Federal Court  Cour fédérale

Date: 20170925

Docket: T-2011-15

Citation: 2017 FC 857

Ottawa, Ontario, September 25, 2017

PRESENT: The Honourable Mr. Justice Roy

BETWEEN:

APOTEX INC.

Applicant

and

MINISTER OF HEALTH AND ATTORNEY GENERAL OF CANADA

Respondents

JUDGMENT AND REASONS

I. Overview

[1] In what is in the process of becoming a veritable saga concerning its Apo-Omeprazole Magnesium Tablets [or Apo-Omeprazole], the applicant is once again before this Court on a judicial review application, presumably pursuant to section 18.1 of the *Federal Courts Act* (RSC, 1985, c F-7). The relief sought is concerned with the decision of the Minister of Health [the Minister or the respondent] to cancel the reconsideration of Apotex's submission concerning a

Notice of Compliance [NOC] in respect of Apotex's Apo-Omeprazole (omeprazole magnesium) Tablets and to treat its submission as withdrawn. That is the decision of the Minister of November 16, 2015, cancelling the reconsideration which the applicant wants squashed; the applicant also seeks that the Minister continue to process its submission without fettering her discretion "by insisting on strict compliance with policies and guidelines which do not have force of law". The applicant seeks an alternative remedy:

- to direct the Minister to submit its preferred question to a reconsideration panel;
- to direct that it be afforded two hours to argue its case relative to its preferred question;
- to direct that it be permitted to make submissions to the Reconsideration Panel concerning "missed opportunities" for dispute prevention and/or earlier resolution of the dispute;
- to direct the Minister's delegates to be prohibited from having *ex parte* discussions with the Reconsideration Panel.

[2] The applicant, Apotex Inc. [Apotex], manufactures and distributes pharmaceutical products, primarily generic versions of drugs that were first marketed by other manufacturers. All drug manufacturers must obtain a NOC from the Minister of Health to sell new drug products in Canada (section C.08.002(1) of the *Food and Drug Regulations*, CRC, c 870 [*Regulations*]). A NOC can be obtained in several ways. In this case, the mechanism for seeking a NOC for a generic version of an existing approved drug is the "abbreviated new drug submission" [or ANDS]. If the ANDS meets the requirements of the *Food and Drugs Act* [the Act], RSC, 1985, c F-27 and the *Food and Drug Regulations*, the Minister issues a NOC (para C.08.004(1)(a)).

[3] One of the criteria that an ANDS must meet is demonstrating that the drug is "bioequivalent" to the existing drug, referred to as the "Canadian reference product" [or CRP]. Bioequivalence is not defined in the *Regulations*, but Health Canada has published guidelines on how companies can demonstrate bioequivalence. For our purpose, it will suffice to refer to the notion of "bioequivalent" as described by Dr. Scott Appleton, who testified by affidavit for the respondent. Dr. Appleton holds degrees in pharmacology and toxicology, including a Doctorate (Ph. D.), as well as a Post-Doctoral Fellowship from Tulane University. He described bioequivalence at para 22 of his affidavit:

> The generic drug is considered to be bioequivalent to the CRP once it has been determined that it can be expected to have the same systemic effects as the CRP when administered to patients under the conditions specified in the labeling of the "innovative drug".

[4] Apotex originally filed an ANDS in 2000 for "Apo-Omeprazole" tablets, an anti-ulcer drug. That submission was understood to be approved on March 7, 2003, given that the examination of the submission had been completed but placed on patent hold. In other words, the NOC would not issue until requirements of the *Patented Medicines (Notice of Compliance) Regulations* (SOR/93-133) were met, which, as I understand it, was on the expiration of a patent owned by AstraZeneca Canada Inc. (*Apotex Inc. v Canada (Health)*, 2012 FCA 322 [*Apotex*], at para 4). Health Canada later revoked approval because the ANDS lacked a study showing bioequivalence to the CRP when the drug is taken with a high calorie/high fat meal. Eventually, in 2013, Apotex submitted a high calorie/high fat study (OMEC03), but the Minister refused to issue a NOC because she was not satisfied with the results of the study and the study design.

[5] Apotex pursued a reconsideration process offered by Health Canada, but the Minister ultimately refused reconsideration after the parties could not agree on a proper question to put to an external expert panel. Health Canada wanted to focus on bioequivalence and the only study, actually conducted in 1998, offered to demonstrate bioequivalence under fed conditions, the main reason why the approval given earlier had been revoked through a "Notice of Non-Compliance Withdrawal Letter" [or NONW] of February 9, 2009. In fact, the need to consider bioequivalence under fat fed conditions goes back to December 2008 when the Minister advised Apotex that its original examination was not completed in spite of the letter of March 2003. I note that this initial ANDS, which did not include a fat fed study resulted in the notice of Notice of Non-Compliance Withdrawal Letter on February 9, 2009. The Minister denied a request for reconsideration on July 27, 2009. An ANDS was resubmitted in 2013. It is that process which started in 2013 that gives rise to this latest judicial review application.

[6] The record at the time the decision was made to refuse reconsideration, on November 16, 2015, shows that Apotex's proposed questions focused on whether Apo-Omeprazole was "safe and effective" rather than "bioequivalent". During the hearing of this case, Apotex's counsel suggested that the company knew it had to show bioequivalence, but hesitated to use that term in proposing reconsideration questions because it was concerned the Minister was fettering her discretion by strictly applying the bioequivalence standards in the guidelines. That was certainly not evident on the face of the exchanges, over a number of weeks, between Apotex and the Minister's agents. Rather, the evidence points in the direction of Apotex seeking to circumvent the requirement to show bioequivalence.

[7] Apotex is asking the Court to quash the Minister's November 16, 2015, decision to cancel the reconsideration process. The applicant argues that the Minister's proposed question results from the fettering of the Minister's discretion and does not meet its legitimate expectations. The respondent argues firmly that the question submitted by the Minister does not signal any fettering of its discretion and the applicant cannot validly expect that its question will prevail. Furthermore, the respondent argues that the matter cannot be returned for the reconsideration to take place on the basis that the question proposed by the Minister would be reasonable. In the view of the respondent, that is an alternative that is not possible since it is not a remedy sought by the applicant in its notice of application of December 1, 2015.

[8] For the reasons that follow, there is no fettering of discretion and the legitimate expectations of the applicant are not defeated.

II. Legislative and policy framework

[9] Setting out the legislative and policy framework within which a manufacturer like Apotex obtains a NOC provides necessary context for the facts. There are three key legislative and policy aspects to this file: obtaining a NOC for an ANDS; meeting the "bioequivalence" criterion; and the reconsideration process.

[10] A NOC following an abbreviated new drug submission is based on less information than would be the case for a completely new drug, but the Canadian reference product and the drug for which compliance is sought must be, *inter alia*, bioequivalent. The requirement for a drug manufacturer to obtain a NOC before selling a new drug in Canada is set out under subsection

C.08.002(1) of the *Regulations*. That provision provides that an ANDS, but also other types of submissions, must be "satisfactory" to the Minister for her to issue the NOC:

C.08.002 (1) No person shall sell or advertise a new drug unless	**C.08.002 (1)** Il est interdit de vendre ou d'annoncer une drogue nouvelle, à moins que les conditions suivantes ne soient réunies :
(a) the manufacturer of the new drug has filed with the Minister a new drug submission, an extraordinary use new drug submission, an abbreviated new drug submission or an abbreviated extraordinary use new drug submission relating to the new drug that is satisfactory to the Minister;	**a)** le fabricant de la drogue nouvelle a, relativement à celle-ci, déposé auprès du ministre une présentation de drogue nouvelle, une présentation de drogue nouvelle pour usage exceptionnel, une présentation abrégée de drogue nouvelle ou une présentation abrégée de drogue nouvelle pour usage exceptionnel que celui-ci juge acceptable;
(b) the Minister has issued, under section C.08.004 or C.08.004.01, a notice of compliance to the manufacturer of the new drug in respect of the submission; and	**b)** le ministre a délivré au fabricant de la drogue nouvelle, en application des articles C.08.004 ou C.08.004.01, un avis de conformité relativement à la présentation;
(c) the notice of compliance in respect of the submission has not been suspended under section C.08.006.	**c)** l'avis de conformité relatif à la présentation n'a pas été suspendu aux termes de l'article C.08.006.
(d) [Repealed, SOR/2014-158, s. 10]	**d)** [Abrogé, DORS/2014-158, art. 10]
...	(…)
(2) A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following:	**(2)** La présentation de drogue nouvelle doit contenir suffisamment de renseignements et de matériel pour permettre au ministre d'évaluer l'innocuité et l'efficacité de la drogue

	nouvelle, notamment :
…	(…)

It is clear that the ultimate purpose of the *Regulations* is to establish the safety and effectiveness of a new drug one wishes to sell or advertise in Canada. Not only does that transpire from the *Regulations*, but the Supreme Court of Canada, in another case involving omeprazole (but not omeprazole magnesium), commented that "(t)he *FDA* objective is 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, [2006] 2 SCR 560, para 12).

[11] If an innovator wishes to bring to market a new drug, its submission must include, pursuant to C.08.002(1):

> (g) detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended;
>
> (h) substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions recommended;

As Justice Layden-Stevenson noted in *Reddy Cheminor Inc.v Canada (Attorney General)*, 2003 FTC 542, 233 FTR 271, this kind of information is typically voluminous; the evidence in that case suggested that it could range from 100 to 300 volumes of data.

[12] There is fortunately a less expensive route that is made available in appropriate cases: the abbreviated new drug submission [or ANDS]. If a manufacturer wishes to copy a marketed drug, as opposed to bringing to market a completely new drug, it may avoid providing voluminous

detailed reports and data demonstrating the required safety and effectiveness. The *Regulations* allow for a comparison with the Canadian reference product, a term defined in the *Regulations* in the following fashion:

C.08.001.1 For the purposes of this Division,	**C.08.001.1** Les définitions qui suivent s'appliquent au présent titre.
Canadian reference product means	***produit de référence canadien*** Selon le cas :
(a) a drug in respect of which a notice of compliance is issued under section C.08.004 or C.08.004.01 and which is marketed in Canada by the innovator of the drug,	**a)** une drogue à l'égard de laquelle un avis de conformité a été délivré en application des articles C.08.004 ou C.08.004.01 et qui est commercialisée au Canada par son innovateur;
(b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued under section C.08.004 or C.08.004.01 cannot be used for that purpose because it is no longer marketed in Canada, or	**b)** une drogue jugée acceptable par le ministre et qui peut être utilisée pour la détermination de la bioéquivalence d'après les caractéristiques pharmaceutiques et, le cas échéant, les caractéristiques en matière de biodisponibilité, lorsqu'une drogue pour laquelle un avis de conformité a été délivré en application des articles C.08.004 ou C.08.004.01 ne peut être utilisée à cette fin parce qu'elle n'est plus commercialisée au Canada;
(c) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in	**c)** une drogue jugée acceptable par le ministre qui peut être utilisée pour la détermination de la bioéquivalence d'après les caractéristiques pharmaceutiques et, le cas échéant, les caractéristiques en matière de biodisponibilité, par

paragraph (a); (*produit de référence canadien*)	comparaison à une drogue visée à l'alinéa a). (*Canadian reference product*)

[my emphasis]

