2009; Change [*sic*] et al. 2008; Kim et al. 2008). Additionally, fibrinolytic agents are generally administered intravenously and under supervision of a physician since they are used to treat patients with serious conditions (e.g. patients with myocardial infarction, acute thrombotic stroke, arterial thromboembolism) and thus are not considered appropriate for 'self-care'. Furthermore, the serious contraindications for these products such as active internal bleeding, haemorrhagic cerebrovascular disease, bleeding diatheses, pregnancy, uncontrolled hypertension, invasive procedures in which haemostasis is important, and recent trauma – including vigorous cardiopulmonary resuscitation (Rang et al. 2009), are also considered potential safety concerns for oral products in the absence of clinical trials demonstrating long-term oral safe use of fibrinolytic enzymes.
>
> [Emphasis added.]

[46] The 2011 IRN concluded that more clinical evidence was required to show that the health benefits of a product containing one of these enzymes outweighed the risks of their use without physician supervision. It indicated that adequate evidence had to be filed to "support the safety in

the general healthy population and not a subpopulation which will be monitored closely by a physician (e.g. hypertensive patients, patients with acute myocardial infarction).” It also set out a series of reasons why the evidence in the licence application was insufficient.

[47] C-RNA responded to the 2011 IRN by providing a number of revisions to its application, as well as additional studies and references. C-RNA argued that the concerns about fibrinolytic enzymes did not apply to lumbrokinase as none of the research referenced by the NNHPD specifically implicated lumbrokinase as a high-risk enzyme preparation. It also contended that intravenous fibrinolytics would have no effect if administered orally, and that oral fibrinolytics had a safer profile.

[48] Another IRN issued in 2013 raised similar issues to those raised in the 2011 IRN, and set out a 14-point list of identified deficiencies in the studies filed by C-RNA. It referred C-RNA to the 2012 Guideline, which had been issued in the interim, and asked C-RNA to provide evidence to support the product’s safety and efficacy in humans taking into account the requirements for a “high risk” category product. C-RNA’s response to the 2013 IRN included its responses to the list of identified deficiencies, and expressed disagreement with the NNHPD’s analysis on a number of matters. It also provided additional references and supporting documents, and raised a concern that the NNHPD’s approach to the evidence was more suited to other drugs than NHPs.

[49] On September 17, 2013, the NNHPD issued a Notice of Refusal. The NNHPD noted that, due to the inconsistency and uncertainty in the data, it could not conclude that Boluoke did not pose a bleeding risk in a healthy sub-population due to its anti-coagulant, anti-platelet and

fibrinolytic potential. The NNHPD found that it was not possible to establish a favourable "risk versus benefit profile" to support the health claims, and noted that the internal bleeding risk could not be mitigated for over-the-counter (OTC) use. In particular, the NNHPD noted that the majority of the clinical data is derived from "populations with hypercoagulable states" that is not directly applicable to a healthy subpopulation intended for OTC use.

[50] The term "hypercoagulable state" refers to a condition associated with a predisposition to develop blood clots. As explained in a helpful scientific primer agreed to by the parties and filed pursuant to an Order of Prothonotary Aalto, the blood coagulation system involves a balance between the coagulation (clot forming) system and the fibrinolytic (clot resolving) system. Where coagulation overbalances fibrinolysis, the system becomes hypercoagulable. Where the reverse occurs—a hypocoagulable state—there is a higher chance of bleeding. Health Canada's concerns were thus in essence that if a coagulation system is already in balance (or is already hypocoagulable), introducing a fibrinolytic might render it hypocoagulable (or more so), with an associated risk of internal bleeding. Studies with subjects in a hypercoagulable state therefore may not demonstrate safety in those not in such a state.

B. *The Second Application*

[51] After the 2013 refusal, there was a call between the NNHPD and C-RNA about a possible pathway for lumbrokinase to be licenced as part of a "professional use" program. There was little evidence filed before me regarding the nature of this program. An email exchange between Health Canada employees referred to a "*Non-prescription Professional Use products* framework," suggesting that there was an existing or anticipated framework or program to cover

non-prescription products with some degree of professional oversight. However, no framework documents, guidelines or other details were filed. In any case, based on the material filed and the subsequent discussion of the issue, the idea appears to have been some form of approval involving health professional monitoring or oversight for a period of time to allow for the accrual of post-market safety data before moving the product to OTC availability.

[52] C-RNA re-submitted its application on January 2, 2014, seeking an NHP licence for Boluoke in the "Non-traditional" category. C-RNA indicated in a cover letter that it had decided to "accept NHPD's suggestion" and was re-submitting the application under "the new practitioner NHP category." The application included new supporting evidence, but the bulk of the evidence came from its previous submissions. While the product licence application form itself contained the same health claims as the first application, namely "[t]o reduce blood viscosity" and "[t]o improve circulation/hemorrheology," an attached Efficacy and Evidence Summary Report indicated that it was seeking claims that were limited to reducing blood viscosity and improving circulation "in hypercoagulable blood state."

[53] The NNHPD issued an IRN on August 13, 2014. The IRN reiterated the view that, as communicated in the 2013 refusal:

> …the body of clinical trial evidence for lumbrokinase is of insufficient quality to provide confidence that the product is not a risk with respect to internal bleeding. As internal bleeding is a serious health risk that cannot be mitigated through labeling and is not self-diagnosable, the NNHPD's position is that the current evidence is not appropriate to support its safe use as an over-the-counter (OTC) product.

[54] The IRN also indicated that the NNHPD had examined the option of restricting the sale of lumbrokinase to health care professionals. To do so, it consulted with an "external practicing hematologist" to see if a post-market monitoring plan could be developed to manage risks and obtain post-market safety data. Based on this consultation, the NNHPD concluded that available tests could not predict bleeding risk, so practitioner oversight would be limited to reacting to symptoms suggestive of bleeding. Such a management strategy was not considered appropriate given the risk-benefit balance. The hematologist's review of the clinical evidence was also said to reinforce the NNHPD's view that the data did not support safety of lumbrokinase for general use. The NNHPD therefore asked C-RNA for additional clinical data.

[55] After some calls and email exchanges to try to clarify the concerns, C-RNA responded to the 2014 IRN in October. This response included a contention that Health Canada's review of the evidence constituted "nit-picking" not based on facts, and a suggestion that the NNHPD had "veered off from its original founding principles." C-RNA provided extensive submissions on these founding principles, and summarized the evidence on lumbrokinase and its safety. It also again criticized the assumption that lumbrokinase was a bleeding risk and the categorization as a "high risk" product. To counter the hematologist's conclusions, C-RNA provided four expert reports that described potential monitoring tests and spoke to the safety of lumbrokinase. C-RNA also set out further risk mitigation strategies, including laboratory testing to identify patients who are hypercoagulable.

[56] On June 23, 2015, the NNHPD refused the second application. The 2015 Notice of Refusal repeated that the evidence was insufficient to support the safety of Boluoke for OTC use,

as the clinical trial evidence was mainly limited to conditions of hypercoagulable state and did not support licensing to a health population. It again noted that the risk of internal bleeding was not self-diagnosable and could not be mitigated through labeling.

[57] With respect to a professional use option, the 2015 refusal noted that this would have to be a temporary measure for market access, since a product that needed ongoing monitoring and supervision would meet the Prescription Drug List criteria for regulation under the *Food and Drug Regulations*. The NNHPD concluded that licensing as a professional use NHP was not supported since there was no validated monitoring in Canada for lumbrokinase that could be used to monitor bleeding risk. The NNHPD considered the monitoring options discussed in the expert opinion reports, but concluded that they were not recommended since they were not available in Canada and/or did not have an appropriately validated reference range predictive of bleeding. There were also concerns about the feasibility of collecting data during the professional use term, in part because such data was again likely to be directed to patients with a hypercoagulable state and therefore would not establish safety in a healthy population.

C. *Reconsideration/Reassessment and Refusal*

[58] C-RNA requested reconsideration of the 2015 refusal pursuant to section 9 of the *NHP Regulations*. That section provides that if an applicant requests reconsideration of a refusal, the Minister shall give the applicant an "opportunity to be heard in respect of the application," and shall reconsider the application after that opportunity: *NHP Regulations*, ss 9(2)–(3). After the reconsideration, a licence is to be granted if the requirements of section 7 are met, or a "final notice" setting out reasons for refusal will be issued: *NHP Regulations*, s 10.

