Federal Court  Cour fédérale

Date: 20170201

Docket: T-1516-15

Citation: 2017 FC 127

Ottawa, Ontario, February 1, 2017

PRESENT: The Honourable Mr. Justice Phelan

BETWEEN:

APOTEX INC

Applicant

and

MINISTER OF HEALTH and ATTORNEY GENERAL OF CANADA

Respondents

JUDGMENT AND REASONS

I. Introduction

[1] This judicial review is in respect of a decision by the Minister of Health that had the effect of rejecting Apotex Inc.'s [Apotex] Abbreviated New Drug Submission [ANDS] for 100 mg capsules of the drug Apo-Progesterone.

[2] The real matter in dispute is the conduct of a panel of toxicological experts [Reconsideration Panel or Panel] within Health Canada tasked with advising on the merits of an initial decision to issue a Notice of Non-Compliance/Withdrawal [NON-W] for Apo-Progesterone, and its recommendation to the Minister's delegate.

[3] The concern from the Minister of Health's perspective was that Apo-Progesterone had "unusually high" levels of the non-medicinal ingredient Sodium Lauryl Sulfate [SLS].

II. Background

A. *Preliminary*

[4] Apotex is Canada's largest pharmaceutical manufacturer, producing over 300 pharmaceuticals. It is primarily a "generic drugs" manufacturer and is well versed in the pharmaceutical regulatory approval process.

[5] The Minister of Health [Minister] is responsible for administering the *Food and Drugs Act*, RSC 1985, c F-27, and the *Food and Drug Regulations*, CRC, c 870. The sale of a new drug in Canada requires Ministerial approval in the form of a Notice of Compliance [NOC].

[6] The decision on the acceptability of submissions for an NOC is delegated to the Director General of the Therapeutic Products Directorate [DG and TPD respectively]. In the case of generic drugs, companies must submit an ANDS that establishes equivalence to a "reference" product that has been approved in Canada.

[7] Apotex's drug, Apo-Progesterone, was to be a generic version of the reference product Prometrium. The purpose of Apo-Progesterone was "as an adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma". The medicinal ingredient in both drugs is 100 mg of progesterone.

[8] The Minister's overarching responsibility in this drug approval process is to be satisfied of the safety and efficacy of the new drug. Toward that end, the ANDS must contain sufficient information and material for the Minister to be able to assess safety and efficacy. Therefore, the manufacturer must supply information on every ingredient (medicinal or non-medicinal), as well as any additional information required by the Minister.

[9] In respect of an ANDS, the DG acts on the advice of the Bureau of Pharmaceutical Science [BPS] within the TPD which has the operational responsibility for evaluating each ANDS. The evaluation consists of a review of the drug's active pharmaceutical ingredients, the manufacturing process, and all of the drug's ingredients as to potency, purity, stability, and safety.

[10] After review of the ANDS, the DG may approve the drug by issuing an NOC. If the DG is not satisfied, the DG notifies the company who then has the opportunity to supplement its ANDS.

[11] Where, after a comprehensive review, the DG finds the submission deficient or incomplete, a Notice of Non-Compliance [NON] issues. And, where following a sponsor's

response to a NON the DG is of the view that the submission remains deficient, a NON-W issues.

[12] In the event of a NON-W, a manufacturer may request that the decision be reconsidered in accordance with the Guidance for Industry: Reconsideration of Final Decision Issued for Human Drug Submissions [Guidance]. This is described as a formal dispute resolution mechanism.

[13] The Guidance in place at the relevant time provided that the DG was to determine the appropriate procedures. The DG may appoint a panel to advise him or her on the dispute; this panel could be an external panel, an existing Scientific Advisory Committee, or an internal panel within Health Canada.

[14] The Guidance provides that if the sponsor files in the Federal Court during the reconsideration process, the reconsideration will be terminated.

[15] Irrespective of what type of panel is struck, the reconsideration of an ANDS – a matter of factual dispute – proceeds with the BPS and the sponsor attending a meeting with the panel, which includes formal presentations followed by a question and answer period.

Subsequently, the Office of Science [OOS]within the TPD prepares a summary of the process and information considered, including the advice received. From that it makes a recommendation to the DG, who then determines whether or not to uphold the NON-W.