[13] The brand name drug (it is typically the case) marketed by the innovator is copied, and the "generic drug" will receive a NOC as long as it satisfies the conditions prescribed by the *Regulations*. It is C.08.002.1 that is particularly relevant. I reproduce it in its entirety in view of its importance in this case:

C.08.002.1 (1) A manufacturer of a new drug may file an abbreviated new drug submission or an abbreviated extraordinary use new drug submission for the new drug where, in comparison with a Canadian reference product,	**C.08.002.1 (1)** Le fabricant d'une drogue nouvelle peut déposer à l'égard de celle-ci une présentation abrégée de drogue nouvelle ou une présentation abrégée de drogue nouvelle pour usage exceptionnel si, par comparaison à un produit de référence canadien :
(a) the new drug is the pharmaceutical equivalent of the Canadian reference product;	**a)** la drogue nouvelle est un équivalent pharmaceutique du produit de référence canadien;
(b) the new drug is bioequivalent with the Canadian reference product, based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics;	**b)** elle est bioéquivalente au produit de référence canadien d'après les caractéristiques pharmaceutiques et, si le ministre l'estime nécessaire, d'après les caractéristiques en matière de biodisponibilité;
(c) the route of administration of the new drug is the same as that of the Canadian reference product; and	**c)** la voie d'administration de la drogue nouvelle est identique à celle du produit de référence canadien;
(d) the conditions of use for the new drug fall within the conditions of use for the Canadian reference product.	**d)** les conditions thérapeutiques relatives à la drogue nouvelle figurent parmi celles qui s'appliquent au

	produit de référence canadien.
(2) An abbreviated new drug submission or an abbreviated extraordinary use new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following:	**(2)** La présentation abrégée de drogue nouvelle ou la présentation abrégée de drogue nouvelle pour usage exceptionnel doit contenir suffisamment de renseignements et de matériel pour permettre au ministre d'évaluer l'innocuité et l'efficacité de la drogue nouvelle, notamment :
(a) the information and material described in	**a)** les renseignements et le matériel visés :
(i) paragraphs C.08.002(2)(a) to (f), (j) to (l) and (o), in the case of an abbreviated new drug submission, and	**(i)** aux alinéas C.08.002(2)a) à f), j) à l) et o), dans le cas d'une présentation abrégée de drogue nouvelle,
(ii) paragraphs C.08.002(2)(a) to (f), (j) to (l) and (o), and subparagraphs C.08.002.01(2)(b)(ix) and (x), in the case of an abbreviated extraordinary use new drug submission;	**(ii)** aux alinéas C.08.002(2)a) à f), j) à l) et o) et aux sous-alinéas C.08.002.01(2)b)(ix) et (x), dans le cas d'une présentation abrégée de drogue nouvelle pour usage exceptionnel;
(b) information identifying the Canadian reference product used in any comparative studies conducted in connection with the submission;	**b)** les renseignements permettant d'identifier le produit de référence canadien utilisé pour les études comparatives menées dans le cadre de la présentation;
(c) evidence from the comparative studies conducted in connection with the submission that the new drug is	**c)** les éléments de preuve, provenant des études comparatives menées dans le cadre de la présentation, établissant que la drogue nouvelle :
(i) the pharmaceutical equivalent of the Canadian reference product, and	**(i)** d'une part, est un équivalent pharmaceutique du produit de référence canadien,
(ii) where the Minister considers it necessary on the basis of the pharmaceutical	**(ii)** d'autre part, si le ministre l'estime nécessaire d'après les caractéristiques

and, where applicable, bioavailability characteristics of the new drug, bioequivalent with the Canadian reference product as demonstrated using bioavailability studies, pharmacodynamics studies or clinical studies;

pharmaceutiques et, le cas échéant, d'après les caractéristiques en matière de biodisponibilité de celle-ci, est bioéquivalente au produit de référence canadien selon les résultats des études en matière de biodisponibilité, des études pharmacodynamiques ou des études cliniques;

(d) evidence that all test batches of the new drug used in any studies conducted in connection with the submission were manufactured and controlled in a manner that is representative of market production; and

d) les éléments de preuve établissant que les lots d'essai de la drogue nouvelle ayant servi aux études menées dans le cadre de la présentation ont été fabriqués et contrôlés d'une manière représentative de la production destinée au commerce;

(e) for a drug intended for administration to foodproducing animals, sufficient information to confirm that the withdrawal period is identical to that of the Canadian reference product.

e) dans le cas d'une drogue destinée à être administrée à des animaux producteurs de denrées alimentaires, les renseignements permettant de confirmer que le délai d'attente est identique à celui du produit de référence canadien.

(3) The manufacturer of a new drug shall, at the request of the Minister, provide the Minister, where for the purposes of an abbreviated new drug submission or an abbreviated extraordinary use new drug submission the Minister considers it necessary to assess the safety and effectiveness of the new drug, with the following information and material:

(3) Le fabricant de la drogue nouvelle doit, à la demande du ministre, lui fournir, selon ce que celui-ci estime nécessaire pour évaluer l'innocuité et l'efficacité de la drogue dans le cadre de la présentation abrégée de drogue nouvelle ou de la présentation abrégée de drogue nouvelle pour usage exceptionnel, les renseignements et le matériel suivants :

(a) the names and addresses of the manufacturers of each of the ingredients of the new drug and the names and addresses of the manufacturers of the new

a) les nom et adresse des fabricants de chaque ingrédient de la drogue nouvelle et les nom et adresse des fabricants de la drogue nouvelle sous sa

drug in the dosage form in which it is proposed that the new drug be sold;	forme posologique proposée pour la vente;
(b) samples of the ingredients of the new drug;	**b)** des échantillons des ingrédients de la drogue nouvelle;
(c) samples of the new drug in the dosage form in which it is proposed that the new drug be sold; and	**c)** des échantillons de la drogue nouvelle sous sa forme posologique proposée pour la vente;
(d) any additional information or material respecting the safety and effectiveness of the new drug.	**d)** tout renseignement ou matériel supplémentaire se rapportant à l'innocuité et à l'efficacité de la drogue nouvelle.
(4) For the purposes of this section, in the case of an abbreviated new drug submission, a new drug for extraordinary use in respect of which a notice of compliance has been issued under section C.08.004.01 is not a Canadian reference product.	**(4)** Pour l'application du présent article, dans le cas d'une présentation abrégée de drogue nouvelle, la drogue nouvelle pour usage exceptionnel à l'égard de laquelle un avis de conformité a été délivré en application de l'article C.08.004.01 n'est pas un produit de référence canadien.
[my emphasis]	[je souligne]

[14] The scheme of the *Regulations* appears to be relatively straight forward. The goal is to have safe and effective medicines; in order to achieve that goal the manufacturer may bring an ANDS if the conditions are met, one of which being that the new drug is bioequivalent with the Canadian reference product. As I read para C.08.002.1(1) and (2), this is not a discretionary option. The goal is for medicines to be safe and effective, and the way to get there passes through section C.08.002.1, which includes bioequivalence. As I read the *Regulations*, those requirements cannot be circumvented.

[15] The Minister must therefore consider the bioequivalence between the Canadian reference product and the new drug in its generic version. If the generic product is bioequivalent to the reference product, which has already been approved, then it should be acceptable despite not providing “detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended” and “substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended” (para C.08.002 (2)(g) and (h)), which undeniably constitutes a heavy burden. But bioequivalent it must be.

[16] The *quid pro quo* is that the ANDS does not include the voluminous information described at C.08.002(2)(g) and (h) as seen at C.08.002.1(2)(a)(*i*). If the requirements of C.08.002.1 are satisfied by a generic manufacturer, it will not have to present the extensive evidence that was required of the innovator. Pursuant to subsection C.08.004(1), the Minister must issue a NOC if the ANDS complies with subsection C.08.002.1 as set out above. The NOC that would be issued in those circumstances “shall constitute a declaration of equivalence for that new drug” (C.08.004(4)).

[17] The ANDS is submitted to the Therapeutic Products Directorate [or TPD] at Health Canada. It is naturally the Minister of Health who has the authority to issue the NOC; this authority is typically delegated to the Director General of the TPD.

III. Context

[18] It is helpful to put this case in its broader context before considering further the mechanism of "reconsideration" that is the subject of the challenge in this case.

[19] The NOC sought by Apotex in the early 2000's had received a positive reception from Health Canada. On March 7, 2003, Health Canada wrote to Apotex to confirm that the examination of the ANDS for Apo-Omeprazole (Omeprazole magnesium) was completed. It is not disputed that this signalled a positive examination, but the final determination could not be communicated in view of the fact that there was a patent in place.

[20] On December 5, 2008, Apotex was advised that its ANDS was not "approvable at this time". The reason for the position change was that the earlier decision was based on the ingestion of the tablet in circumstances where the person was fasting (OMEC14) and where the meal was low in fat and calories (OMEC13 and OMEC16). It appears that with greater experience with this kind of medication, Health Canada came to the realization that submissions had to include the full spectrum, from fasted to standard fed conditions. That includes not only low fat/low calorie meals, but also high fat meals. Thus, the satisfaction of the bioequivalence requirement needed evidence under both fasted and standard fed conditions, which the ANDS did not provide.

[21] The letter went on to request that Apotex submit a high fat fed pharmacokinetic study, or a high fat fed pharmacodynamics study in patients or any other scientific rationale with data that

would support evidence of bioequivalence. Given the delay in reaching a negative conclusion, Health Canada offered its assistance in discussing an appropriate study design and committed to quickly consider the evidence in the context of the entirety of the submission and to perform an expeditious review in order to decide on the disposition of the submission.

[22] Two things appeared to be very clear. Health Canada was insisting on bioequivalence and evidence of bioequivalence had to be under both fasted and high fat fed conditions. We now know that Apotex never produced satisfactory evidence of bioequivalence under high fat fed conditions in its initial ANDS.

[23] Non-compliance was found by the Minister and reconsideration was denied. Apotex challenged on judicial review more than a year later. Apotex sought to argue before this Court that it was entitled to its NOC because it claimed that it had acquired a vested right. In *Apotex Inc. v Canada (Health)*, 2011 FC 1308; 400 FTR 28, my colleague Justice Robert Barnes reported that following the December 5, 2008, letter, the Minister issued a notice of non-compliance withdrawal letter for Apo-Omeprazole Tablets. A request for reconsideration of the decision to issue the Notice of Non-Compliance was also denied, this time on July 28, 2009. The Challenge to the three "decisions" was brought on August 26, 2010. Apotex had argued that the "decisions" were "unlawful, unreasonable, unfair, discriminatory, illogical, scientifically untenable and biased" (para 14). Barnes J. concluded that the application was out of time. Nevertheless, my colleague considered if Apotex had a vested right in view of the March 7, letter. If there is a vested right to a NOC, arguably there may be an entitlement to bring judicial review at any time to enforce the vested right. He concluded:

> [33] It seems quite obvious to me that until a NOC is issued, a proponent enjoys no vested interest in a favourable outcome at least with respect to issues that properly fall within the Minister's lawful discretion (ie. pertaining to public safety and efficacy). There is no legal significance attaching to an application for a NOC that has been placed on patent hold. The Minister is fully entitled to revisit scientific issues at any point in the process up to the actual issuance of a NOC. It is only at that point that the Minister's examination is completed in accordance with C.08.004 of the *Food and Drug Regulations*, RSC 1985, c F-27.