[59] C-RNA's request for reconsideration raised two primary issues: (1) the classification of lumbrokinase as a "high risk" product; and (2) a concern that the NNHPD "selectively ignored" much of the evidence. With respect to each of these, C-RNA raised a number of sub-arguments. In addition to its substantive concerns, C-RNA made requests regarding the selection of the reviewing officers, and requested a face-to-face meeting to present and answer questions.

[60] On receipt of the reconsideration request, Health Canada conducted an internal review. Prior to convening a meeting with C-RNA, it concluded that there were concerns with how the evidentiary requirements and the Prescription Drug List criteria were communicated to C-RNA before the 2015 refusal. Health Canada therefore decided to "reinstate" the application. On September 24, 2015, the NNHPD sent a "final notice" on the reconsideration, advising that "[t]he submission will recommence at Assessment and this letter will serve as a Submission Reinstatement Notice." The NNHPD indicated that during this further assessment it might require more information, and offered the opportunity to meet with the NNHPD if still requested.

[61] C-RNA took the NNHPD up on the offer of a meeting, and a meeting was arranged for December 2, 2015. At that meeting, representatives from C-RNA met with NNHPD staff, and provided a written and oral presentation. The presentation set out C-RNA's case for licensing, raised issues with NNHPD's "actions and rationales" to date, and asked the question "what would it take for NNHPD to approve lumbrokinase?" At the conclusion of the meeting, the parties agreed that the NNHPD would look to complete its review of the application by the end of January 2016.

[62] The NNHPD sent another IRN on February 1, 2016. The IRN again stated that the evidence filed was insufficient to support the safe use of lumbrokinase and asked for further evidence. The IRN provided a specific response to four studies that had been raised in C-RNA's application, and noted that the majority of the evidence that C-RNA provided "pertains to conditions that infringe on the principles and factors used in establishing prescription status for health products and are insufficient to support the safe use of this product in the target subpopulation." The IRN set out further detail on the principles for determining prescription status, and stated that the recommended uses proposed for Boluoke were not acceptable, as the conditions (blood viscosity and hemorheology) evoke considerations that could not be addressed without involvement of a health care practitioner.

[63] C-RNA responded to the 2016 IRN, restating its case, responding to the identified concerns regarding the studies, but providing no new information.

[64] On July 8, 2016, Health Canada sent a final notice to C-RNA indicating that it upheld the decision to refuse to issue a product licence. The decision attached an Issue Analysis Summary (IAS) prepared by an "Impartial Reviewer" who was a Manager with NNHPD, which included a recommendation to uphold the refusal. That recommendation was accepted by an Acting Director General at NNHPD, who upheld the decision and reasons communicated in the 2015 Notice of Refusal. The IAS sets out reasons similar to those set out in the 2015 refusal:

> The clinical trials involving LK [lumbrokinase] have been conducted predominantly in individuals with more serious health conditions such as ischemic cerebrovascular disease or diabetic with complications (including peripheral neuropathy, coronary heart disease, diabetes nephrosis, dementia, etc.). As a result, there is a scarceness of studies conducted in otherwise healthy

> individuals such as those envisioned as typically [*sic*] consumers for NHPs and of the available studies where extrapolation to an otherwise healthy person may be broached (e.g., Liu 2007; Deng 2000; Pan 2008; Yan 2008), there are limitation[s].
>
> […]
>
> Therefore, in contextualising all of the available information to the safety of LK when utilised in otherwise healthy persons, it is necessary to bear in mind the prevailing assumptions and expectations regarding NHPs. NHPs are intended for conditions where the consumer is to able to self-manage both the risks of the condition and of the product, used limited practitioner oversight and/or on-going involvement. …
>
> A key aspect of NNHPD's current mandate is to ensure that Canadians have access to NHPs that are safe, effective and of high quality. Consequently, access could be defined as not specific to a particular product and more so to a range of products. Within the range of available products, each should be associated with favourable benefit-to-risk enabling the consumer to self-select the most appropriate product for managing their health needs. …
>
> [Emphasis added.]

[65] The IAS included a list of references and an appendix that summarized clinical evidence reviewed in the prior assessment, and referred to the SEAR prepared in the assessment of Boluoke. The SEAR contains a review and analysis of the evidence submitted by C-RNA. It appears to have been a "working document," updated over time as more information was submitted. In particular, the first 46 pages of the SEAR appear to have been prepared during the initial assessment of the application. The remaining 26 were prepared during the reassessment and include analysis of studies previously considered in the initial assessment.

[66] Having reviewed the regulatory and factual framework, I turn to the specific issues raised by C-RNA.

V. Analysis

A. *Health Canada's Decision was Reasonable*

[67] C-RNA argues that Health Canada misinterpreted the *NHP Regulations*, and that it unreasonably refused its application. As previously noted, C-RNA separated these two arguments in its submissions. I will address the arguments using that structure, while recognizing that they are not entirely independent.

[68] Each of these arguments goes to the merits of the refusal and the reasons for it. Such issues are reviewed on a reasonableness standard: *Winning Combination (FC)* at paras 28–29; *North American Nutriceutical Inc v Canada (Attorney General)*, 2012 FC 1044 at paras 78–79.

[69] In oral submissions, C-RNA argued that the correctness standard should apply to Health Canada's interpretation of the *NHP Regulations*. I disagree. Even prior to the Supreme Court of Canada's decision in *Vavilov*, issued after the hearing of this matter, it was clearly recognized that deference should presumptively be given to administrative decision-makers on questions of interpretation of their "home statute": *Canada (Human Rights Commission) v Canada (Attorney General)*, 2018 SCC 31 at para 27; *Canada (Minister of Citizenship and Immigration) v Vavilov*, 2019 SCC 65 at para 25; *Winning Combination (FC)* at para 28. There is no basis under either the pre-*Vavilov* or post-*Vavilov* framework to depart from that presumption in this case. Both Health Canada's interpretation and its application of the *NHP Regulations* are thus reviewable on the reasonableness standard. *Vavilov* simply confirms this: *Vavilov* at paras 16–17, 23–25.

(1) Health Canada did not err in its interpretation of the *NHP Regulations*

[70] I agree with C-RNA that the *NHP Regulations* are to be interpreted using the "modern" approach to interpretation that has prevailed since at least *Re Rizzo & Rizzo Shoes Ltd*, [1998] 1 SCR 27. There, Justice Iacobucci adopted Professor Driedger's formulation that "the words of an Act are to be read in their entire context and in their grammatical and ordinary sense harmoniously with the scheme of the Act, the object of the Act, and the intention of Parliament": *Rizzo* at para 21. In the case of a regulation, part of the interpretive context is the statute under which the regulations are promulgated—in this case, the *FDA*: *Bristol-Myers Squibb Co v Canada (Attorney General)*, 2005 SCC 26 at paras 37–38.

[71] The Supreme Court has confirmed that this analytical framework applies whether it is a court or an administrative decision-maker that is interpreting the legislative provision: *Vavilov* at paras 117–124. While an administrative interpretation may not bear the formalities of a court decision, and may even be implicit, a reasonable interpretation should be consistent with the text, context and purpose of the legislation: *Vavilov* at paras 121–123.

[72] C-RNA asserts that Health Canada unreasonably interpreted the *NHP Regulations* by introducing terms and requirements not found in the regulations: (a) the need to demonstrate safety in a "healthy population"; (b) reference to "over-the-counter" and "self-care" as the model for use of NHPs; and (c) a requirement that the "benefits" of Boluoke outweigh its "risks." For the following reasons, I disagree that Health Canada's interpretation of the *NHP Regulations* was unreasonable.

(a) *"Healthy population"*

[73] C-RNA argues that the *NHP Regulations* do not require it to show safety or efficacy in a "healthy population," and that Health Canada has unreasonably read that term into the regulations by requiring evidence of safety in such a population. C-RNA notes that subsection 5(*g*) of the *NHP Regulations* only refers to demonstrating safety and efficacy of the NHP when used in accordance with the "recommended conditions of use." C-RNA argues that adding a requirement to show safety in a "healthy population" narrows the regulations, contrary to the general policy of making NHPs more available rather than less.

[74] I do not consider Health Canada's interpretation of subsection 5(*g*) unreasonable. While subsection 5(*g*) refers to safety when the NHP is used in accordance with the "recommended conditions of use," this cannot be considered in isolation from its context. That context includes, significantly, that NHPs are necessarily sold without a prescription, since prescription products are excluded from the definition of NHPs: *NHP Regulations*, s 2(2). As a result, they can be taken without medical supervision as part of an individual's program of "self-care" or "self-medication."