B. *Dispute*

[16] On October 31, 2012, Apotex submitted its ANDS for Apo-Progesterone 100 mg capsules. It adequately responded to inquiries on dosage forms.

[17] On January 8, 2014, the TPD sent a Request for Clarification [clarifax] inquiring about the "unusually high level" of SLS in the proposed formulation. SLS is a non-medicinal ingredient that has been used as an excipient for over 50 years in Canada and around the world.

[18] SLS constituted [redacted][1] per capsule and would result in a daily intake of SLS of up to [redacted][2] per day.

[19] Apotex recognized that the use of SLS in this degree of concentration would be an issue for Health Canada. In its ANDS it relied on the fact that the US Food and Drug Administration [FDA] had approved an Apotex product (Apo-Cyclosporine) which results in an even higher maximum daily intake of SLS.

Apotex acknowledged that the amount of SLS in its Apo-Progesterone exceeded the maximum potency for SLS listed in the FDA's Inactive Ingredient Guide, a database of non-medicinal ingredients in FDA approved drug products.

[20] In relying on the FDA approval of Apo-Cyclosporine, however, Apotex did not provide particulars of the FDA filing regarding SLS levels nor did Apotex provide the basis for the FDA

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approval. There was no reference in the ANDS to Apotex's other products marketed in Canada – none of which have comparable SLS levels.

[21] The Health Canada clarifax of January 8, 2014, noted that the information on Apo-Cyclosporine was not acceptable given that the two drugs had considerably different characteristics and Apo-Cyclosporine had not been approved in Canada.

[22] Following a series of exchanges between Apotex and Health Canada, the Minister issued a Notice of Non-Compliance [NON] on April 17, 2014.

[23] On December 29, 2014, the Minister issued a NON-W.

[24] On March 16, 2015, Apotex filed a request for reconsideration of the NON-W. It asked for a further review, the rescission of the NON-W, and issuance of an NOC, or alternatively that the matter be determined by an external panel.

[25] The DG established an internal four-person panel. A meeting was convened on June 5, 2015, where Apotex was asked about, but not provided with, three studies concerning SLS that were available online. This is one part of Apotex's complaint of breach of procedural fairness.

[26] Prior to the meeting, the Chair had prepared notes for a decision and circulated them to panel members. This is another element of Apotex's challenge to procedural fairness.

[27] The issue before the panel remained the issue raised on January 8, 2014 – the safety and efficacy of the new drug containing the SLS levels to which Health Canada had referred.

C. *SLS Final Decision*

[28] Following the meeting between the panel and the representatives from Health Canada and from Apotex, the panel issued its report on July 16, 2015, concluding that the evidence was not sufficient to support the limit of [redacted][3] of SLS (maximum daily intake of [redacted][4] SLS) in Apo-Progesterone capsules as proposed by Apotex.

[29] The evidence consisted of several repeat dose studies on rats and one study on dogs. The Bureau of Metabolism, Oncology and Reproductive Sciences [BMORS] had previously rejected one of the studies, a rat study, that suggested a limit of [redacted][5] of SLS daily would be acceptable. The BMORS's conclusion had led to the NON-W.

[30] The panel reviewed the toxicological evidence for SLS, including the report by Apotex's consultant SafeBridge Consultants, BMORS's review reports, and assessments available in the public domain.

[31] The panel concluded that overall the evidence with respect to toxicology of SLS suffered from multiple shortcomings, was of generally low quality, and did not meet current regulatory standards.

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[32] Further, the panel opted to take a conservative approach in assessing SLS due to the fact that the evidence put forward by Apotex was incomplete, sometimes unpublished, and did not comply with Good Laboratory Practice. The studies cited by Apotex were missing important information on the SLS being tested and the evaluation of toxicological endpoints.

[33] The panel went on to address the major point of disagreement – BMORS's conclusion, referred to above, regarding the rat study. That study was missing critical information, and the data gap meant that the NOAEL (no observable adverse effects level) was not reliable.

[34] The panel referred to three publications from the European Chemicals Agency [ECHA], the Organization for Economic Co-operation and Development [OECD], and the National Industrial Chemicals Notification and Assessment Scheme [NICNAS], found on their respective websites, which supported the BMORS's position. These were publicly available and were not considered by Apotex.