[24] Apotex appealed (2012 FCA 322; 443 NR 291). The Federal Court of Appeal agreed with the Federal Court that Apotex's application was out of time. Furthermore, the Court rejected the argument that the Minister is compelled to issue a NOC once Apotex was notified that the submission was satisfactory, at the time, for the purpose of the *Regulations*. The purpose of the Act and the *Regulations* being to bring safe and effective medicines to market, the Court of Appeal found that it would be absurd to "construe the Regulations in such a way that the Minister could be compelled to issue a NOC even if she was not satisfied that the drug in question is safe and effective" (para 30). Moreover, the Court of Appeal did not accept that Apotex had a legitimate expectation that the NOC would be issued once the patent hold was over: the legitimate expectation doctrine does not confer substantive rights of the nature sought.

[25] As can be seen, the Federal Court of Appeal was insistent that the safety and effectiveness of the drug was the governing principle. The Minister was entitled to come to the conclusion that more was needed in order to be satisfied of the safety and effectiveness. That in effect was the long and short of it. The concerns about safety and efficacy were found to be *bona fide*:

> [44] Before leaving this point, I have considered Apotex' submission that it was "unfair and arbitrary" for the Minister's officials to prefer the negative result of a 2008 review of its submission over the positive result obtained in 2002 when, it alleges, there had been no material change in circumstances. I have also considered its argument that the conduct of the Minister's officials gives rise to a reasonable apprehension of bias.
>
> [45] Apotex' evidence on these points was addressed by the Minister.
>
> [46] On the whole of the evidence I find that Apotex has failed to establish that the Minister's safety and efficacy concerns were not *bona fide*. The evidence is consistent with there being significant uncertainty within the Therapeutic Products Directorate of Health Canada about the appropriate bioequivalence requirements to be applied to proton pump inhibitors. Such scientific uncertainty does not detract from the *bona fides* of the Minister's safety and efficacy concerns.

[26] While Health Canada was steadfast that bioequivalence had to be established on the full spectrum (from fasting to high fat fed meals) in order to be satisfied that the drug is bioequivalent, and thus was safe and effective, it was also willing to assist in creating a study that could prove to be appropriate. It stated plainly that any other scientific rationale with data that would support evidence of bioequivalence would be received. The data thus produced would be reviewed expeditiously. Obviously, nothing happened and OMEC03 was not produced. A Notice of Non-Compliance Withdrawal Letter with respect to that first submission was issued and, as noted by Barnes J., reconsideration was denied on July 27, 2009. It took more than a year to apply to this Court on judicial review, which was found to be fatal in and of itself. Moreover, the two federal courts commented on the ability of the Minister to seek more information to ascertain bioequivalence.

[27] Finally, on February 4, 2013, Apotex refiled its ANDS; this time it included the 1998 fed study with a high fat meal, the OMEC03 study, after it sought to offer a study that was found to be inadequate. It was not successful and notice of non-compliance was issued on November 28, 2013.

[28] In the end, the various chapters in this particular episode boil down to this. Apotex was on its way to approval for its Apo-Omeprazole Tablets on March 7, 2003, on the basis of studies that did not include high fat/high calorie meals. However, the regulator concluded on December 5, 2008, that approval could not be given because bioequivalence was not demonstrated: evidence of bioequivalence under both fasted and standard fed conditions was found to be necessary. Instead of providing the evidence of bioequivalence, Apotex chose to challenge the decision arguing that rights had vested; it was unsuccessful before this Court and the Federal Court of Appeal. Apotex ultimately submitted its 15-year old OMEC03 study as its only study meant to satisfy the concerns about bioequivalence.

[29] The Notice of Non-Compliance of November 28, 2013, is explicit that not only the standards to determine bioequivalence between Apotex's new drug and the Canadian reference product under high fat fed conditions were not met, but equally important Health Canada complained that the test meal (760 calories instead of the required 1000) was not a standard high calorie/high fat meal; indeed, the sampling protocol was not adequate, the study was not adequately powered and three enteric-coated tablets were administered instead of only one. The letter offers precise guidance concerning what would be required in the design and implantation of a new study. There was no new study and there has not been a new one.

IV. Reconsideration

[30] Instead of devising a new study with a view to satisfy Health Canada's requirement that there be bioequivalence under high fat/high calorie fed meal or challenging the refusal on judicial review, Apotex chose to seek "reconsideration".

[31] As the document "Guidance for Industry – Reconsideration of Final Decisions Issued for Human Drug Submissions" states, Health Canada has put in place a policy the purpose of which is to resolve drug submission-related disputes; it applies to ANDS.

[32] If the Minister issues a notice of non-compliance withdrawal for a drug submission, the sponsor can request a reconsideration process described in a policy document.

[33] The *Guiding Principles for Dispute Resolution* require staff to "resolve disputes in a fair and timely manner, using the most appropriate dispute resolution mechanism." The principles are fairness, accountability, and accessibility. The reconsideration process is a formal dispute resolution mechanism and is intended to be used when informal dispute resolution mechanisms have failed.

[34] The sponsor files the request for reconsideration and the Office of Science recommends to the Director General of the Therapeutic Products Directorate a process to be followed to address the reconsideration request, which could include referring the issues to an external panel, reviewing the issues within the Office of Science, or a combination.

[35] The Director General decides what process to follow and informs the sponsor. Here, the matter was to be handled by a reconsideration panel. Its composition is determined by the sponsor (Apotex) and by the affected Directorate (Therapeutic Products Directorate) each recommending a panel member with the Director General appointing the panel's chair.

[36] The more difficult issue may well be the determination of the parameters, or mandate, of the Reconsideration Panel. In this case, Apotex and the Director General were incapable to reach an agreement on the question to be posed to the Panel, which led to the cancellation of the process on November 16, 2015. That constitutes the only decision which is the subject of the judicial review.

[37] The Reconsideration Policy does not detail how the sponsor and Health Canada are to agree on the question put to the Reconsideration Panel. The Policy simply states that "the Office [of Science] will work with the sponsor and the review bureau/centre to draft specific questions to be posed" to the Scientific Advisory Committee or the Panel. However, the Policy provides clear indications of the type of issues that could go to a reconsideration panel. Thus, the Policy lists examples of issues that are generally appropriate for referral to an external panel:

- interpretation of available data;
- disagreement in applied methodology; and
- relative weights given to data impacting on the risk/benefit assessment of the submission information.

The Policy also indicates what issues are generally inappropriate for referral to an external panel:

- submission of false information;
- allegations of bias;
- matters in which regulatory policy/guidance or procedures are the dominant concern; and
- an issue on which the Directorate has available recent external independent expert opinion.

[38] Obviously, the Policy contemplates issues of a technical nature. Matters of regulatory policy or procedure are not contemplated. Furthermore, the Policy is focused on discrete issues to be brought before the Panel whose role is purely advisory:

> The roles and responsibilities of the Panel, and the process for obtaining its advice will be the same as for the SAC outlined in Section 5.3.1(a). Consistent with its advisory role, the Panel will not be asked to make a decision on the submission; rather, advice will be solicited through one or more direct questions related to the specific outstanding issue(s) identified.
>
> [my emphasis]
>
> (Policy, 5.1.3(b) Reconsideration Panel)

[39] I fail to see how that process can be understood to suggest that it constitutes, for all intents and purpose, an appeal of sorts. It is rather a process put in place to address discrete issues of a technical nature where the Director General of the Therapeutic Products Directorate plays a central role. She appoints the panel chair; she will receive the advice of a panel; she will make the reconsideration decision. The Panel members have expertise relevant to the resolution of the matter raised, not on matters of regulatory guidance or procedure. Issues around data, methodology and weight to be given to data impacting on the risk/benefit assessment are apposite. Are not matters in which regulatory policy or procedures are the dominant concern.

[40] In a sense, the Director General is not wrong to say that it is her process: she makes the final reconsideration decision and the advice is for her. She may also refuse a reconsideration filed for decisions that are not eligible. Indeed, her role is defined in the following fashion in the Policy:

> The Director General of TPD or BGTD or his/her designate is responsible for:
>
> - refusing Reconsiderations filed for decisions that are not eligible;
> - deciding whether to consider information filed in the Request of Reconsideration;
> - deciding on the process for the disposition of the Request for Reconsideration;
> - deciding on the use and membership of the Scientific Advisory Committee or Reconsideration Panel (if applicable); and
> - making the Reconsideration decision.
>
> (Policy, 4. Roles and Responsibilities)

Obviously, a director general who would not be acting in good faith or would display bias, for instance, may well attract scrutiny on judicial review despite the high degree of discretion reposed in her. Fairness commands no less. But there is no such allegation here.

[41] I have not found any indication suggesting that the sponsor has an unhampered ability to raise whatever issue it sees fit. In fact, it is quite the opposite. Issues that may be ripe for reconsideration appear rather to be of a particular ilk. That may well be why the Policy requires that the Drug Submission sponsor work with the Office of Science in the Therapeutic Products Directorate to draft questions to be posed to the Reconsideration Panel. Contrary to what Apotex

asserted, the reconsideration process is not adversarial with the Panel as a judge of the matter raised by a sponsor. It is rather a process where experts in a field will provide advice to a Director General on discrete issues that have been identified in questions agreed to by the sponsor and Office of Science of the TPD. It is a way to avoid disputes: as stated in the Policy, "(i)f, at any time during the Reconsideration process, the sponsor files a Notice of Application to the Federal Court to resolve the matter, the Directorate will terminate the Reconsideration process". That reconsideration process resulted in an impasse in this case. While Apotex insisted that the question to be posed to the Reconsideration Panel had to turn on whether its new drug is safe and effective, the Therapeutic Products Directorate was of the view that the focus of the question had to be on bioequivalence.

V. The reconsideration process: the Question

[42] Apo-Omeprazole belongs to a class of drugs termed "proton pump inhibitors" or "PPIs". PPIs inhibit gastric acid production to address problems such as ulcers. PPIs are unstable in acidic conditions; therefore, they are made with an enteric coating for protection in the stomach so they can pass into the intestine where they are absorbed into the body. The Canadian reference product for the Apo-Omeprazole ANDS is "Losec", which has no restrictions on what food it can be taken with.

[43] The Notice of Non-compliance of November 28, 2013, was based on the conclusion that the new drug did not comply with section C.08.002.1 of the *Regulations*, which requires that the new drug be bioequivalent with the Canadian reference product. The letter of November 2013 states:

> In order to demonstrate the safety and effectiveness of Apo-Omeprazole (omeprazole magnesium) delayed release tablets, there is a requirement to demonstrate bioequivalence with the Canadian reference product under both fasting and high fat fed conditions. […]
>
> The standards to determine bioequivalence under single dose high fat fed conditions…were not met by Study OMEC03.
>
> Furthermore, there were numerous design issues with the study including: the test meal was not a standard high calorie, high fat meal; the sampling protocol was not adequate to define the drug concentration-time profiles; the study was not adequately powered; and three enteric coated tablets were administered when only one was required, likely contributing to the multiple peak concentration-time profiles that were seen.
>
> The decision to recommend a Notice of Non-Compliance for this submission was based on the totality of the data that has been provided…
>
> In order to demonstrate the safety and efficacy of your product, please provide data from an appropriately designed and executed comparative bioavailability study conducted under high fat, high calorie fed conditions…

[44] The NON also lists comments that should be taken into consideration by the applicant before designing and implementing a new study, including using a standard high calorie, high fat meal of 1000 calories with 50% or 500-600 calories derived from fat (2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 120 grams of hash browns, 240 millilitres of whole milk). The test meal in OMEC03 was 760 calories, with 53% (405 calories) derived from fat.