[75] Importantly, Health Canada's concern about the evidence of safety in a healthy population was connected to the difficulties of self-diagnosing whether one is in a hypercoagulable state. If a member of the Canadian public cannot themselves assess whether they are in a hypercoagulable state, they cannot determine whether they fall within the group for whom the product is recommended, or in a group for whom the product presents potential safety

risks. In such circumstances, it is not unreasonable to conclude that the requirement to file evidence demonstrating safety includes evidence that the NHP is safe for the general population.

[76] To recognize this context in assessing whether there is adequate evidence of a product's "safety" is not improperly reading restrictions into the *NHP Regulations* as C-RNA suggests. It is interpreting and applying the regulations based on their "text, context and purpose," as required by the modern principle of interpretation: *Rizzo* at para 21; *Vavilov* at para 120. Indeed, it would be unreasonable, and potentially even reckless, for Health Canada not to consider this non-prescription context in assessing whether the safety of an NHP was adequately established.

[77] C-RNA asserts that many consumers consult with health professionals, including natural health care professionals in particular, regarding the use of NHPs. Be that as it may, the availability of NHPs without a prescription means that they may be readily purchased and taken without such oversight or advice. This ready access and broad availability of NHPs is one of the features and goals of the *NHP Regulations*. I therefore do not view Health Canada's insistence on satisfactory evidence showing safety in a "healthy population" to be adding words to or misinterpreting the regulations.

[78] I reach this conclusion whether the "recommended conditions of use" in C-RNA's application are limited to use by those in a "hypercoagulable state" or not. As noted above, C-RNA's application form identified the recommended use and purpose as being to "reduce blood viscosity" and "improve circulation/hemorrheology," without further limitation or reference to a hypercoagulable state. Elsewhere, C-RNA states that it is seeking claims to reduce

blood viscosity and improve circulation "in hypercoagulable blood state." Various iterations of these health claims were put forward during the assessment process.

[79] If the recommended use is not limited to a particular class of patients, the requirement to demonstrate safety when used in accordance with the "recommended conditions of use" would cover anyone that might seek to reduce blood viscosity or improve circulation. Demonstrating safety in only a subset of that population, namely those with hypercoagulable states, would clearly be insufficient. Even if the recommended use is considered limited to those in hypercoagulable states, it is reasonable for Health Canada to require evidence of safety in a healthy population. The non-prescription context, the inability for a member of the public to assess whether they are in a "hypercoagulable state," and the fundamental statutory and regulatory focus on safety as a priority supports the reasonableness of requiring that safety be demonstrated in healthy populations.

[80] Such a requirement does not "narrow" the regulations, as C-RNA argues. While the *NHP Regulations* implemented a different approach to approval of NHPs so that they could be available for use by Canadians, the policy of the regulations is not to make NHPs available regardless of safety concerns. To the contrary, safety remains a central requirement for regulatory approval. Ensuring that a product is safe for all those who may take it before it is licensed is in no way contrary to the basic policy of the *NHP Regulations*.

[81] C-RNA relies on *Apotex v Canada (Health)*, 2013 FC 1217 [*Apo-Telmisartan*], in which Justice Kane rejected interpretation arguments based on the "broad scheme" of the *Food and*

Drug Regulations in favour of the "ordinary meaning": *Apo-Telmisartan* at paras 98–144. I agree with the Minister that this case does not assist C-RNA. Justice Kane applied the *Rizzo* principles to the regulatory interpretation question before her, considering the words of the regulations and other interpretive tools such as drafting conventions, as well as the context of the regulatory and statutory scheme: *Apo-Telmisartan* at paras 98, 108–109, 125–128, 139–144. The same *Rizzo* approach applies here, but beyond that, the interpretation of "medicinal ingredients" in the context of the *Food and Drug Regulations* is of little assistance in assessing the requirement to file evidence of safety in the *NHP Regulations*. The same is true of C-RNA's reference to paragraphs 136 to 150 of *Apotex Inc v Canada (Health)*, 2015 FC 1161 [*Apo-APIPL*], in which Justice Manson applied the *Rizzo* interpretive principles to the particular regulatory issue before him.

[82] C-RNA's related argument that Health Canada did not define "healthy population" is unpersuasive. Health Canada's communications included detailed descriptions of identified shortcomings in the studies filed. It was clear that Health Canada was concerned that the evidence filed related mainly to subjects with a hypercoagulable state and that it was looking for evidence showing safety among the broader population, not limited to those under medical care for blood conditions. Indeed, as early as 2011, Health Canada advised C-RNA that "[t]he evidence must support the safety in the general health population and not a subpopulation which will be monitored closely by a physician[.]" C-RNA's stated concern in its submission on reconsideration that the guidance documents do not define "healthy populations" seems largely to be a semantic argument rather than any real attempt to address the concerns raised by Health

Canada. I see no basis on which a licence applicant could have reasonably misunderstood what Health Canada was looking for.

[83] Finally, I am also unpersuaded by C-RNA's argument that the requirement for evidence showing safety in healthy populations inappropriately shifts the *NHP Regulations* from being "use-based" to being "user-based." Both the "recommended conditions of use" and the assessments of safety and efficacy necessarily imply consideration of who may be using the product. In other words, there is no use without a user, and it is not inappropriate to consider both elements of that equation in assessing safety.

(b) *"Over-the-counter" and "self-care"*

[84] C-RNA's argument that other terms used by Health Canada, such as "over-the-counter" and "self-care," are not found in the *NHP Regulations* is of no merit. While the term "over-the-counter" is not used in the *NHP Regulations* (or, for that matter, the *FDA* or the *Food and Drug Regulations*), it is commonly used to describe non-prescription products and is fair shorthand for drugs available without a prescription. The fact that NHPs are by definition available without a prescription comes directly and expressly out of the regulations: *NHP Regulations*, s 2(2). Thus all NHPs are intended to be available for OTC use. Referring to NHPs as "non-prescription" products or being for "non-prescription use" would clearly be consistent with the *NHP Regulations*. I fail to see how using the term "over-the-counter" or OTC changes this in any way.

[85] Similarly, the term "self-care"—along with related terms such as self-medication, self-diagnosis, self-manage, or self-direct—simply describe the context in which many Canadians take NHPs and other OTC medications. They are terms used in both the RIAS and the underlying Standing Committee Report that C-RNA relies on. I see nothing unreasonable in Health Canada's use of those terms or its reliance on the context those terms describe in making a decision on NHP licensing.

(c) *"Risk vs benefit"*

[86] C-RNA argues that Health Canada inappropriately required it to demonstrate that the benefits of Boluoke outweighed the risks of the product. Such an assessment is contemplated in both the 2006 Guideline (which indicates that the "totality of evidence…must be in support of the benefits of the product outweighing any risks") and the 2012 Guideline (which indicates that the "benefit-to-risk profile of a product is always considered prior to a product licensing decision being made"). C-RNA asserts that the *NHP Regulations* contain no risk-benefit requirement or analysis, and that it was unreasonable to impose one.

[87] I do not agree that it is unreasonable for Health Canada to consider the balance between risk and benefit in considering whether to licence an NHP. Subsection 5(*g*) requires an applicant to file evidence demonstrating the "safety and efficacy" of the NHP. In my view, the reference to "safety" in the context of the *NHP Regulations* inherently implies consideration of risks to health. This is so even though, as C-RNA submits, something can be considered "safe" even if it has associated risks. Similarly, "efficacy" implies consideration of benefit, as the efficacy of the product is its ability to bring about the desired health benefit, *i.e.*, the health claim made by the

product. Thus the introduction to the 2012 Guideline that correlates safety to risk and efficacy to benefit is not unreasonable:

> This guidance document provides information to help product licence applicants determine the evidence (type and amount of data) to provide as part of a product licence application to support the safety (risk) and efficacy (benefit) of natural health products (NHPs) that make modern health claims.
>
> [Emphasis added; footnote omitted.]

[88] I agree with C-RNA that the concepts of safety and efficacy as set out in subsection 5(*g*) are interrelated. However, I do not agree with its contention that efficacy implies safety, particularly for an NHP, or that an efficacious NHP is necessarily safe. To the contrary, a product might be very effective in bringing about a particular health result, and yet be unsafe because it also poses other health risks. Similarly, a product may be very safe, but have little or no efficacy in bringing about a particular health claim.

[89] Rather, the concepts of safety and efficacy are interrelated in part because what is considered acceptably safe for a health product may depend on the product's effectiveness. Put more plainly, we might accept a somewhat greater safety risk in a product that works very well, or accept a lower health benefit in a product that is very safe. At the same time, a product that is dangerous may be unacceptable regardless of how effective it is. While less relevant in the circumstances of this case, it is worth noting, as the 2012 Guideline does, that safety and efficacy are also interrelated because an ineffective product may impact health by not treating a condition in the manner expected, or causing a consumer to forego other treatment options.