[35] The panel did, however, agree with Apotex that gavage studies in rats may not be a suitable method of determining SLS toxicity (gavage is the force feeding of the animal by a tube directly into the stomach).

[36] The panel rejected Apotex's position that a one-year dog study should be accepted instead of a rat study. The rat study showed effects on the liver and kidney, whereas the dog study did not contain the detailed information necessary for a critical review.

[37] Finally, the panel concluded that the USFDA approval of cyclosporine capsules containing SLS was not sufficient to support Apotex's contention that its SLS levels for Apo-Progesterone were safe and effective. The panel found firstly that the claim was missing documentation, and secondly that the TPD did not approve excipient levels based solely on the fact that such levels had been approved by foreign regulatory agencies.

[38] The above recitation of the panel findings shows that the exercise engaged in by the panel was detailed, technical, and based on expert knowledge.

[39] Thereafter, the OOS accepted the panel's conclusion recommending the ANDS not be approved. The OOS reviewed the panel report and added some further comment by way of support for the recommendation.

[40] The DG accepted the recommendation of the panel that the NON-W be upheld, which had been supported by the OOS.

In a letter dated July 16, 2015, the DG communicated her decision that the level of SLS in the formulation for Apo-Progesterone "is not considered qualified". This is the Final SLS Decision.

[41] Apotex made subsequent attempts to obtain a reconsideration of the panel's reconsideration; this is referred to below.

[42] The judicial review was filed September 8, 2015, more than 30 days after the Final SLS Decision.

III. Analysis

A. *Issues*

[43] There are three issues in this judicial review:

1. Should the judicial review be dismissed because it is out of time?
2. Was the Final SLS Decision made in a procedurally fair manner?
3. Is the Final SLS Decision reasonable?

B. *Standard of Review*

[44] It is well settled that procedural fairness in the reconsideration process is subject to the correctness standard of review (*Apotex Inc v Canada (Health)*, 2015 FC 1161 at para 55).

[45] It is also well settled, and agreed here, that the standard of review of the Final SLS Decision is reasonableness as set forth in *Dunsmuir v New Brunswick*, 2008 SCC 9 at para 47, [2008] 1 SCR 190 [*Dunsmuir*], "reasonableness is concerned mostly with the existence of justification, transparency and intelligibility within the decision-making process. But it is also concerned with whether the decision falls within a range of possible, acceptable outcomes which are defensible in respect of the facts and law."

C. *Out of Time*

[46] The issue of timeliness was not raised until the filing of memorandas of argument. Apotex suggests that this was somehow unfair; however, given that a motion to strike a judicial review is only rarely granted as a preliminary matter, there was nothing unfair in the Respondent's conduct.

[47] The elements to be examined, as outlined in *Apotex v Canada (Health)*, 2012 FCA 322 at para 12, leave to appeal to SCC refused, 35209 (April 25, 2013), while not exclusive, include whether:

- there was a continuing intention to dispute the issue;
- the application has some merit;
- there is any prejudice to the Respondent flowing from the delay; and
- there is a reasonable explanation for the delay.

[48] Following the July 16, 2015 Final SLS Decision (which is the operative decision for the purposes of judicial review and the calculation of the 30-day time limit), Apotex's CEO was in contact with the DG to communicate Apotex's views on the procedure, and in late July he indicated that Apotex wished to meet and to have the matter considered again.

[49] On August 6, 2015, the DG indicated that she was not favourably inclined to Apotex's request and on August 27, 2015, in response to similar repeated requests, the DG again wrote to inform Apotex that the situation would not change.

[50] Apotex has suggested that it was somehow led on by the DG to think that a reconsideration of the reconsideration might occur. This is an unfair and unreasonable interpretation of the DG's words and actions. Apotex has gone so far as to imply, based on two recent judgments of Justice Manson in *Apotex Inc v Canada (Health)*, 2015 FC 1161 and *Apotex Inc v Canada (Health)*, 2016 FC 673, that Health Canada was somehow antagonistic to Apotex.

[51] These two decisions are irrelevant, and neither they nor this record even comes close to establishing such antagonism. It was a desperate plea to excuse Apotex's failure to file on time with this Court.