[45] That set the stage for what was to follow. Apotex responded to the NON in January 2014 stating that the submitted studies were sufficient to establish the safety and effectiveness of the product. I note that Apotex relies on the safety and effectiveness of its product while the Minister speaks of the requirement to establish bioequivalence. There is a difference. The company did

not submit a new study. Apotex's response to the NON's primary objection that OMEC03 did not meet the standards to determine bioequivalence was three-fold:

- TPD approved the earlier version of the ANDS for the same drug in 2003 and accepted the low fat "fed" study submitted at that time;
- TPD's approval of other PPI products shows there is no therapeutic relevance to TPD's alleged deficiencies with the OMEC03 study; and
- Since numerous omeprazole and omeprazole magnesium products that are not bioequivalent to each other have all been approved by TPD and are interchangeable, strictly meeting the standards in the 2012 bioequivalence guidelines with respect to one CRP is not relevant to safety, effectiveness, or interchangeability.

[46] Fundamentally, the Minister required bioequivalence because the law requires it, while Apotex wanted its new drug to be found safe and effective in spite of a lack of evidence that there was bioequivalence when the tablet is used on a high fat/high calorie meal. Apotex seemed to argue that it should have received the NOC on the basis of the 2003 studies, that OMEC03 is good enough, and that it is discriminated against because other products have not been given de same level of scrutiny.

[47] The Notice of Non-compliance Withdrawal letter of July 28, 2014, made essentially the same points as the notice of non-compliance:

> The high fat study OMEC03 that was submitted under Control Number 162270 to satisfy the criterion of demonstrating bioequivalence under high fat/high calorie fed conditions, failed to meet bioequivalence criteria as the 90% confidence interval of the relative mean AUCt is outside of the acceptance range of 80-125%. Furthermore, the results of the study were not meaningful due to poor study design and no useful information could be obtained in regard to the performance of the enteric coat of the delayed release tablet under high fat/high calorie fed conditions.

> A study conducted under high fat/high calorie fed conditions that, at a minimum, produces reliable evidence is required to demonstrate the performance of Apo-Omeprazole (omeprazole magnesium) delayed release tablets relative to the CRP. This study will provide necessary evidence of the safety and efficacy of the test product under the extremes of the conditions of use that will be realized in patients. This requirement has been met by all other generic Proton Pump Inhibitor (PPI) products that are approved in Canada. The requirement to demonstrate bioequivalence to the CRP in a high fat/high calorie fed study has been established through industry and scientific experts as evidenced by the findings of the Expert Advisory Committee on Bioavailability and Bioequivalence (EAC-BB, now the Scientific Advisory Committee-BB or SAC-BB) and is furthermore an internationally accepted practice.

[48] The battle lines were drawn. In June 2015, Apotex submitted its Request for Reconsideration package, which says that the contentious issue is whether the entire submission, including all of the bioavailability study data, the nature of the therapy, the approval of other products and other factors sufficed to establish the safety and efficacy of Apo-Omeprazole. Health Canada's Bureau of Pharmaceutical Sciences, on the other hand, sought to focus the question for the Reconsideration Panel on bioequivalence, and specifically whether OMEC03 provided reliable evidence of bioequivalence under fed conditions. What followed is an exchange of correspondence about suggested questions that never even attempted to bridge the divide. I have underlined the essential ingredient of each question.

[49] On September 18, 2015, both parties submitted their proposed questions for the panel:

- Apotex proposal: Based on all available information, including the approval of other PPI's, does the submitted information reasonably suffice for a conclusion that Apo-Omeprazole Tablets <u>are safe and effective and thus also entitled to an NOC</u>?

- Bureau proposal: Does the data from study OMEC03 suffice to demonstrate the relative performance of Apo-Omeprazole (omeprazole magnesium) tablets under high fat/high calorie fed conditions to the Canadian reference product in order to make a regulatory determination of bioequivalence?

[50] The Office of Science reviewed both drafts and prepared the following question:

> Have Apo-Omeprazole (omeprazole magnesium) enteric coated tablets been demonstrated to be bioequivalent to the Canadian reference product, under fed conditions?

[51] On October 5, 2015, Duane Terrill from Apotex wrote to Health Canada rejecting the proposed question from the Office of Science:

> The question that we submitted is whether or not the submitted information suffices for a conclusion that the product is safe and effective. This is clearly the one and only relevant question.
>
> Your proposed question is whether or not the product has "been demonstrated to be bioequivalent to the Canadian reference product, under fed conditions?"
>
> That question is ambiguous. The answer depends on the definition of "bioequivalent under fed conditions". The question can be interpreted as presuming that it is mandatory to fully meet, with a high fat meal, the criteria in the latest version of the guideline. If that presumption is made, the question becomes pointless, as we do not dispute that the answer would be "no" based on that interpretation of the question.

There was nothing ambiguous in the suggested question posed by Health Canada and, in the context, it is certainly not more ambiguous than whether or not the product is safe and effective. The question simply asks if Apotex's product is bioequivalent under fed conditions. That leaves much room for the Reconsideration Panel to opine on the central notion of bioequivalence under fed conditions. There needed to be bioequivalence and, in the view of the Minister, there was the

requirement that it also be under fed conditions at least since December 2008. As a matter of fact, Health Canada staff responded on October 9, 2015, indicating that they were not going to change the question because "bioequivalence is one of the four pre-conditions in order to obtain an ANDS." I would have thought that C.08.002.1 makes the requirement of bioequivalence amply clear. That would be the essential rationale for Health Canada to refuse questions where the issue would be to seek advice on whether the new drug is safe and effective in spite of the fact that the high fat/high calorie test failed.

[52] Mr. Terrill responded on October 13, 2015, with an amended question:

> Does the available information, including the submitted bioequivalence studies, reasonably suffice to conclude that Apo-Omeprazole tablets are safe and effective?

[53] In that email of October 13, 2015, Mr. Terrill would tend to demonstrate that Apotex was sticking to its contention that the Reconsideration Panel had to review the product for its safety and effectiveness, whether there is bioequivalence or not:

> With respect to (a), the issue highlighted in our Request for Consideration is NOT whether or not Apotex submitted a bioequivalence study with a high fat meal meeting the confidence criteria in the guideline. We do not deny that same was not done, so whether or not it was done cannot be what is at issue. The issue raised is whether or not, despite our not having provided such a study, the available information suffices to adequately demonstrate safety and effectiveness, to at least the same extent as other approved products.
>
> The Director General has agreed that our Request for Reconsideration will go to a panel. It follows that the question cannot be whether or not we submitted a study fully meeting the purported criteria (we agree that we did not). But must be whether or not what was submitted nevertheless reasonably suffices to demonstrate safety and effectiveness.

[underlined in the original]

I note that in that same email, Mr. Terrill introduces the notion of meeting criteria in the guideline:

> 1. As we explained, your proposed question is unacceptable by reason of being ambiguous, in that "bioequivalence" must be established in the fed state specifically, and presumably also to meet criteria in a guideline. If the Panel interprets the question in that way, the Panel's work would be improperly constrained.

Mr. Terrill speaks of "presumably". His speculation is not supported by any evidence that I could find on this record. In the exchanges, the respondent has been consistent that her position has been, and still is, that bioequivalence is that which is referred to in the *Regulations*, nothing else. Strict adherence to criteria has never been a requirement. Mr. Terrill's presumption is not based on the evidence I have been able to review.

[54] The Director General responded with a letter to Apotex on October 27, 2015 (the Reconsideration Panel members are copied on the letter; the Reconsideration Panel was to meet on October 30, 2015), explaining why she could not agree with Apotex's latest proposed question. She said that the only scientific issue in the NONW letter was "whether the results of the high-fat study provide accurate estimates of AUCt and Cmax relative to the Canadian reference product." She added that it is not the panel's role to interpret regulations or recommend a product's approval, but rather to review the scientific issues upon which a negative decision on the drug submission was issued. She proposed yet another question:

> Do the results from study OMEC03 provide reliable evidence of the bioavailability characteristics of Apo-omeprazole delayed

> release tablets in order to assess safety and effectiveness through bioequivalence with the Canadian reference product as required in C.08.002.1(2) of the *Food and Drug Regulations*?

[55] On October 28, 2015, Mr. Terrill again rejected Health Canada's proposed question, arguing that such a narrowing of the issue constituted fettering of discretion in that it premised the review on the need for a high fat meal meeting confidence criteria in the bioequivalence guidelines. Mr. Terrill also asked that the panel be permitted to identify missed opportunities for early dispute resolution and that Apotex be given 2 hours to present to the panel instead of the allotted 45 minutes.

[56] It is not easy to understand how referring directly to the provision in the *Regulations* which calls for "sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug" constitutes a fettering of discretion. Nevertheless, that is the position advanced.

[57] On November 6, 2015, the Director General wrote back to Apotex proposing another version of the question that allowed for consideration of the entire submission. She stated that if this approach was unacceptable, she would consider the reconsideration request withdrawn and declare the NONW final. Her final proposed question was:

> Do the results from study OMEC03, examined as part of the totality of evidence contained in this Abbreviated New Drug Submission, provide reliable evidence of the bioavailability characteristics of Apo-omeprazole delayed release tablets in order to assess safety and effectiveness through bioequivalence with the Canadian reference product as required in C.08.002.1(2) of the *Food and Drug Regulations*? Why or why not?

Again, the reference to subsection C.08.002.1(2) must be concerning the requirement that the ANDS addresses the requirement of bioequivalence. Two days later, Apotex reiterated the same position.

[58] Hence, on November 16, 2015, the Director General wrote to Apotex that it was cancelling the reconsideration and finalizing the NONW that had been issued on July 28, 2014. The relevant part of the decision states:

> You disagree with the question I have proposed for the reconsideration panel, and despite my comment that I am prepared to be somewhat flexible, you did not provide an alternative. The question that I have posed in the November 6, 2015 letter is not a fettering of my discretion as you claim, but is an approach in line with assessing whether the regulatory requirement C.08.002.1(2) of the Food and Drug Regulations has been met.
>
> You also continue to request that the scope of the panel be expanded to deal with your objections to the process itself, which I take to mean going back to revisit your company's previous submissions. This is not the purpose of a reconsideration. A reconsideration panel is put together to provide expert analysis and advice on a scientific question, and not to address information or issues that were not expressed in the negative decision letter.
>
> Since we remain at an impasse, and as I indicated in my letter of November 6, 2015, the reconsideration of this submission, control number 162270 is cancelled and the Notice of Non-Compliance-Withdrawal issued on July 28, 2014 is now final.

[59] That is the "decision" that Apotex would want to see judicially reviewed.

VI. Issues and analysis

[60] The applicant challenges the decision made by the Director General to cancel the reconsideration of Apotex's submission in respect of its Omeprazole Magnesium Tablets. The AND submission is treated as withdrawn. It is not disputed that the Director General is the Minister of Health's delegate for the purpose of the decision made.

[61] As shown in the preceding section, Apotex argued that the reconsideration exercise ought to be about whether or not its new drug is safe and effective; the Minister contends that the manufacturer of a new drug, according to section C.08.002.1 of the *Regulations*, may file an AND submission that compares the Canadian reference product, such that the new drug is bioequivalent, based on the pharmaceutical and, when the Minister considers it necessary, bioavailability characteristics.