[90] C-RNA is correct that this balancing between safety and efficacy is not spelled out in the *NHP Regulations*. No particular approach to assessing safety and efficacy is set out. Rather, the assessment is left to the Minister. As the Federal Court of Appeal noted, "[t]hese are matters for the Minister to decide": *Winning Combination (FCA)* at para 58.

[91] The Minister has clearly taken an approach to safety and efficacy that includes consideration of a balancing between the two. This approach is set out in both the 2006 and 2012 Guidelines. I cannot conclude that this approach to assessing the regulatory requirements of "safety" and "efficacy" and exercising the discretion to issue a product licence is unreasonable in the context of the *NHP Regulations*. Nor is expressing this through the commonly understood language of "risk-benefit," or requiring an applicant to demonstrate that an NHP's health benefits outweigh its risks before it is licensed, unreasonable.

[92] I also note that C-RNA does not appear to have raised any concern with having to demonstrate that the benefits of Boluoke outweighed its risks at any time during the regulatory process, or to have argued that such a requirement is contrary to the *NHP Regulations*. Health Canada's 2013 refusal of C-RNA's first application included reference to the need for the benefit to outweigh the risk. So did its 2014 IRN and the 2015 refusal. As set out above, this approach has been in the Minister's Guidelines since at least 2006. Yet despite raising a number of criticisms during the process, C-RNA did not challenge the need for a positive risk-benefit balance. While the Minister did not object to C-RNA raising the issue on this judicial review, applicants are generally precluded from raising new arguments on judicial review that have not

been raised before the administrative decision-maker: *Alberta (Information and Privacy Commissioner) v Alberta Teachers' Association*, 2011 SCC 61 at paras 22–26.

[93] I therefore reject C-RNA's arguments that Health Canada unreasonably interpreted the *NHP Regulations*.

(2) Health Canada's refusal of the application was reasonable

[94] C-RNA argues that Health Canada acted unreasonably in its assessment of Boluoke by (a) treating it as a "high risk" product under the 2012 Guideline; (b) applying too high a standard for evidence of safety; (c) refusing to license Boluoke when licences had been issued for other oral fibrinolytic enzyme products; (d) failing to accept the potential for mitigation of safety risks; and (e) ignoring evidence that favoured a finding that Boluoke is safe. While C-RNA asserted that a number of these matters also raised issues of procedural fairness, I find that they go to the merits of the decision rather than the process by which that decision was reached and are therefore more appropriately considered to be challenges to the substantive reasonableness of the decision. For the reasons below, I disagree that any of C-RNA's arguments shows Health Canada's decision to be unreasonable.

[95] In assessing these arguments, which invoke both the particular health concerns flagged by Health Canada and its review and assessment of the scientific evidence, I am particularly mindful of the caution that the Court is "not to act as an academy of science": *Greenpeace Canada v Canada (Attorney General)*, 2016 FCA 114 at paras 60–61. The Court does not sit in review of the scientific judgment of those to whom the legislation assigns the task of assessing

safety and efficacy. As a general observation, I view a significant portion of C-RNA's arguments on reasonableness as an invitation to do just that.

(a) *Treatment of Boluoke as a "high risk" product*

[96] As noted above, Health Canada's 2012 Guideline classifies NHPs making modern health claims into one of three risk categories, and provides guidance on the nature of the evidence expected to demonstrate safety and efficacy in each category. The 2012 Guideline describes the high risk category as follows:

> **High Level of Risk:**
>
> This level applies to those products/ingredients that, through their intended use, present a serious health risk. This category includes NHPs with the narrowest safety margin and effective dose range, as well as those used for treatment, cure, and prevention of serious diseases that require supervision by a health care practitioner, or are debilitating or potentially life threatening without effective treatment (refer to section 2.4.1. for the definition of serious disease/condition claims). High level of risk includes, but is not limited to, schedule A disease/conditions.
>
> [Emphasis added.]

[97] Lumbrokinase was considered to be a "high risk" product based on Health Canada's concerns about its fibrinolytic activity and resulting concerns about internal bleeding, and the associated concern that the conditions that it is generally used to treat are conditions that usually involve health practitioner supervision. The IAS that gave the reasons for the final refusal stated the following:

> A general concern of substances that may enhance the breakdown of forming/formed clots (fibrinolytics) or inhibit platelet aggregation (anti-thrombotics) to prevent initial clot formation is the risk of internal bleeding, which may be tolerable when

> considered in the context of potentially life-threatening conditions (e.g., treatment of myocardial infarctions or pulmonary embolisms). However, in the context of an NHP, where the majority of evidence relates to the purported efficacy of a substance as an anti-platelet therapy, a reasonable assumption would be that the substance is inherently riskier. …
>
> Similarly, the trepidation with LK are typical of the therapeutic class (e.g., fibrinolytic agents). Hence, the categorization of LK as high risk, in the absence of likely or certain evidence of bleeding is not an unreasonable postulation given its therapeutic applications and fibrinolytic activity.
>
> […]
>
> The predominant uses of LK as evidenced in the submitted clinical trials and reflected through the clinical experiences of the experts (when LK is administered to cancer patients, persons with atherosclerosis, blocked veins, blood clots, etc.), its ability to significantly influence not only tPA and the absence of clinical trial investigating its pharmacokinetics contribute to the gaps in the evidence. While efficacy of LK is not the focus of the IAS, the information on its clinical applications includes a report of it effects being comparable to warfarin (Su et al. 2006), a prescription drug that is used to treat or prevent blood clots in veins or arteries, which can reduce the risk of stroke, heart attack, or other serious conditions. …
>
> [Emphasis added; typographical errors corrected.]

[98] C-RNA argues that there was no basis to consider Boluoke as "high risk." It states that Boluoke does not claim to treat or cure a serious disease, that it ought to properly be considered a "food," and that Health Canada's decision to categorize Boluoke as high risk was based on information related to intravenous fibrinolytic products that are not comparable to Boluoke as an oral capsule.

[99] I disagree that the categorization of Boluoke as high risk was unreasonable. With respect to the question of health claims, C-RNA's licence application states that Boluoke is to be used to

"reduce blood viscosity" and "improve circulation/hemorrheology." Its proposed amendments to these claims were variations on one or both of these themes. As noted above, elements of C-RNA's application also indicated that it sought approval of these claims specifically "in hypercoagulable blood state." Either way, the claims indicate that they are intended to provide a health benefit in connection with blood viscosity and/or coagulation, even if they do not expressly use the words "treat," "cure" or "prevent." Indeed, as early as 2011, Health Canada gave its view that the claims "reduce blood viscosity" and "improve circulation" related to the fibrinolytic activity of lumbrokinase. It maintained this position throughout, noting in its final rejection in 2016 that "it is clear that the therapeutic benefits for LK are directed towards cardiovascular health."

[100] The scientific primer agreed to by the parties indicates that patients with high blood viscosity (hyperviscosity) can have neurologic complaints such as loss of vision, and can be associated with various acute and chronic conditions including being a factor associated with heart disease and stroke. Similarly, hypercoagulable states are associated with a predisposition to develop blood clots, which can result in pulmonary embolism, cerebral venous thrombosis, heart attack and stroke. Based on these descriptions, it is not unreasonable to associate lumbrokinase with the "treatment, cure and prevention of serious diseases." Indeed, I note that "thrombotic and embolic disorders" are expressly listed on Schedule A (now Schedule A.1) to the *FDA*, referred to in the 2012 Guideline as indicating a high risk categorization. Again, this association is reasonable even if the health claims are not phrased as "will treat blood hyperviscosity" or "for prevention of pulmonary embolism."

[101] The same is true of Health Canada's decision not to treat Boluoke as a food. The 2012 Guideline does indicate that demonstrating food use of a medicinal ingredient can support the safety of the ingredient. However, while earthworms have traditionally been used as a food, the same cannot be said of Boluoke, which contains a refined extract derived from earthworms. The conclusion that Boluoke is a high risk product is not inconsistent with the possibility that safety of other NHPs may be shown through evidence of their use as a food.

[102] C-RNA's asserts that Health Canada's concern about internal bleeding, and thus its high risk categorization, was based on a comparison to intravenous drugs and an "erroneous assumption" that Boluoke would be administered intravenously. It points to the passage from the 2011 IRN underlined at paragraph [45] above, suggesting that the problems with the NNHPD's analysis began with this error.