[52] It was unreasonable in fact and an error in law for Apotex to think that the DG could grant a further reconsideration. The DG was *functus* as of July 16, 2015, and it is unreasonable to confuse a polite negative response with some positive expectation of a further reconsideration.

[53] The record is thin as to a reasonable justification for delay. At best, Apotex's CEO had an honest but mistaken belief that his further reconsideration request might be accepted.

[54] However, since that seems to be the case, Apotex would be on the horns of a dilemma. Under the Reconsideration Guidelines, if Apotex had filed its judicial review, any reconsideration (or the hope thereof) would end because the Guidelines stipulate that filing with the Federal Court terminates any reconsideration.

[55] I am prepared to accept that this was the situation facing Apotex, and thus it has a reasonable explanation for delay.

[56] Apotex argued that if the August 6 negative response is the commencement of the 30-day filing period, it made its filing within 30 days (filed after the Labour Day weekend).

[57] A continuing intention to dispute and the existence of some merit to the judicial review are clearly established and have not been seriously challenged.

[58] The Respondent says that the lateness causes prejudice. However, this is a theoretical prejudice confined to doing some kind of violence to the principle of "finality of decisions". There is no actual prejudice; that is, no one took steps to their detriment in reliance on the finality of the decision. Furthermore, the delay is short (being approximately 22 days late).

[59] Given these factors and the significant public interest in decisions related to the public's health, Apotex's request for an extension of time (if needed, and it is) is granted.

D. *Procedural Fairness*

[60] With respect to the procedural fairness issues, these are examined separately from the reasonableness of the Decision.

(1) External Panel

[61] Apotex complains that it was unfair that an external review panel was not established in accordance with its request. However, there is nothing in the Guidelines which would serve to create a legitimate expectation for such an appointment. The Guidelines acknowledge a discretion – "may" be appropriate to appoint an external panel – which the DG possesses. As Justice Kane found in *Apotex Inc v Canada (Health)*, 2013 FC 1217 at para 76, 445 FTR 64, there is no hard and fast rule that a reconsideration should be conducted by an external panel.

[62] Apotex has not challenged the appointment process except in respect of it not being an external panel.

[63] Although Apotex had a right and legitimate expectation to an independent and impartial panel in accordance with the Guidelines, this does not mean that it had a right to an external panel (or that only an external panel could be independent and impartial). Internal panels were contemplated by the Guidelines so long as their conduct (and ultimate decision) was independent and impartial.

[64] This panel was instructed on the requirement of impartiality, and I fail to see that it departed from this requirement.

[65] The fairness of the reconsideration process must take into account that it was an expert panel which was appointed – a panel whose existing knowledge and expertise was central to the process.

(2) Reasonable Apprehension of Bias

[66] Apotex complains that the Chair of the panel, by creating a draft memorandum which he indicated that he intended to use in the final decision, showed either that he had a closed mind or that there was a reasonable apprehension that he had decided the matter before hearing from Apotex.

[67] There is debate, even in judicial circles, about whether a decision maker should - to use an outmoded expression - “put pen to paper” before a hearing. While the preferred practice may be not to do so for many of the concerns raised here, whether the existence of a “draft” establishes a reasonable apprehension of bias depends on how far it has gone toward being cast in stone.

[68] In this case, I do not see evidence that the Chair had cast his decision. It is evident that these were preliminary thoughts, and that he and the other panel members who had a copy of the draft kept an open mind. In fact, the panel accepted Apotex’s submissions in respect of one matter (that of gavage) where the draft pointed to a different conclusion. The panel took into account any new information presented.

[69] In my view, a reasonable person taking a realistic, thoughtful, and practical view of the circumstances would not conclude that any panel member would likely decide the case unfairly. The cases relied on by Apotex can be distinguished on their facts. It is one thing to make notes and to sketch out potential conclusions (as in this case); it is quite another to arrive at a hearing with a draft decision essentially ready to be signed or delivered.

[70] I cannot find a basis to uphold Apotex's complaint.

(3) Opportunity to be heard

[71] Apotex complains that the panel did its own research and raised three new studies at the hearing, thus depriving it of a full opportunity to be heard and to address the studies from OECD, ECHA and NICNAS.