A. *Arguments*

[62] Fundamentally, Apotex's argument is that the Minister fettered her discretion in deciding that the reconsideration exercise had to focus on bioequivalence instead of allowing it to establish safety and efficacy (memorandum of fact and law, paras 3, 5, 24, 39, 47, 48, 53). The whole focus of Apotex has been, both in its evidence and in its memorandum of fact and law, that it would rather argue its case on the basis that its new drug is safe and effective, thus avoiding as much as possible the bioequivalence step. Although it met requirements under low fat/low calorie meals and the absorption of its tablets on an empty stomach, its 1998 study using a high fat/high calorie meal was only submitted fifteen years later, after a trip to the Federal

Courts to argue unsuccessfully that it had gained a vested right to a NOC without evidence about a fat fed meal. The applicant has conceded in its memorandum of fact and law that "in relation to the "fed" study, the criteria were not met by its ANDS" (para 56). Apotex's solution was to avoid the high fat/high calorie meal to show the Reconsideration Panel that its new drug is safe and effective.

[63] While not pointing to anything in the evidence to support the argument, Mr. Terrill, for Apotex, claims that the Minister also fettered her discretion in insisting that the question be about strict compliance with the bioequivalence criteria that are found in the guidelines.

[64] The applicant includes in its "fettering" argument that other products that would not meet strict compliance with bioequivalence were approved in the past.

[65] Apotex also offered an argument about its legitimate expectations being defeated: the Minister had created expectations that she would follow a procedure that included working with a sponsor to draft the questions to be posed to the Reconsideration Panel that would address the issues in dispute. The applicant seems to go as far as suggesting that the issues it raised are to go to the Reconsideration Panel (memorandum of fact and law, para 90). Such was its expectation.

[66] The Minister denies that discretion was fettered in any way. She followed the *Regulations* that control in the circumstances.

[67] These *Regulations* provide for a more expeditious pathway when a manufacturer wishes to copy a drug that has already received a NOC. Detailed reports of the tests made to establish the safety of the new drug are not required; nor is there the necessity of substantial evidence of clinical effectiveness of that new drug. That has been already established with respect to the Canadian reference product.

[68] However, the *Regulations* have some requirements for the new drug to compare with the Canadian reference product. In order to compare, to be able to use the expeditious pathway, the AND submission filed deals with:

- the new drug is the pharmaceutical equivalent;
- the new drug is bioequivalent;
- the route of administration of the new drug is the same;
- the conditions of use fall within those for the Canadian reference product.

As the Minister points out, C.08.002.1(2)(c)(i) states unequivocally that the ANDS "shall contain sufficient information and material to unable the Minister to assess the safety and effectiveness of the new drug, including the following … (c) evidence from the comparative studies conducted in connection with the submission that the new drug is … (i) the pharmaceutical equivalent of the Canadian reference product." It is the presence of pharmaceutical equivalence and bioequivalence to the Canadian reference product that allows for the extrapolation to the generic drug of the safety and effectiveness already demonstrated by the Canadian reference product through detailed reports to establish the safety and substantial evidence of the clinical effectiveness.

[69] It is at the price of satisfying the prescribed conditions, including pharmaceutical equivalence and bioequivalence, but without having to present “detailed reports” and “substantial evidence”, that the NOC will issue.

[70] The Minister says that the guidelines published by Health Canada (Conduct and Analysis of Comparative Bioavailability Studies and Comparative Bioavailability Standards: Formulations Used for Systemic, May 2012) are purely for the assistance of the industry. They have been created following consultations with the industry and they are explicit that they are guidance documents. Alternate approaches are possible. They provide:

> Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.
>
> Guidance documents are administrative documents not having the force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

[71] The Minister asserts that the ANDS does not comply with the requirements of C.08.002.1 of the *Regulations*: the evidence was simply not sufficient to establish that the new drug is bioequivalent. It is not only that the standards to determine bioequivalence were not met; there were also numerous design issues with the study “such that no useful information could be obtained in regard to the performance of the enteric-coat of the Apo-Omeprazole delayed release

tablet under high fat fed conditions", in the words of Dr. Scott Appleton of the Bureau of Pharmaceutical Sciences, in the TPD, in his comprehensive report of July 23, 2014. The Notice of Non-Compliance Withdrawal Letter followed shortly thereafter (July 28, 2014). With such deficient data, it was insufficient to meet the requirement for bioequivalence.

[72] The need for a high fat/high calorie meal, which emerged after the initial acceptance of Apotex's submission with such study in 2003, after gaining experience with similar products, was explained by Dr. Appleton:

> The rationale for testing or challenging an enteric coated tablet with food is that a meal delays the emptying of the stomach's contents into the small intestine (gastric emptying). The rate of gastric emptying of any meal can be predicted by its volume and nutrient density. Nutrient density is sensed mainly in the small intestine where receptors feed information (nervous and endocrine signals) back to the stomach to delay emptying by altering the patterns of gastric motility. The presence of fat in the small intestine is the most potent inhibitor of gastric emptying.
>
> Therefore, a key element of the design of a fed bioequivalence study is the selection of the meal that will be given to volunteers prior to administration of the test and reference products. It is clear that the type of meal that is administered to volunteers in a fed bioequivalence study can greatly affect the outcome and the utility of the study as follows:
>
> > A meal that is high in fat and calories will provide maximal evidence as to how the enteric coating of a delayed release tablet will behave when exposed to an acidic environment for an extended period of time as it would be in the stomach of a patient who took the product after a large meal.
> >
> > Additionally, it has been suggested that the pH of the stomach may not be uniform after a meal and the enteric coated tablet could be exposed to regions of higher PH which could break down the coating, resulting in the premature release of the drug.

> A high fat meal may result in the tablet becoming coated in fat or a fatty emulsion resulting from the meal, which can affect the release of the drug from the tablet.
>
> A meal that is low in fat and in calories will not challenge the enteric coat of the tablet to the same extent that a high fat/high calorie meal will.
>
> Although it is referred to as one of the "extremes" of the conditions under which a tablet might be taken (the fasting state being the other "extreme"), a standard high fat/high calorie meal is a meal that one would reasonably expect that a person might have for breakfast (*e.g.* 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 120 grams of hash browns and 240 millilitres of whole milk).
>
> A fed bioequivalence study in which a high fat/high calorie meal (>50% of calories from fat, as shown above) is administered will serve (in conjunction with the required bioequivalence study under fasting conditions) to maximally challenge the enteric coat of the enteric coated tablet. In doing so, it will provide confidence that the enteric coated product will perform in a manner similar to the CRP under all of the conditions of use (that is in the range of fed states from fasted to high fat/high calorie fed).

[73] What is more, the Notice of Non-Compliance Withdrawal Letter of July 28, 2014 provides the explanation for the conclusion reached and confirms that all generic Proton Pump Inhibitors approved have met the requirement:

> The high fat study OMEC03 that was submitted under Control Number 162270 to satisfy the criterion of demonstrating bioequivalence under high fat/high calorie fed conditions, failed to meet bioequivalence criteria as the 90% confidence interval of the relative mean AUCt is outside of the acceptance range of 80-125%. Furthermore, the results of the study were not meaningful due to poor study design and no useful information could be obtained in regard to the performance of the enteric coat of the delayed release tablet under high fat/high calories fed conditions.

> A study conducted under high fat/high calorie fed conditions that, at a minimum, produces reliable evidence is required to demonstrate the performance of Apo-Omeprazole (omeprazole magnesium) delayed release tablets relative to the CRP [Canadian reference product]. This study will provide necessary evidence of the safety and efficacy of the test product under the extremes of the conditions of use that will be realized in patients. This requirement has been met by all other generic Proton Pump Inhibitor (PRI) products that are approved in Canada. The requirement to demonstrate bioequivalence to the CRP in a high fat/high calorie fed study has been established through industry and scientific experts as evidenced by the findings of the Expert Advisory Committee on Bioavailability and Bioequivalence (EAC-BB, now the Scientific Advisory Committee-BB or SAC-BB) and is furthermore an internationally accepted practice.

[74] As for the reconsideration process, the Minister's position is that bioequivalence is a regulatory pre-condition. Accordingly, the question to a reconsideration panel in this case would have to be whether the study submitted could provide reliable evidence to assess bioequivalence, as must be done under C.08.002.1(1) and (2) of the *Regulations*. The Minister did not ask whether the applicant had complied with the guidelines; rather the issue put in the proposed questions relates to the presence of reliable evidence to satisfy the bioequivalence with the Canadian reference product. In effect, the Minister insisted that the decision on safety and effectiveness passes through bioequivalence while Apotex sought to circumvent the requirement. The position is encapsulated in the following passage from the last attempt made by the Director General at explaining the position:

> From Health Canada's perspective, the only issue under dispute for this submission is what was outlined in the Notice of Non-Compliance – Withdrawal (NON-W) letter of July 28, 2014, and reiterated in my letter of October 27, 2015 – namely, the interpretations of the results from study OMEC03 and integration of these results with the other results you have submitted for this product. As such, while I am prepared to be flexible with the framing of the question, in order to satisfy the regulatory

> requirement for this abbreviated new drug submission, the question must lead the Panel to make a recommendation on whether study OMEC03 substantiates bioequivalence of your product with the Canadian Reference Product.
>
> ….
>
> Generic drugs, which are reviewed through an Abbreviated New Drug Submission, must establish bioequivalence with the Canadian Reference Product. It is through establishing bioequivalence that a generic drug demonstrates safety and effectiveness. While a drug may be deemed to be safe and effective, it cannot be assumed to also be bioequivalent. The latter characteristic is essential for the Minister to grant a Notice of Compliance (NOC) through the ANDS pathway for a generic drug. Health Canada's Guidance Document related to generic drug submissions were drawn up in consultation with industry to establish a consistent and predictable interpretation of the Regulations, and are being followed in this submission.
>
> ….
>
> Based on the rationale I have provided in my letter of October 27, 2015 and in this correspondence, I am prepared to reconvene an external Reconsideration Panel to deliberate on the following question:
>
> > Do the results from study OMEC03, examined as part of the totality of evidence contained in this Abbreviated New Drug Submission, provide reliable evidence of the bioavailability characteristics of Apo-omeprazole delayed release tablets in order to assess safety and effectiveness through bioequivalence with the Canadian Reference Product as required in C.08.002.1 (2) of the *Food and Drug Regulations*? Why or why not?

[75] This last proposed question is also rejected by Apotex.

B. *Issues and standard of review*

[76] The parties substantially agree on the issues that need to be addressed:

(1) The Minister suggests that the issue of fettering her discretion is: Did the Minister fetter her discretion by insisting that the question asked of the Reconsideration Panel address bioequivalence? Apotex speaks in terms of fettering the discretion by mechanically applying the bioequivalence criteria as an absolute requirement; and

(2) The Minister puts forth that the legitimate expectation issue is: Did Apotex have legitimate expectations to be allowed to seek a reconsideration process? Apotex is slightly more precise by qualifying the legitimate expectation as disallowing a reconsideration process which deals with the issues put forward by Apotex.