[103] I believe C-RNA significantly misreads the passage. As I read it, there is no assumption that Boluoke will be administered intravenously. To the contrary, Health Canada is assessing the "potential safety concerns for oral products" and the absence of evidence "demonstrating long-term oral safe use of fibrinolytic enzymes" [emphasis added]. Health Canada appears to be underscoring the serious nature of fibrinolytics as evidenced by the fact that they are used to treat patients with serious conditions, and are therefore administered intravenously and under medical supervision. In other words, the reason that fibrinolytics raised safety concerns for self-care is not that they are administered intravenously, but that they present such risks and are used to treat such serious conditions that they are generally seen in a medical setting in which they are administered intravenously and under physician care. I also note that of the three scientific

papers cited by Health Canada in the 2011 IRN as sources for the "concern of the safety of fibrinolytic enzymes," at least one bears a title indicating that it relates to "combined use of nattokinase and aspirin," suggesting oral and not intravenous administration.

[104] In any event, it is clear from both the identified passage and from the extensive later communications from Health Canada that the safety concern about the risk of internal bleeding stemmed from lumbrokinase's activity as a fibrinolytic agent, not its route of administration. This concern was based on the physiological mechanisms of action and evidence of potential bleeding risks arising in both pharmaceutical and natural fibrinolytics and intravenous and oral administration. There was no dispute that lumbrokinase has fibrinolytic activity, and that it shows this activity when administered orally. Indeed, this was the very ground on which C-RNA sought approval of Boluoke as an NHP.

[105] Health Canada's concern about risk of internal bleeding stemmed from demonstrated risks arising in products in the same therapeutic class. While C-RNA sought to draw distinctions based on asserted mechanisms of action and other activity, its own application was based on the lumbrokinase being "one of the most powerful fibrinolytic agents." As noted by Health Canada in the passage reproduced at paragraph [97], the available evidence showed lumbrokinase to have effects similar to oral warfarin, a drug that is only available by prescription.

[106] C-RNA's demands that Health Canada produce specific evidence showing that oral lumbrokinase can cause internal bleeding, and its submission that Health Canada's failure to do so shows that its assessment was unreasonable, show a misunderstanding of the nature of the

concern and the onus that was on C-RNA. Health Canada's concern was reasonably based on its scientific assessment of the evidence before it, and it was not required to "prove" that lumbrokinase is unsafe. Rather, the onus was on C-RNA under the *NHP Regulations* to file information in support of its application demonstrating the safety and efficacy of lumbrokinase. This fundamental framework error seems to permeate much of C-RNA's submissions to Health Canada and to this Court, in which the NNHPD is denounced as unreasonable for not producing studies showing the dangers of lumbrokinase. Health Canada is not required to show that a product is unsafe; an applicant is required to show that it is safe. While Health Canada could clearly not manufacture safety concerns entirely out of thin air, there is no evidence that it did so. It raised a supported and reasonable concern about safety, based on reasoned reference to safety evidence of similar products, including oral fibrinolytics, and the product under review. Having done so, the onus was on C-RNA to provide information to address that concern with evidence that satisfied Health Canada of Boluoke's safety.

[107] C-RNA also claims that the categorization of lumbrokinase as "high risk" is inconsistent with an entry in a chart apparently prepared by a Health Canada official in about 2012. That chart compares various information with respect to lumbrokinase and nattokinase. The final row in the chart is entitled "Previous Risk Classification," and the entry for lumbrokinase is "[w]ould recommend Type III in health adults (product is ***not likely*** to cause any adverse health consequences)" [emphasis in original], whereas the entry for nattokinase is a higher Type II risk. I am unable to draw any conclusions about the reasonableness of Health Canada's categorization from this document. I have no information about what the "Previous Risk Classification" row signified in the chart, when or whether it applied, or whether the stated recommendation was

adopted. In any case, even if Health Canada's risk assessment with respect to lumbrokinase changed, about which there is no information, this does not alone render the later categorization unreasonable.

(b) *Applying too high a standard for evidence of safety*

[108] C-RNA argues that Health Canada's approach to the evidence of safety effectively required it to meet the stringent standards applicable to non-NHP drugs under the *Food and Drug Regulations*. I see no evidence that Health Canada demanded an unduly stringent level of evidence.

[109] As the Court of Appeal stated in *Winning Combination (FCA)*, the very existence of the *NHP Regulations* implies different regulatory standards for the assessment of the safety and efficacy of NHPs and of other drugs: *Winning Combination (FCA)* at paras 14, 45, 58. However, this does not mean that the requirement to demonstrate safety and efficacy is a low hurdle, or that Health Canada is required to accept information that has scientific shortcomings, particularly in respect of a product for which there are identified safety concerns.

[110] The various communications between Health Canada and C-RNA, including the 2015 Notice of Refusal, the subsequent 2016 IRN and the final refusal in 2016, as well as the SEAR prepared internally by Health Canada, set out the nature of Health Canada's review of the various scientific and non-scientific information submitted. From review of these, one can see that Health Canada was not satisfied with the limited evidence filed related to healthy populations, based on issues such as the small number of subjects, duration, absence of statistical

analysis, absence of control groups and discussion of clinical relevance, absence of measurement of hemorheology parameters, and the purposes of the studies.

[111] At no point did Health Canada suggest to C-RNA that it must file evidence equivalent to that required for other drugs under the *Food and Drug Regulations*. To the contrary, Health Canada consistently pointed to its guidelines related to the *NHP Regulations*, which contain guidance on the types of evidence that would be expected, and set out its concerns regarding the shortcomings in the evidence provided. C-RNA's generalized statements that requiring further evidence amounts to requiring evidence of a standard equivalent to that required for other drugs is unpersuasive in this context.

(c) *Other products*

[112] C-RNA claims that it was unreasonable for Health Canada not to grant a licence for its lumbrokinase product when licences have been granted for products containing nattokinase and serratiopeptidase. As noted above, the evidence shows that the three enzymes were part of a broader review by Health Canada of natural fibrinolytics. For example, the IRN sent to C-RNA in 2011 referred to the evidence that would be necessary to support products containing any of the three enzymes. Health Canada approved serratiopeptidase as an NHP in 2013, and a nattokinase product in 2018.

[113] I agree with the Minister that the approval of nattokinase and serratiopeptidase products has no bearing on the reasonableness of the refusal to license Boluoke. The Court has no information regarding what safety studies were filed in support of the nattokinase or

serratiopeptidase products. Even if it did, it is within neither the expertise nor the mandate of the Court to attempt to compare such safety information filed in a different application to determine its applicability to Boluoke. Health Canada was required to assess each product licence application on the basis of the relevant information put forward and available in that application. The outcome of one application is not and cannot be determinative of the outcome of another: *Reddy-Cheminor Inc v Canada (Attorney General)*, 2003 FCT 542 at paras 34–36, aff'd 2004 FCA 102; *North American Nutriceutical* at paras 98, 102–104.

[114] C-RNA argues that it was Health Canada that made nattokinase and serratiopeptidase relevant, by treating them together in 2011 and by referring to nattokinase studies in identifying the bleeding concern. It argues that it is unreasonable to treat them all together, and then approve two of the products but not the third. I disagree. The fact that the safety concerns about the three products arose as part of a broader assessment of natural fibrinolytics does not mean that each has the same safety profile. Nor does it mean that the safety evidence filed by other applicants can be relied on by C-RNA, or assumed to be relevant to Boluoke. The NNHPD addressed these differences in the IAS using another fibrinolytic, bromelain, as an example:

> It is equally acknowledged that not all ingredients asserted to have fibrinolytic properties are regarded as being of higher risk in spite of having similar investigations. As an example, while bromelain has been investigated as an oral drug for the treatment of systemic coagulation-related diseases, its efficacy appears to be of lesser clinically significance than LK and is associated with more studies in persons with less serious underlying health conditions.
>
> [Emphasis added.]

[115] C-RNA criticizes this comparison, suggesting that it indicates that lumbrokinase was being criticized for being a more effective medication. This misses the point. A product with

greater fibrinolytic activity may have greater safety risks precisely because of that higher activity. Both the relative risks and, importantly, the relevant safety studies affect the analysis.