[72] Given the nature of the reconsideration – a factual review conducted by experts – it is to be expected that a panel would update themselves on the "state of the art" and potentially review well known (to experts in the field) and publicly available sources.

[73] Apotex had the very same ability and they had, internally and through consultants, the capacity to do the same.

[74] Further, when asked about these studies at the hearing, Apotex did not request time either at the hearing or at any time following to deal with what they now say was new evidence. There was adequate time between the close of the meeting/hearing and the release of the panel's

recommendation to ask for an opportunity to make submissions on these studies. A party who feels that it has been subjected to procedural unfairness must raise this with the first-instance forum (*Hennessey v Canada*, 2016 FCA 180 at paras 20-21, 267 ACWS (3d) 479). Despite ample opportunity to do so, Apotex did not.

[75] Apotex makes too much of a panel member's request to the Chair that he send her the studies because she had not found them. This is hardly an admission of obscurity, and such a request does not establish that the studies were not well known or publicly available. The convenience in having the person with the studies forward them along is not evidence of hidden or unknown works. Apotex has not shown that it could not have found the publications, nor has it shown that it could not have exercised its right to make submissions on this material.

[76] Furthermore, Apotex cannot complain that it was not asked to submit documentation on Apo-Cyclosporine during the panel's question and answer period. Apotex knew that the Apo-Cyclosporine issue with the FDA and the supporting documents and rationale were front and centre in this case. It knew that the SLS levels were problematic for Health Canada.

It was Apotex's burden to make its case and to address these issues. It was not for the panel to draw out Apotex on these points.

(4) Regulatory Standards

[77] Lastly for these procedural fairness issues, Apotex complains that the panel and later the DG concluded as a matter of law that the formulation "did not meet current regulatory

standards". Apotex contends that the panel cannot make legal conclusions and failed to identify the particular regulatory standards in issue.

[78] Apotex mischaracterizes the panel's reference to regulatory standards. The phrase was used in the context of the scientific evidence put forward by Apotex. The reference indicates that Apotex's evidence and the studies it relied upon were deficient in such areas as Good Laboratory Practice, description of SLS, and evaluation of endpoints.

[79] It was well within the panel's mandate to comment upon the nature and quality of Apotex's scientific evidence.

[80] Therefore, Apotex's complaint of breach of natural justice/procedural unfairness is not accepted.

E. *Reasonableness of Decision*

[81] Apotex asserts that the Final SLS Decision was unreasonable because it did not consider the approval of products by the FDA which contain SLS and the related clinical experience.

[82] The criteria against which to assess the Final SLS Decision have already been laid out in reference to the test in *Dunsmuir*. As indicated earlier, the Court owes deference to this expert panel on matters of fact within its expertise.

[83] Contrary to Apotex's contention that the FDA approval was not considered (or considered adequately), the record shows that the Minister, throughout this process, continually raised the issue of the SLS levels and offered multiple opportunities for Apotex to provide evidence to establish that high levels of SLS could be accepted.

[84] From the very beginning, Health Canada officials sought out the details, documents, and rationale behind the FDA's approval of Apo-Cyclosporine. The panel found that the TPD did not approve excipient levels based solely on the fact that they had been approved by foreign regulatory agencies.

[85] The TPD practice is consistent with the Minister's obligation to be "satisfied" as to the safety and efficacy of a new formulation. To merely accept a foreign approval – absent legislative authorization – would be an abdication of Ministerial responsibility.

[86] Apo-Cyclosporine is a different drug, used for different purposes and for a different patient base. There is nothing unreasonable in the panel or the Minister requiring Apotex, who bore the burden of proof, to justify the acceptance of levels of SLS in Apo-Progesterone similar to those in Apo-Cyclosporine.

[87] The panel found that Apotex had not justified its position with respect to reliance on the FDA approval of Apo-Cyclosporine. I can find nothing unreasonable in this conclusion, which was made well within the panel's area of expertise.

[88] Therefore, this ground of review is also dismissed.

IV. Conclusion

[89] For all these reasons, this judicial review will be dismissed with costs.

JUDGMENT

THIS COURT'S JUDGMENT is that the application for judicial review is dismissed with costs.

"Michael L. Phelan"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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