[77] There was no substantive discussion by the parties of the standard of review applicable to the issues to be determined. The Minister states that procedural fairness issues carry a standard of correctness; that is not a novel proposition (*Mission Institution v Khela*, 2014 SCC 24, [2014] 1 SCR 502, at para 79). She relies on the standard of reasonableness with respect to issues of fact, discretion and policy. In fact, the presumption goes further in that the Supreme Court has ruled regularly since *Alberta (Information and Privacy Commissioner) v Alberta Teachers' Association*, 2011 SCC 61, [2011] 3 SCR 654 that "the interpretation by the tribunal of "its own statute or statutes closely connected to its function, with which it will have particular familiarity" should be presumed to be a question of statutory interpretation subject to deference on judicial review" (para 34).

[78] If reasonableness is the appropriate standard of review, the reviewing court will show deference and intervention will be warranted only if the outcome does not fit within a range of acceptable, possible outcomes, in recognition that these kinds of questions do not lend themselves to one specific or particular result. The Court may disagree with the decision, yet that disagreement does not lead to the decision being unreasonable. The reviewing court will be concerned with justification, transparency and intelligibility within the decision-making process

in its search of reasonableness (*Dunsmuir v New Brunswick*, 2008 SCC 9, [2008] 1 SCR 190, para 47).

[79] That however does not answer what standard applies in our case. As for the legitimate expectation doctrine, it seems to proceed from the very notion of procedural fairness (*Baker v Canada (Minister of Citizenship and Immigration)*, [1999] 2 SCR 817 [*Baker*]). It is one of the participatory rights that are deserving of protection as a matter of fairness. To the extent there is some legitimate expectation, the standard of review will be correctness.

[80] In the case of a tribunal or Minister that fetters the discretion conferred by law, there is binding authority (*Stemijon Investments Ltd. v Canada (Attorney General)*, 2011 FCA 299) that "(a) decision that is the product of a fettered discretion must *per se* be unreasonable" (para 24). That is because a discretion of a certain scope cannot be abridged without, in effect, rewriting the law.

[81] Unfortunately for Apotex, it did not make a convincing case that the Minister fettered her discretion or that there were legitimate expectations which were not met. I begin with the latter.

(1) Legitimate expectations

[82] The doctrine of legitimate expectations is procedural in nature. The following passage taken from *Judicial Review of Administrative Action in Canada*, ((loose leaf), Thomson Reuters Canada, updated August 2012) was cited with approval by the Supreme Court in *Agraira v*

Canada (Public Safety and Emergency Preparedness), 2013 SCC 36, [2013] 2 SCR 559 [*Agraira*] at para 95:

> The distinguishing characteristic of a legitimate expectation is that it arises from some conduct of the decision-maker, or some other relevant actor. Thus, a legitimate expectation may result from an official practice or assurance that certain procedures will be followed as part of the decision-making process, or that a positive decision can be anticipated. As well, the existence of administrative rules of procedure, or a procedure on which the agency had voluntarily embarked in a particular instance, may give rise to a legitimate expectation that such procedures will be followed. Of course, the practice or conduct said to give rise to the reasonable expectation must be clear, unambiguous and unqualified.

[83] In *Canada v Mavi*, 2011 SCC 30, [2011] 2 SCR 504, the Supreme Court defined the doctrine as follows:

> [68] Where a government official makes representations within the scope of his or her authority to an individual about an administrative process that the government will follow, and the representations said to give rise to the legitimate expectations are clear, unambiguous and unqualified, the government may be held to its word, provided the representations are procedural in nature and do not conflict with the decision maker's statutory duty. Proof of reliance is not a requisite. See *Mount Sinai Hospital Center*, at paras. 29-30; *Moreau-Bérubé v. New Brunswick (Judicial Council)*, 2002 SCC 11, [2002] 1 S.C.R. 249, at para. 78; and *C.U.P.E. v. Ontario (Minister of Labour)*, 2003 SCC 29, [2003] 1 S.C.R. 539, at para. 131. It will be a breach of the duty of fairness for the decision maker to fail in a substantial way to live up to its undertaking: Brown and Evans, at pp. 7-25 and 7-26.

[84] However, the doctrine of legitimate expectations does not create substantive rights; the applicant cannot succeed on the merits, except perhaps if the conduct of officials is such that

there is a legitimate expectation that the discretion will be exercised in favour of the applicant. In *Agraira*, one reads at para 97:

> [97] An important limit on the doctrine of legitimate expectations is that it cannot give rise to substantive rights (*Baker*, at para. 26; *Reference re Canada Assistance Plan (B.C.)*, [1991] 2 S.C.R. 525, at p. 557). In other words, "[w]here the conditions for its application are satisfied, the Court may [only] grant appropriate procedural remedies to respond to the 'legitimate' expectation" (*C.U.P.E. v. Ontario (Minister of Labour)*, 2003 SCC 29, [2003] 1 S.C.R. 539, at para. 131 (emphasis added)).

[85] I have looked long and hard to find evidence of legitimate expectations being violated here. Apotex's position is predicated on its expected right to submit its issue, as it wants framed, as if this reconsideration process was an appeal of some sort. It is not so much a process that Apotex claims to be entitled to as the right to ask its question. At paragraph 90 of its memorandum of fact and law, on reads that "(t)he Reconsideration Policy contemplates a process where the External Panel opines on the issues raised by the manufacturer in the request for reconsideration" [my emphasis]. The Reconsideration Policy does no such thing.

[86] In the case at hand, it is clear that the fundamental difference between the parties is that Apotex did not want to be confronted to a question the focus of which would be the bioequivalence of its product compared to the Canadian reference product. It is noteworthy that the only high fat meal study offered in 2013 was a study that was on the shelves since 1998. It was not presented when the applicant made its ANDS resulting in a decision in March 2003. Instead of submitting it once it was determined that the submission cannot be successful in December 2008 without a fat fed study, Apotex challenged the decision on the basis that it had vested rights to the decision of 2003 when there was no such study. To no avail in this Court and

the Court of Appeal, where the Court commented that it would "be an absurd result to construe the Regulations in such a way that the Minister could be compelled to issue a NOC even if she was not satisfied that the drug in question is safe and effective" (*Apotex*, para 30). Indeed, the reasons given for requiring a study with a high fat meal are compelling.

[87] After the unsuccessful trip to the federal courts, Apotex still did not present its 1998 study; instead it submitted a comparative bioavailability study that was conducted with a different test product (Apo-Omeprazole tablets (omeprazole base)). That study did not provide any useful information concerning the new drug (Apo-Omeprazole (omeprazole magnesium)), according to the affidavit of Dr. Appleton. Apotex presented its 1998 study only when it refiled its ANDS in 2013 in order to satisfy the requirement of bioequivalence where the new drug is consumed with a high fat meal. As already indicated, the study failed, including because the study had poor study design.

[88] As a result, Apotex argues that it can get a reconsideration panel, irrespective of the failure on bioequivalence, to opine on the safety and effectiveness of the new drug by asking the Panel a question whose focus is on the safety and effectiveness of its drug, thus avoiding bioequivalence. There is nothing that I can find in the Reconsideration of Final Decisions Issued for Human Drug Submissions that could lend itself to the contention that it can support the legitimate expectation that Apotex can treat the reconsideration process as its appeal on any issue, including the issue of the safety and effectiveness of a new drug, using the short cut that is the abbreviated new drug submission. The policy does not allow to circumvent the requirement for bioequivalence found in the *Regulations*. The types of issues that can be referred are rather

interpretation of available data, methodology and relative weight given to data. The list is most probably not exhaustive, but it signals what can appropriately be brought before such a panel. As I read the questions proposed by the respondent, they fall squarely within those parameters dealing with bioequivalence. These questions were categorically rejected by Apotex which decided early on that its best chance was in bringing its case, as if it was an appeal, before the Reconsideration Panel on the basis that its new drug satisfies the ultimate test that a drug must be safe and effective. That cannot be a legitimate expectation about procedure or practice that is clear, unambiguous and unqualified.

[89] A fair reading of the Policy leads to the conclusion that it applies to disputes stemming from a notice of non-compliance withdrawal letter. That letter of July 28, 2014 is solely concerned with the bioequivalence of Apotex's product falling short on the basis of the submitted study (OMEC03). As Apotex acknowledges at paragraph 26 of its memorandum of fact and law, the reconsideration is geared towards the scientific disagreement in the case of a rejected submission. Disputes on scientific issues may be addressed by a panel having the appropriate expertise; the panel can provide a useful opinion to the Director General who will decide in the end.

[90] The legitimate expectation is concerned with Apotex being given a fair opportunity to draft a question which would address one issue eligible to be brought before a reconsideration panel: specific outstanding issues are to be identified and the panel members will be selected for their expertise relevant to the resolution of the matter. The Reconsideration Panel is not the

regulator. The Court finds that Apotex was given a better than fair opportunity to draft, in consultation with the Office of Science, a question that would be eligible.

[91] The difference between the parties became unshakeable when it became apparent that each party wished for the question to deal with different issues. It is not that Apotex was not given the opportunity. The opportunity was there, but the two ships were sailing in the fog in different directions. The Director General eventually refused reconsideration, as she is entitled to under the Policy (section 4). There was a fair opportunity given. As I will try to show in the next section, if there was any discretion, it was concerning how bioequivalence can be demonstrated, not whether or not the new product is safe and effective; there cannot have been a legitimate expectation about safety and effectiveness and have Apotex's question accepted for the referral to the Reconsideration Panel's consideration. Not only what is invoked by Apotex is not a practice that is clear, unambiguous and unqualified, but it calls for a particular outcome on the merits.

(2) Fettering of discretion

[92] There is fettering of discretion where the decision-maker confines the exercise of discretion by refusing to consider factors that are legally relevant. Guidelines are useful. I suspect manufacturers would clamour for indications as to what the administration would consider to be bioequivalent, given that "bioequivalence" is not defined in the *Regulations*. As the Supreme Court put it in *Kanthasamy v Canada (Citizenship and Immigration)*, 2015 SCC 61, [2015] 3 SCR 909, following in the footsteps of *Baker* and *Agraira*:

> [32] There is no doubt, as this Court has recognized, that the Guidelines are useful in indicating what constitutes a reasonable interpretation of a given provision of the *Immigration and Refugee Protection Act*: *Agraira*, at para. 85. But as the Guidelines themselves acknowledge, they are "not legally binding" and are "not intended to be either exhaustive or restrictive": *Inland Processing*, s. 5. Officers can, in other words, consider the Guidelines in the exercise of their s. 25(1) discretion, but should turn "[their] mind[s] to the specific circumstances of the case": Donald J. M. Brown and The Honourable John M. Evans with the assistance of Christine E. Deacon, *Judicial Review of Administrative Action in Canada* (loose-leaf), at p. 12-45. They should not fetter their discretion by treating these informal Guidelines as if they were mandatory requirements that limit the equitable humanitarian and compassionate discretion granted by s. 25(1): see *Maple Lodge Farms Ltd. v. Canada*, [1982] 2 S.C.R. 2, at p. 5; *Ha v. Canada (Minister of Citizenship and Immigration)*, [2004] 3 F.C.R. 195 (C.A.), at para. 71.

[93] In the context of section 25 of the *Immigration and Refugee Protection Act* (SC 2001, c 27), which allows the responsible minister to grant an exemption from any applicable criteria or obligations of the Act if justified by humanitarian and compassionate considerations, the *Baker* Court found that "(t)he guidelines show what the Minister considers a humanitarian and compassionate decision, and they are of great assistance to the Court in determining whether the reasons of officer Lorenz are supportable" (para 72). Guidelines are obviously not to be discarded. Brown and Evans have written in their *Judicial Review of Administrative Action in Canada*:

> 12:4421 Accordingly, a decision-maker must be prepared to entertain and consider representations that are designed to show not only that, properly interpreted, a rule or policy does not cover the facts of a particular matter, but also that even if it does, an exception should be made in light of the facts of the particular case. Thus, to treat a policy as binding prior to its application may be seen as being premature.