[116] On this application for judicial review, C-RNA filed an expert affidavit from a licenced naturopath that reviewed the 2012 comparison chart described above at paragraph [107] and concluded, among other things, that "the safety profile of lumbrokinase in this document is much better than that of nattokinase." This expert evidence was not before Health Canada and cannot affect the reasonableness of Health Canada's decision: *Association of Universities and Colleges of Canada v Canadian Copyright Licensing Agency (Access Copyright)*, 2012 FCA 22 at para 19. In any case, even leaving aside that the Health Canada chart was prepared long before the approval of a nattokinase product, and therefore could not take into account any information filed in the interim, C-RNA's onus on its licence application was not to demonstrate that lumbrokinase was safer than nattokinase. It was to satisfy Health Canada that Boluoke was safe and effective when used in accordance with the recommended conditions of use. While Health Canada might find comparisons to other products relevant for consideration, they do not form a basis to conclude that Health Canada's assessment is unreasonable.

(d) *Mitigation*

[117] In oral submissions, C-RNA raised an argument that Health Canada's conclusion that the risks of lumbrokinase could not be mitigated was unreasonable and contrary to its own guidelines. C-RNA points to the 2012 Guideline, which indicates that risk mitigation strategies may include "[l]imiting to a sub-population who will benefit." It argues that Boluoke could be limited to those with hypercoagulable conditions, and says that Health Canada's insistence on

evidence of safety in “healthy populations” and its refusal to accept labelling or monitoring by healthcare professionals contradicts its own approach.

[118] C-RNA’s argument appears to focus on certain aspects of the 2012 Guideline to the exclusion of others. Notably, the discussion of mitigation in the 2012 Guideline is introduced by the statement that “[o]nly safety risks that can be mitigated by advisory information such as warning statements or contraindications for mild to moderately harmful outcomes are acceptable for licensed NHPs” [emphasis added]. Health Canada concluded that advisory information could not adequately mitigate risks, since the public could not themselves determine whether they were in the relevant sub-population or not. C-RNA put forward no information to contradict this conclusion. To the contrary, it submitted in response to an IRN that the best way to identify the presence of hypercoagulable blood states is through laboratory testing.

[119] Health Canada also concluded that there was no validated monitoring in Canada for lumbrokinase that could be used to monitor bleeding risk, and that the tests proposed by C-RNA for this purpose, including through a number of expert reports, were not recommended due to unavailability and/or lack of predictive reference ranges. While C-RNA disagrees with this conclusion, this is not a basis for finding it unreasonable. Health Canada raised the potential for practitioner monitoring, received evidence on the issue, and concluded that it was not satisfied that the information supported an approach based on post-market monitoring. Based on the information before the Court, I am unable to conclude that it was unreasonable for Health Canada to conclude that the risk-mitigation strategies proposed by C-RNA were insufficient to mitigate the identified risk of internal bleeding.

(e) *Ignoring evidence*

[120] The licence application for Boluoke and the information provided in response to Health Canada's IRNs included a substantial number of articles, studies, reports and clinical trials. These are reviewed and considered in the SEAR document prepared by Health Canada during the assessment, and are also summarized as an appendix to the IAS that forms the reasons for the 2016 refusal of the reconsideration.

[121] C-RNA argues that Health Canada ignored a variety of evidence that supported the application, including data relating to safety in healthy subjects. It points to, for example, a Phase I clinical trial (Chinese Academy of Sciences 1991), and studies on people with recurrent oral aphthous ulcers (Yang 2008), primary hypertension (Ye 2007) and early stage diabetes (Huang 2009). It also claims that Health Canada ignored the fibrogenic effects of lumbrokinase (Zhao 2007), said to balance its fibrinolytic effects and increase safety, and evidence of the pharmacokinetics of lumbrokinase (Chong, undated).

[122] The difficulty with this argument is that it is directly contradicted by the SEAR and the IAS, which show that the evidence C-RNA claims was ignored was in fact reviewed and considered by Health Canada. Indeed, a number of the studies that C-RNA claims were "ignored" were directly referenced in communications with C-RNA even prior to Health Canada's refusal. Nor is there any convincing indication that Health Canada unduly focused on certain aspects of the studies, took a selective view of them, or inappropriately summarized them.

[123] C-RNA's argument really amounts to an assertion that Health Canada did not give enough weight to certain parts of the clinical evidence, and did not reach the conclusions that C-RNA says should be drawn from it. This amounts to no more than a request that the Court act as an "academy of science" and reassess the evidence that was filed. This is not the Court's function.

[124] I therefore conclude that Health Canada's decision was reasonable, both as to its interpretation and approach to the *NHP Guidelines*, and its refusal of C-RNA's application for a product licence for Boluoke.

B. *Health Canada's Decision was Fair*

[125] In addition to challenging the reasonableness of the refusal, C-RNA says that the process leading to the refusal was unfair. On judicial review of such issues, the Court must be satisfied that the requirements of procedural fairness have been met: *Demitor v Westcoast Energy Inc (Spectra Energy Transmission)*, 2019 FCA 114 at para 26. Whether this is characterized as being review on a "correctness" standard, a "fairness" standard, or "not…according to any particular standard of review," the ultimate question for the Court is whether the procedure was fair having regard to all the circumstances: *Mission Institution v Khela*, 2014 SCC 24 at para 79; *North American Nutriceutical* at para 80; *Winning Combination (FC)* at para 25; *Demitor* at para 26.

[126] The Minister does not dispute that they were under a duty to act fairly in the review and determination of C-RNA's product licence application. The question then becomes what degree of procedural fairness is applicable, a matter that is assessed based on the non-exhaustive factors

outlined in paragraphs 21 to 28 of *Baker v Canada (Minister of Citizenship and Immigration)*, [1999] 2 SCR 817.

[127] In *Apo-APIPL*, Justice Manson considered the degree of procedural fairness owed in the context of an Import Ban under the *Food and Drug Regulations*. Having considered the context and the *Baker* factors, he described the required degree of fairness as being at the "mid-to-low end of the spectrum": *Apo-APIPL* at paras 77–82. A number of the contextual factors addressed by Justice Manson, including the nature and purpose of the legislative policy, the administrative context, the Minister's expertise and discretion, and the economic nature of the interests at stake, are the same or similar in this case. I agree that "mid-to-low end of the spectrum" is an appropriate description of the level of fairness owed to applicants under the *NHP Regulations*. The decision at issue in *Apo-APIPL* was a non-final decision, whereas the decision at issue in this case is a final decision, which may suggest a somewhat higher level of procedural fairness. However, I consider that this difference is already accounted for by the fact that the common law duty of fairness is supplemented by specific procedural requirements in respect of refusal and reconsideration before a final decision is made: *NHP Regulations*, ss 9 and 10.

[128] As Justice Manson noted, even at the mid-to-low end of the spectrum, fairness requires notice and a reasonable opportunity to present one's case and respond to what is presented in opposition: *Apo-APIPL* at paras 82–83, 113. To fulfill this purpose, notice must provide adequate information to allow meaningful participation: *Apo-APIPL* at para 113. This is consistent with the description of Justice Phelan that fairness will be met where the applicant "knew what the

issues were, had a full opportunity to address those issues, and received a clearly reasoned expression of the Minister's opinion": *Apotex Inc v Canada (Health)*, 2009 FC 452 at para 46.

[129] C-RNA raises a fairly lengthy list of concerns with the process. Having reviewed these concerns in the context of the assessment procedure as a whole and the information on the record, I cannot agree that C-RNA was treated unfairly. While the process was certainly lengthy, and while the reconsideration process did not follow a standard form, I am satisfied that the process was fair having regard to all the circumstances. C-RNA was made aware of what the issues were, was given a number of opportunities to address those issues with both evidence and argument before the refusal and on reconsideration, and received a reasoned decision that considered C-RNA's representations and explained the Minister's position.

(1) Disclosure regarding the consulting hematologist

[130] As described above, during the course of the assessment of C-RNA's application, NNHPD officials consulted with an external hematologist. C-RNA claims it was unfair that it was not provided with the name and/or credentials of this hematologist in order to allow it to assess and properly respond to their comments. It also takes issue with how the discussions with the hematologist were recorded and suggests that the hematologist was not asked the right questions.

[131] I disagree that in these circumstances there was an obligation to disclose the identity of the hematologist. NNHPD told C-RNA that it had consulted with a practising hematologist, and set out both the nature of that consultation and the hematologist's views on the question of a

potential monitoring program. The hematologist was not a decision-maker but only a consulted professional with respect to one aspect of the decision. Health Canada remained the party that needed to be satisfied as to the safety of Boluoke. C-RNA was clearly told what issues the hematologist's views were solicited on, was told what those views were, and had the opportunity to respond to them. In my view, this is sufficient in this context to satisfy the requirement to know what the issues are, and have a meaningful opportunity to address them.

[132] Nor was NNHPD obliged to ask any particular questions of the hematologist, or to record its responses in any particular way. The NNHPD was perfectly entitled to seek external input on a relevant matter requiring particular knowledge. It was not obliged to ask particular questions, record either the questions or the answers to them in a written report, or provide full disclosure of all aspects of that consultation to C-RNA to meet the relatively modest requirements of fairness applicable in the matter.

(2) Disclosure of the SEAR and comparison chart

[133] C-RNA argues that fairness required Health Canada to provide it with the SEAR and the 2012 chart in which lumbrokinase was compared to nattokinase. It argues that since it did not know Health Canada's views on the particular issues expressed in those documents, it was unable to respond to them and was thus unable to meaningfully participate in the process. I disagree. Fairness in this context does not require complete disclosure of every internal working document prepared by Health Canada in its assessment of a licence application. It requires notice of the relevant issues with sufficient information and detail to allow the applicant to

meaningfully respond. That information was provided by Health Canada in the various IRN documents and decisions during the course of the assessment of C-RNA's application.

[134] I note that this is not a case in which an issue identified in an internal document was material to the outcome but was not disclosed to the party. To the contrary, the reasons the licence for Boluoke was refused were the same reasons previously identified by Health Canada and that C-RNA had a number of opportunities to address: the concern about a risk of internal bleeding, the absence of adequate evidence of safety to address this concern, the need for practitioner oversight, and the inability to address the concern through labelling since hypercoagulable states could not be self-diagnosed.

[135] In this regard, C-RNA's specific contention that not having the SEAR meant that it did not know Health Canada's position on whether lumbrokinase was on a monograph, and thus whether paragraph 6(1)(*a*) of the *NHP Regulations* applied, is without merit. Paragraph 6(1)(*a*) provides that the Minister shall dispose of a licence application within 60 days if "the only information submitted by the applicant under paragraph 5(g)" is contained in a monograph for the medicinal ingredient contained in Health Canada's *Compendium of Monographs*. There is no evidence that there is a monograph for lumbrokinase in the *Compendium*, and in any event, this was not the "only information" on safety and efficacy filed. C-RNA's reliance on this paragraph is wholly misplaced.

(3) Disclosure of communications with foreign regulatory authorities

[136] C-RNA makes a similar disclosure argument with respect to Health Canada's communications with health agencies in other countries regarding licensing of lumbrokinase. C-RNA asserted in its application that Boluoke had been approved in China and the United States. However, the application included only limited documentation confirming the extent and nature of these approvals to allow Health Canada to assess them or their relevance.

[137] The SEAR prepared by Health Canada showed that it reviewed the documentation provided and found that the Chinese approval was for treatment of ischemic cerebrovascular disease, which was considered a condition not appropriate for self-care. Reference to adverse drug reaction monitoring websites in China were apparently also reviewed, despite the fact that they were in Chinese, and found not to contain relevant information. The NNHPD also made inquiries of other countries, and apparently received responses only from Australia, Brazil, and Oman, each indicating that no lumbrokinase products were available by prescription or non-prescription.

[138] In its August 2015 letter seeking reconsideration of the refusal of the licence, C-RNA suggested that NNHPD "intentionally refused to recognize" that lumbrokinase had been available and used safely for many years in other countries. As part of its reconsideration, Health Canada initiated further correspondence with counterparts in Hong Kong, Australia and at the European Medicines Agency. Each advised that there were no lumbrokinase products authorised in their jurisdictions.

[139] The IAS that accompanied the final refusal decision analyzed the available information regarding foreign approval of the product. With respect to the US, the IAS concluded that it could not infer product safety given the US regulatory framework and the proposed distribution model (*i.e.*, OTC) in Canada. In particular, it noted that C-RNA's own website recommended taking Boluoke under a physician's guidance. With respect to China, the IAS noted that the lumbrokinase products approved in China were classified as chemicals and that China had characterized lumbrokinase as a prescription drug. Overall, the IAS said that the NNHPD had received limited information regarding other regulatory bodies and therefore could not further explore the opportunity to leverage decisions by other regulatory bodies to the licensing of Boluoke under the NHP framework.

[140] C-RNA argues that there was no evidence that Health Canada made inquiries of the United States or China, or went on available websites to confirm information. It also asserts that the NNHPD did not ask the right questions of the foreign agencies, and that there was inadequate follow up with them to obtain further information. C-RNA argues that it was unfair for Health Canada not to have disclosed these emails to it during the assessment process so that it could respond to the information received.

[141] Again, in my view there was no breach of the requirements of procedural fairness. To the extent that C-RNA wished to rely on foreign approvals as information relevant to the safety and effectiveness of Boluoke, it had the onus to present such information in its application. Having failed to provide adequate information on the issue, it can hardly fault Health Canada for failing to "ask the right questions" or adequately follow upon on the inquiries it undertook to

supplement the information in the application. Nor does the duty of fairness applicable in this case require disclosure of every communication that Health Canada had with foreign agencies, particularly on matters that were presumably known to C-RNA such as the registration status of its product in other countries.

(4) The recommendation to reapply under a professional use category

[142] After C-RNA's first application was refused, the NNHPD and C-RNA had a telephone call to discuss a possible pathway to approval of Boluoke as a "professional use" product. C-RNA states that NNHPD suggested that C-RNA reapply under this category, and argues that this was unfair for two reasons. First, the category did not exist, such that C-RNA was essentially misled into filing a reapplication rather than seeking reconsideration of its first application, or challenging the NNHPD's decision on judicial review. Second, it argues that the result was that the NNHPD applied the new 2012 Guideline to its reapplication rather than the 2006 Guideline that it should have applied.

[143] These arguments are unpersuasive. While there was no evidence before me that there was a formal "professional use" category or program, it is clear that the NNHPD gave serious consideration to a potential pathway to licensing that involved practitioner oversight during a period of time to allow for post-market safety data to accumulate. The fact that this approach was ultimately rejected based on Health Canada's assessment that there was no viable monitoring program, and that post-market safety data pertaining to a hypercoagulable population would not show safety in a healthy population, does not render it unfair to propose such an approach for consideration. In any case, the potential for a regular NHP product licence was also considered

for Boluoke, both on the original application and on the reassessment, such that the consideration of a potential "professional use" licence simply gave C-RNA more avenues for potential licensing.

[144] As to the applicability of the 2012 Guideline, I agree with the Minister that at all times, what was ultimately applicable was the *NHP Regulations*, and the requirement that C-RNA show the safety and efficacy of Boluoke. Regardless of which guideline applied, it could not be exhaustive or restrictive: *Apotex v Canada (Health)*, 2017 FC 857 at paras 92–93. Further, while the different guidelines gave different degrees of detail regarding the evidence that could be filed to support safety and efficacy, and took a slightly different approach to the framework for consideration, there is no evidence that the 2012 Guideline imposed a different or higher obligation on C-RNA. C-RNA's assertion that it would have been approved had the NNHPD applied the 2006 Guideline is both impossible for the Court to assess and is undermined by the fact that its first application was refused under that guideline. In any case, I am not satisfied that C-RNA has pointed to any material differences in the guidelines that show that it was materially prejudiced by the use of the 2012 Guideline, even if it could establish a right to have its application determined under the 2006 Guideline.

(5) The reconsideration process

[145] Finally, C-RNA contends that the reconsideration process was conducted unfairly. In particular, it argues that it received a reinstatement and reassessment, but not the reconsideration provided for under the *NHP Regulations*. It also asserts that Health Canada did not follow its own reconsideration process, since it did not send an invitation letter regarding the meeting to

C-RNA, and since the individuals who made the determination to reinstate the application were also involved in the reassessment.

[146] As set out above, the regulatory requirements for a reconsideration set out in the *NHP Regulations* are fairly limited. Paragraph 9(3)(*a*) states that on a reconsideration of a refusal, the Minister shall give the applicant an "opportunity to be heard in respect of the application," while paragraph 9(3)(*b*) states that after that opportunity, the Minister shall reconsider the application.

[147] The parties referred to two Health Canada documents regarding the conduct of a reconsideration under subsection 9(3). One is a guidance document dated October 2008 entitled "*Reconsideration Process: Natural Health Products Directorate, Version 1.0.*" The other is dated March 11, 2016, is marked "Draft" and is entitled "*Standard Operating Procedure: Reconsideration of Decisions Issued for Natural Health Products Submissions – Reconsideration Process Standard Operating Procedure.*" The latter, which I will term the "FDALO SOP," was issued by the Food and Drugs Act Liaison Office (FDALO), and states that it is to be read in conjunction with the NNHPD Reconsideration Process guidance document, which I understand to be the former document.