> …
>
> Moreover, a policy that is so detailed and definitive that it is replete with exceptions, is apt to be regarded as an exercise of a legislative power that the agency does not possess.
>
> Nevertheless, valid guidelines and policies can be considered in the exercise of discretion, provided that the decision-maker puts his or her mind to the specific circumstances of the case. Indeed, a court may refer to guidelines issued to those entrusted with the exercise of discretion as an indication of the factors to be considered by the decision-maker and, perhaps, their relative weight, when reviewing a discretionary decision for unreasonableness.

[94] It is not completely clear what discretion is alleged to have been fettered by the respondent in the questions that were proposed. According to its factum, the Minister would have fettered her discretion by mechanically applying the bioequivalence criteria as an absolute requirement. I must say that I have not found anything of the sort in any of the questions offered by the Minister. It is not accurate to state that the questions proposed by the respondent invited the Reconsideration Panel to treat bioequivalence criteria as mandatory. There is simply no evidence to give an air of reality to the contention that the Minister was bent on restricting the Reconsideration Panel to strict adherence to the guidelines. With all due respect, I have not found any persuasive evidence to that effect. Quite the opposite. The only issue that is before this Court is the decision of the Director General on November 16, 2015, to cancel the reconsideration sought by Apotex. The reason for the cancellation is the disagreement expressed by Apotex with all the proposed questions offered by the respondent including the last one presented on November 6. I reproduce it again for ease of reference:

> Do the results from study OMEC03, examined as part of the totality of evidence contained in this Abbreviated New Drug Submission, provide reliable evidence of the bioavailability characteristics of Apo-omeprazole delayed release tablets in order to assess safety and effectiveness through bioequivalence with the Canadian reference product as required in C.08.002.1(2) of the *Food and Drug Regulations*? Why or why not?

[95] The reason for the need to discuss bioequivalence is given in that same letter. It is because, "in order to satisfy the regulatory requirement for this abbreviated new drug submission, the question must lead the Panel to make a recommendation on whether Study OMEC03 substantiates bioequivalence of your product with the Canadian Reference Product." Clearly, the Director General is referring to C.08.002.1 which requires as part of the sufficient information and material evidence from comparative studies about bioequivalence. In other words, it is not possible to circumvent the *Regulations*; when the pathway is an ANDS, the generic drug must establish bioequivalence with the Canadian reference product. The scheme of the *Regulations* is such that "(i)t is through establishing bioequivalence that a generic drug demonstrates safety and effectiveness", says the Director General. In my view, she is correct. C.08.004(1) is unequivocal that "the Minister shall, after completing an examination of … [an] abbreviated new drug submission … (a) if that submission … complies with section … C.08.002.1 … issue a notice of compliance". The predicate to the issuance of a NOC is the compliance with C.08.002.1 which itself calls for evidence of bioequivalence. That question, and all other proposals before, never refers, directly or indirectly, to the guidelines, let alone criteria. It merely posits that the question to the Panel cannot avoid bioequivalence being at the heart of it, not that the drug is safe and effective.

[96] The Federal Court of Appeal is also of that view. In *Apotex Inc. v Canada (Health)*, 2011 FCA 86, 419 NR 300, the Court found:

> [7] We agree with the Minister that all of the arguments of Apotex on this appeal are based on the incorrect premise that it was open to the Minister to assess the safety and efficacy of Apo-ASA without requiring proof of bioequivalence between Apo-ASA and Bayer-ASA.
>
> [8] Pursuant to subparagraph C.08.002.1(2)(c)(ii) of the *Food and Drug Regulations*, the Minister cannot issue a notice of compliance for Apo-ASA on the basis of an abbreviated new drug submission naming Bayer-ASA as the Canadian reference product unless bioequivalence is demonstrated between Apo-ASA and Bayer-ASA. That is because a notice of compliance for a new product based on an abbreviated new drug submission is intended to recognize that the new product and the reference product are the same in certain material respects, including bioequivalence. In other words, even if a proposed new product is safe and effective, it cannot be approved through an abbreviated new drug submission if it is not bioequivalent to the reference product.
>
> [my emphasis]

In view of such binding authority, how can it be validly argued that the Minister fetters her discretion when she does precisely what the *Regulations* require of her and focuses the question on bioequivalence instead of safety and effectiveness?

[97] The purpose of the reconsideration in this case is to ask a panel of experts to consider whether the only fat fed study offered by the applicant, together with the totality of the evidence contained in the AND submission, provides evidence of bioavailabity, as required by law. There is no evidence that the Panel is to be confined to the guidelines. The guidelines do not profess to have the force of law and the respondent has acknowledged that they are not to be treated as law.

[98] The applicant seems to be content to repeat that there was insistence on strict compliance with the bioequivalence criteria. There is no evidence that has been presented. Even an internal communication raised by the applicant does not rise to the level. It is in fact innocuous. But even if that were the case, that would not turn questions to be put to a panel of independent scientific experts into instructions to follow strictly guidelines which provide specifically that alternate approaches are acceptable and that they are administrative in nature without force of law. This looks very much like a straw man.

[99] If the fettering is rather that the Minister had to agree to a question, the focus of which is the demonstration of the safety and effectiveness of the drug, that fettering can only be if the Minister had that discretion. She does not. She could not agree with a question requiring the Reconsideration Panel to opine on safety and effectiveness. That opinion would have been of no use.

[100] The guideline documents feature prominently that they do not constitute law. In fact, the exchange of proposed questions demonstrates that although there was an absolute need to demonstrate bioequivalence because of regulatory constraints, the requirements for how the bioequivalence was to be demonstrated were not cast in stone. The last proposed question, on November 6, 2015, is an illuminating illustration that the Reconsideration Panel would be asked to opine if the only study offered by Apotex, together with the totality of the evidence, provides reliable evidence concerning bioequivalence. Apotex repeated numerous times that it had the "perception" that the guidelines were treated as law. It takes more than a "perception" to claim that discretion was fettered in spite of the clear, unambiguous text of questions. The truth of the

matter is that the exchange of proposed questions showed that Apotex wished to avoid bioequivalence altogether while the Minister felt constrained by the *Regulations*.

[101] The respondent is right to point to numerous statements found in the Comparative Bioavailability Studies to illustrate the available flexibility:

> 1.2 The recommendations included in this guidance respecting study design and conduct, validation of bioanalytical methodology and statistical analysis of data should be followed in order to ensure compliance with the regulations.
>
> 1.4 In the absence of an adequate methodology for bioavailability testing, alternative approaches such as pharmacodynamics studies can be used. In some instances, equivalence may have to be determined by clinical trials with therapeutic end-points.
>
> 2.1 A rationale should be provided to justify which bioequivalence standards will be applied. Scientific justification should be provided for any deviation from the guidance set out in this document….Sponsors are encouraged to consult with Health Canada, in advance of the study, if deviations are substantial.
>
> 2.4.3.2 The meal used in a comparative bioavailability study conducted under fed conditions should allow maximal perturbation of systemic bioavailability of the drug from the drug product. This is generally a high-fat, high-calorie meal. Thus, the default meal, for comparative bioavailability studies under fed conditions, should be a high-fat, high-calorie meal…. Use of a meal other than a high-fat, high-calorie meal should only occur under exceptional circumstances and should be scientifically justified, a priori, by the submission sponsor.

Alternative approaches when scientifically justified or deviations are expressly permitted. None of these have actually been suggested in this case. That includes why it was appropriate to have high fat/high calorie studies for this type of product. As was explained by Dr. Appleton in his affidavit evidence, a low fat/low calorie meal does not challenge the tablet's enteric coat to the

same extent as the high fat/high calorie meal does. On the other hand, the high fat/high calorie meal provides the best evidence concerning how that enteric coat behaves. For instance, this kind of meal may coat the tablet in fat of fatty emulsion which can affect the release of the drug. Hence, the fed study with high fat/high calorie meal at one end, and the absorption of the new drug in fasting conditions, challenge the enteric coating maximally.

[102] The Minister did not fetter her discretion in examining whether there was bioequivalence between the new drug and the Canadian reference product in her effort to articulate an appropriate question for the Reconsideration Panel. Given that bioequivalence is required, the very wording of the proposed questions, and especially the last question, was demonstrative of the flexibility already noted in the guidelines documents.

[103] As indicated earlier, the ANDS pathway allows for compliance to be found in spite of the fact that the assessment of safety and effectiveness would otherwise require detailed reports of tests made to establish the safety of the new drug and substantial evidence of the clinical effectiveness of the new drug (C.08.002.1(2) and (a)(i) and C.08.002 (2)(a) and (h)). The proxy to get to safety and effectiveness of a new drug through an ANDS is to “piggy-back” on the Canadian reference product which has gone through the rigour of presenting “detailed reports of tests” and “substantial evidence”. But the *Regulations* require in those circumstances that there be bioequivalence.

[104] Thus, the Minister cannot fetter a discretion she does not have. She cannot abandon bioequivalence. A reconsideration exercise that would exclude bioequivalence in favour of safety

and effectiveness, as argued for by Apotex, would be outside of the framework of the *Regulations*.

[105] At the hearing, Apotex seemed to adjust its position to now contend that it knew it needed to show bioequivalence, but did not use that term in any of its proposed questions because it feared Health Canada equated "bioequivalence" with the criteria set in the bioequivalence guidelines and, therefore, the question's outcome would be pre-determined. One is hard pressed to find any support for that new contention. There was never any attempt by Apotex to clarify. On the contrary, from iteration to iteration, Apotex remained adamant that it wanted to show that its drug was safe and effective because, in the words of Mr. Terrill, "(t)he issue raised is whether or not, despite our not having provided such a study, the available information suffices to adequately demonstrate safety and effectiveness, to at least the same extent as other approved products." If bioequivalence was part of the equation, Apotex was hiding it very well.

[106] I was tempted to treat the explanation as inadmissible evidence, as not being before the Director General when she took her decision on November 16, 2015. Instead, I have considered the "explanation" and rejected it.

[107] I do not accept that the reference to safety and effectiveness was used as a misnomer for bioequivalence by Apotex. As Apotex put it in its factum, its questions have all along been variations on "Does the available information including the submitted bioequivalence studies, reasonably suffice to conclude that Apo-Omeprazole tablets are safe and effective?" It knows the

difference between the two notions. The evidence is rather that “safe and effective” was used in contradistinction to “bioequivalent”. In essence, the debate has been “safety and effectiveness” versus “bioequivalence”. This was not only during the debate on an appropriate question, but also throughout the official documentation, including the notice of application before this Court, the request for reconsideration itself and even the memorandum of fact and law.