[148] The NNHPD Reconsideration Process guideline is very brief. It sets out the circumstances in which a reconsideration may be commenced, and provides an "Overview of the Reconsideration Process." That overview notes that the Director General of the NNHPD will manage the process and make the decision on reconsideration based on a review by staff who did

not undertake the original assessment. It also notes that the reconsideration will be based only on the information on which the original decision was made, and that new information would not be taken into consideration.

[149] The draft FDALO SOP clearly remains a draft document, as in addition to the "Draft" marking, a number of sections are not completed, and it contains a number of internal notes. The document is more detailed, setting out various steps in the process. Under the FDALO SOP, a request for reconsideration is assessed for eligibility and the eligible applicant is sent an Eligibility Letter inviting them to file a Request for Reconsideration in a prescribed format. The request may be evaluated by internal review, an external panel or a combination, and an Invitation Letter is sent to the applicant setting out the nature of the review and inviting them to meet. The FDALO SOP also sets out the relative involvement of FDALO (which appears to be primarily screening and coordination) and the NNHPD (substantive assessment on the reconsideration, potentially in association with an external panel). Like the NNHPD Reconsideration Process guideline, the draft FDALO SOP contemplates the reconsideration being conducted by assessment officers not involved in the initial assessment.

[150] As the Minister concedes, the process followed in the case of C-RNA's reconsideration was not "textbook." It certainly did not follow the draft FDALO SOP document, as there was no Eligibility Letter or Invitation Letter. Rather, as noted above, the NNHPD did an initial screen and saw grounds for concern in how it had communicated the factors contributing to the classification of lumbrokinase as "high risk" and the application of the Prescription Drug List principles. C-RNA's application was therefore reinstated even prior to the need for an in-person

meeting. Nor did the process follow the NNHPD Reconsideration Process document, as the NNHPD allowed for the possibility of filing new evidence, issuing an IRN after the December 2, 2015 meeting. It appears that Health Canada officials were aware of these differences, as there was some internal discussion regarding what process applied and whether to call the ultimate decision a "reconsideration" decision.

[151] I cannot find that the reconsideration process, considered as a whole, was unfair or failed to comply with the requirements of the *NHP Regulations*, despite the fact that the process did not conform with either potentially applicable document, and apparently did not entirely conform with C-RNA's expectations. In particular, I note that C-RNA did receive a substantive reconsideration of its application, that the reconsideration was undertaken by officials who had not undertaken the original assessment, and that C-RNA had the "opportunity to be heard in respect of the application" through the December 2, 2015 meeting.

[152] The fact that no formal "Invitation Letter" was sent to C-RNA does not affect the fairness of the process. C-RNA was clearly given an opportunity for a meeting, and there were extensive exchanges regarding the nature and form of that meeting. C-RNA gave a thorough presentation at that meeting setting out its views on why its application should be granted. To conclude that there is unfairness because this information was not conveyed through an "Invitation Letter" as described in a draft process document would be to put form well over substance.

[153] I also see no unfairness or "conflict of interest" as C-RNA alleges in the fact that those involved in the initial screening were also designated as assessment officers for the substantive

reconsideration. In any event, the reconsideration itself, and in particular the preparation of the IAS, appears to have been conducted by an NNHPD Manager who was not involved in either the original assessment or the reconsideration screening, and the final decision was made by the Acting Director General of the NNHPD.

[154] The fact that the NNHPD issued an IRN in February 2016, asking for further information, shows that it had decided not to confine its review to information previously filed. This is contrary to the approach described in the NNHPD Reconsideration Process document. However, I agree with the Minister that if anything, this adds to the fairness of the process by giving C-RNA a further opportunity to make its case. Health Canada concluded that certain issues regarding the categorization and the necessary evidence were not communicated clearly enough. Seeking to rectify that by communicating those concerns to C-RNA and giving it a further opportunity to address them cannot be considered unfair. To the contrary, the internal reconsideration process required under the *NHP Regulations* is presumably designed to address not only potential errors in the substantive evaluation of the application, but any remediable unfairness that may have arisen during its review, which a reconsideration may correct: *Re: Sound v Fitness Industry Council of Canada*, 2014 FCA 48 at para 87. I note in this regard that the concerns identified by Health Canada were of an entirely different nature than those identified by the Court in *Winning Combination*, which were found not to be curable on reconsideration: *Winning Combination (FC)* at paras 87, 130, 143; *Winning Combination (FCA)* at paras 46, 87.

[155] Nor do I accept C-RNA's argument that there was a breach of procedural fairness because Health Canada did not answer its questions about what specific evidence it had to file in support of its application. The *NHP Regulations* do not specify a particular form of evidence, and the guidelines provide guidance on what evidence may be filed but do not purport to limit the *NHP Regulations*. Indeed, the 2012 Guideline expressly states that "other options for supporting safety and efficacy may be considered depending on the circumstances." Health Canada referred C-RNA to the information in the guidelines on a number of occasions, and set out in detail the reasons that the evidence filed was not considered sufficient. I do not see the duty of fairness as imposing a higher obligation of guidance on Health Canada. Ultimately, Health Canada's regulatory role is to assess the application filed by C-RNA, and not to act as an advisor or consultant providing extensive detail on what it ought to file.

[156] In my view, the requirements of the *NHP Regulations* and the common law duty of procedural fairness were met in the reconsideration. C-RNA was given notice of refusal of its application with reasons, as required by subsection 9(1) of the *NHP Regulations*. It made a request for reconsideration and was given an opportunity to be heard in respect of the application as required by paragraph 9(2)(*a*). The Minister reconsidered the application after the hearing, as required by paragraph 9(2)(*b*). And the Minister provided a final notice of refusal setting out the reasons for it, as required by subsection 10(2). Throughout, the requirements of notice setting out the substance of the issues, an opportunity to be heard and a decision made by an independent and impartial decision-maker were met. The fact that the process may have been termed a "reassessment" rather than a "reconsideration," and that C-RNA was provided an additional opportunity to provide new evidence during the course of it does not render the process unfair.

VI. Conclusion

[157] I agree with the Minister that the history of the matter shows that throughout the assessment of C-RNA's application for an NHP product licence, Health Canada considered that there was not enough evidence of the safety of lumbrokinase in healthy populations to show that it was safe for non-prescription use. To use Justice O'Keefe's term, this was the "key missing link" in demonstrating safety under recommended conditions of use: *North American Nutriceutical* at para 104. C-RNA filed a variety of other information, and frequently argued both that the evidence that it had filed should be enough and that Health Canada's approach was wrong-headed, but it never filed information satisfactory to Health Canada to fill this gap in the evidence. Health Canada's assessment of safety was conducted on the basis of objective scientific considerations, and in a fair and transparent manner: *Winning Combination (FCA)* at para 94.

[158] The application for judicial review is therefore dismissed.

[159] I encourage the parties to reach an agreement on costs. If they are unable to do so, they may file written submissions on the following basis:

- The Minister shall file written submissions on costs, in letter format, not to exceed three pages single-spaced, by June 26, 2020. The Minister may attach a bill of costs as an appendix.

- C-RNA shall file written submissions on costs, in letter format, not to exceed three pages single-spaced, by July 17, 2020. C-RNA may attach as an appendix a bill of costs and/or

a submission, not to exceed one page, addressing specific line items in the Minister's bill of costs (if filed).

- The Minister may file reply submissions, in letter format, not to exceed one page single-spaced, by July 24, 2020. The Minister may attach as an appendix a submission, not to exceed one page, addressing specific line items in C-RNA's bill of costs (if filed).

- If the foregoing dates are unworkable for the parties, they may consent to extend them, provided all materials are filed by August 14, 2020, or they may address the Court further.

JUDGMENT IN T-1304-16

THIS COURT'S JUDGMENT is that

1. The application for judicial review is dismissed.

2. If the parties are unable to agree on costs, they may be spoken to in accordance with the reasons given.

"Nicholas McHaffie"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

DOCKET:	T-1304-16
STYLE OF CAUSE:	CANADA RNA BIOCHEMICAL INC V CANADA (MINISTER OF HEALTH) AND ATTORNEY GENERAL OF CANADA
PLACE OF HEARING:	TORONTO, ONTARIO
DATES OF HEARING:	NOVEMBER 18-19, 2019
JUDGMENT AND REASONS:	MCHAFFIE J.
DATED:	JUNE 4, 2020

APPEARANCES:

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Rebecca Sewell Karen Lovell	FOR THE RESPONDENTS

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Attorney General of Canada Toronto, Ontario	FOR THE RESPONDENTS