[108] Given that the last question offered by the Minister focused on bioequivalence, as it had to, contrary to what was argued by Apotex, there is no basis to argue that the question is unreasonable. It was legitimate for the Minister to require fat fed studies to establish bioequivalence and Apotex chose to rely on its 15-years old study. The only such study is OMEC03 that Apotex wished to exclude from questions. That question of November 6, 2015, is eminently reasonable. The essential components of the question are bioequivalence and the only fat fed study, to be examined with the totality of the evidence in this ANDS, with a view to determining bioequivalence, not in respect of the guidelines, but in respect of the *Regulations*. This surely satisfies the requirements of reasonableness. Evidently, that does not constitute the question the applicant wants answered, whatever its reasons. But the applicant is not entitled to ask its question as its question would be outside the scope of the *Regulations*. It would be absurd if the applicant had to be allowed, as part of a reconsideration process, to raise issues which cannot be considered, that is that its drug is safe and effective. Only bioequivalence can do. To put it bluntly, the applicant did not have a legitimate expectation that was defeated, the Minister did not fetter her discretion by insisting on the focus to be on bioequivalence and the question is reasonable with its focus on bioequivalence including fat fed conditions. At any rate, strictly speaking, the reasonableness of the question is not squarely before the Court as the applicant

framed its case in terms of legitimate expectations and fettering of discretion in its notice of application.

[109] Apotex referred to other products which were approved without strictly meeting the bioequivalence criteria of the guidelines. The Minister argues that they met bioequivalence requirements. Even if they did not, it seems to me that these examples would tend to show that the respondent does not treat the guidelines with rigidity, thus fettering her discretion. They obviously show deviations.

[110] Furthermore, both in his report of July 23, 2014, and in his affidavit in this case, Dr. Appleton explained what actually took place in these cases. There is no common measure between these cases and the Apo-Omeprazole tablets.

[111] As for the Apo-Pantrozole, it was necessary to demonstrate bioequivalence under fasting and fed conditions. The four bioavailability studies covered fasting and low fat fed; however, Dr. Appleton reports a pharmacodynamics study in high fat fed conditions comparing the new drug to a Canadian reference product and included data from subjects who had taken the drug following a high fat meal. It was approved.

[112] The Apo-Lanzoprazole is limited to administration of the drug before a meal, in a fasted state. Nevertheless, a high fat fed study was asked for and provided: it did not meet the bioequivalence acceptance criteria. However, the high fat fed study confirmed that the new drug performed at least as well as the Canadian reference product. Based on the totality of the data,

the reconsideration panel recommended that it was sufficient to consider the new drug to be bioequivalent to the Canadian reference product. It is noteworthy that this tends to show that reconsideration panels work in their examination of what constitutes sufficient scientific evidence to demonstrate bioequivalence.

[113] In the case of Apo-Omeprazole (omeprazole base) capsules, there was a bioavailability study under fasting conditions and one under high fat fed conditions. The high fat fed study did not meet the criteria. Apotex submitted two more high fat fed bioavailability studies, but using as a comparator reference products that are not Canadian; however, the Canadian reference product, which was not marketed anymore, met the applicable standards for bioequivalence with the non-Canadian reference product. The new drug was approved. Dr. Appleton, in his report of July 23, 2014, wrote that "(t)he Cmax of 127% for the fed study with the CRP was just outside the acceptance limit for Cmax (80-125%); this in combination with the study with US Prilosec that passed acceptance criteria was judged to be acceptable for granting a declaration of bioequivalence with the CRP."

[114] For the sake of completeness, I reproduce the evidence of Dr. Appleton concerning a fourth product, that of AstraZeneca's omeprazole magnesium enteric tablets. However, the pathway chosen was not the ANDS, but rather the Supplemental New Drug Submissions [SNDS]:

> 41. Prior to the approval of AstraZeneca Canada Inc.'s ("AstraZeneca") Losec (omeprazole magnesium) enteric tablets, AstraZeneca marketed an omeprazole capsule formulation. In its submission for approval of Losec (omeprazole magnesium) enteric-coated tablets, AstraZeneca submitted a study under high-fat fed

> conditions. Other studies were provided to support Losec tablets. They were approved in 1995 on the totality of the data submitted as SNDS. Since their approval, more experience has been gained.
>
> 42. As explained during a meeting between Health Canada officials and representatives of Apotex on April 14, 2015, approval for a SNDS involves satisfying the Minister of the safety and efficacy of the drug. A bioequivalence study between Losec's omeprazole capsules and omeprazole magnesium enteric-coated tablets was not required under the *FDR*. Attached and marked as Exhibit **"D"** is a copy of the Record of Decision Apo-Omeprazole Discussion Meeting on April 14, 2015. It is explicitly stated in the Product Monograph that Losec capsules are not bioequivalent to the tablets. The approval of the tablets was based on a number of studies and not the bioequivalence study alone.

[115] This evidence is of no assistance to Apotex if it seeks to show fettering of discretion. It seems to show, on the contrary, that the Minister shows flexibility in her application of the bioequivalence requirement in cases of abbreviated new drug submissions. It also shows that bioequivalence is at the center of an ANDS. It even indicates that the applicant has supplemented in the past studies that were deficient on that front in order to obtain approval. Nothing of the sort was done in this case. In fact, it would appear that the applicant did not have much confidence in the one study that saw the light of day fifteen years after its conclusion. Apotex chose to challenge in court the need for high fat/high calorie evidence, by claiming vested rights in a decision where there was no such evidence, and then offered a study which could not be considered before putting forth OMEC03. Once offered as evidence, it sought to circumvent the bioequivalence requirement by seeking to "appeal" to a Reconsideration Panel that its product is safe and effective.

[116] I would therefore conclude that there is in this case no evidence of fettering of discretion as to the application of the bioequivalence requirement. The evidence is rather to the contrary as the other products reviewed in Dr. Appleton's evidence tend to prove. The Minister has to consider bioequivalence, as per the *Food and Drug Regulations*, and she would be acting outside the *Regulations* if she agreed to circumvent bioequivalence in the reconsideration of the matter. As for her application of bioequivalence, there is no evidence that the guidelines had taken the force of law and were to be treated without the required flexibility. I have found no evidence that other scientifically sound approaches or deviations were forbidden or that Apotex wanted to rely on other scientifically sound approaches to establish bioequivalence. That may very well be because, all along, the applicant wanted an opinion on something other than the bioequivalence of its drug: it wanted to establish before the Panel that its drug is safe and effective. That was not possible because, as the Federal Court of Appeal said in *Apotex* (2011 FCA 86), "even if a proposed new product is safe and effective, it cannot be approved through an abbreviated new drug submission if it is not bioequivalent to the reference product" (para 8).

[117] Lastly, the applicant's reliance on *Apotex Inc. v Canada (Health)*, 2013 FC 1217, a decision rendered by my colleague, Justice Catherine Kane, concerning a different new drug, Apo-Telmisartan, deserves some comments.

[118] This decision is in my view of no assistance to the applicant. The issue on which the applicant was successful was the interpretation given by the Minister to the term "identical medicinal ingredient", at the screening stage, a term found in the definition of "pharmaceutical equivalent" at C.08.001.1 of the *Regulations*. The Court also found that the Minister's position

was inconsistent. This is of no assistance to the applicant: this is not an interpretation of statute case and the Minister has not been inconsistent. There is not in this case a different interpretation given to the *Regulations* based on different circumstances or chemical composition of the drug.

[119] Similarly, the issue that the Reconsideration Panel was cancelled because the question must focus on bioequivalence with the Canadian reference product and not on whether or not the new drug is safe and effective has no kinship with the comments made in the Telmisartan case. Certainly, a question submitted to a reconsideration panel that would avoid a key issue could prove to be problematic. But that is not the case here. The proposed questions do not avert the real or key issue. In the case at bar, it was not appropriate for the Minister to consider any further a question to be put to the Reconsideration Panel that is outside the scope of what can be put before a Panel, that is whether or not a proposed new drug was safe and effective, instead of whether bioequivalence is present.

[120] Counsel for the applicant, submitted, *in extremis*, that if the Minister were willing to consider bioequivalence without fat fed studies, the question would have been acceptable. Of course. That would take the matter back to 2003 when the Minister was willing to accept bioequivalence without a high fat study. That was then. This is not the case since the decision of December 2008. I see no merit in that submission. Neither the NOC nor the Notice of Non-Compliance Withdrawal Letter is challenged.

VII. Conclusion

[121] Apotex's case is predicated on its assertion, repeated numerous times but never demonstrated, that the reconsideration would be limited to the bioequivalence in the guidelines and/or bioequivalence criteria. Guidelines are useful in helping make a determination that the interpretation of a term like "bioequivalence", which is not defined in the *Regulations,* is reasonable, but the guidelines cannot be given the force of law: they were not. The issue put to the Reconsideration Panel had to turn on the notion of bioequivalence. There is no evidence that the questions, as proposed, would signal that the Reconsideration Panel would have to adhere to the strict compliance to the guidelines. The only reference to bioequivalence is always in relation to the *Regulations*, never the guidelines. As the last question offered to Apotex continued to show, a panel of experts was to be asked to opine if the study involving fat fed meals presented by Apotex to satisfy the requirements of bioequivalence, together with the totality of the evidence, provides reliable evidence of bioavailability characteristics in order to assess safety and effectiveness through the bioequivalence with the Canadian reference product. Apotex was not satisfied and chose to challenge before this Court. It failed.

[122] As permitted by the Reconsideration Policy, the Director General can refuse reconsideration for decisions that are not eligible. It was clear in this case that Apotex would not budge and that left little choice but to cancel reconsideration.

[123] The applicant sought a number of remedies: quashing the November 16, 2015 decision to cancel the reconsideration, but directing the Minister to continue the process without fettering

her decision by insisting on strict compliance with policies and guidelines. The question favoured by the applicant ought to be put to the Panel, with its focus on the safety and effectiveness of the new drug. Counsel for the applicant also suggested at the hearing that the Court may be minded to simply return the matter to the Reconsideration Panel on the basis of the last question offered by the Director General on November 6, 2015.

[124] It seems to me that that last-ditch effort on the part of the applicant to salvage something should not succeed as it would require, as a matter of law, that the Court quash the decision of November 16, 2015 which very specifically concluded that "since we remain at an impasse, and as I indicated in my letter of November 6, 2015, the reconsideration of this submission, control number 162270 is cancelled, and the Notice of Non-Compliance – Withdrawal issued on July 28, 2014 is now final". Without quashing the decision under review, there would be no way to send the matter back on the basis of the very question rejected by Apotex. There is no reason to quash that decision as there was no fettering of discretion and legitimate expectations were met. As I have pointed out, the last question, which was rejected by the applicant in spite of being warned that "(i)f your company does not agree or accept this approach, I will consider your reconsideration request withdrawn and will declare the NON-W final", was rejected because it spoke in terms of bioequivalence and fat fed studies. There was no fettering of discretion in a question that is reasonable in the focus put on bioequivalence.

[125] The judicial review application is accordingly dismissed, with costs in favour of the respondent. The parties were in agreement that the costs should be assessed in accordance with Rule 407 of the *Federal Courts Rules* (SOR/98-106).

JUDGMENT in T-2011-15

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

Costs to be determined according to Rule 407 are awarded in favour of the respondent.

"Yvan Roy"

Judge

FEDERAL COURT

SOLICITORS OF RECORD

STYLE OF CAUSE:	APOTEX INC. v MINISTER OF HEALTH AND ATTORNEY GENERAL OF CANADA
PLACE OF HEARING:	VANCOUVER, BRITISH COLUMBIA
DATE OF HEARING:	DECEMBER 7-8, 2016
JUDGMENT AND REASONS:	ROY J.
DATED:	SEPTEMBER 25, 2017

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