Federal Court  Cour fédérale

Date: 20131223

Docket: T-942-12

Citation: 2013 FC 1217

Ottawa, Ontario, December 23, 2013

PRESENT: The Honourable Madam Justice Kane

BETWEEN:

APOTEX INC.

Applicant

and

MINISTER OF HEALTH and
ATTORNEY GENERAL OF CANADA

Respondents

PUBLIC REASONS FOR JUDGMENT AND JUDGMENT
(Confidential Reasons for Judgment and Judgment Issued December 4, 2013)

[1] This is an application for judicial review of a decision of the Director General of the Therapeutic Products Directorate [TPD] of Health Canada on behalf of the Minister of Justice, dated April 12, 2012, which refused to review the Abbreviated New Drug Submission [ANDS] of Apotex for a Notice of Compliance [NOC] for its generic drug, Apo-Telmisartan.

Overview

[2] Health Canada regulates and oversees the drug submission process in Canada. Drug manufacturers, such as the applicant, are required to file a New Drug Submission [NDS] or an Abbreviated New Drug Submission [ANDS] pursuant to the *Food and Drug Regulations*, CRC, c 870 [Regulations] enacted pursuant to the *Food and Drugs Act*, RSC 1985, c F-27 [the Act], in order to have a new drug product approved. The Minister of Health may then issue a Notice of Compliance for the drug, in accordance with the Regulations, if the drug is deemed to be safe and effective.

[3] Telmisartan is an angiotensin receptor blocker used for the treatment of hypertension. It is marketed under the brand name Micardis which is the Canadian Reference Product [CRP] or, in other words, the original product on the market. Several generic versions (also referred to as second entry products) have been approved.

[4] Apotex seeks to market its generic version of Micardis, which is Apo-Telmisartan, and cannot do so until it receives a NOC. Apotex submits that Apo-Telmisartan is pharmaceutically equivalent to the CRP (Micardis).

[5] Apotex submits that the only medicinal ingredient in its product is telmisartan, but notes that the non-medicinal ingredients or excipients include potassium hydroxide. Like Micardis, Apo-Telmisartan is made by a wet granulation process which may cause the medicinal ingredient to interact with an excipient.

[6] Apotex notes that an acid-base chemical reaction may take place in Micardis given the non-medicinal ingredient in that product is sodium hydroxide and some portion is converted to a salt form of telmisartan which would be telmisartan-sodium in the finished tablet (as disclosed in the Screening Rejection Letter). Once ingested, the two disassociate and the telmisartan (i.e. the medicinal ingredient) is absorbed in the body.

[7] In the Apotex product, potassium hydroxide is used. Through the wet granulation process the acid-base chemical reaction may take place converting some of the telmisartan into a salt form of telmisartan which would be telmisartan-potassium. Again, once ingested, the two disassociate and the telmisartan (i.e. the medicinal ingredient) is absorbed in the body.

[8] Apotex agrees that the non-medicinal ingredients differ, but emphasizes that the medicinal ingredient, as the term "ingredient" should be understood, is identical in substance and in quantity; it is telmisartan.

[9] The TPD, which makes the decision on behalf of the Minister of Health, determined that the finished product differs because Micardis is in fact telmisartan-sodium and Apo-Telmisartan is in fact telmisartan-potassium. The Minister has taken the position that the medicinal ingredient found in the finished product or dosage forms must be identical to the CRP.

[10] Apotex submits that this interpretation differs from earlier interpretations and the approval process of other generic manufacturers. In other words, Apotex's position is that it has been treated

differently and held to a different and unprecedented interpretation of the provisions and definitions in the Regulations than other generic drug manufacturers.

[11] Apotex raised two key issues: whether the Minister of Health erred in interpretation of "identical medicinal ingredient" in the definition of "pharmaceutical equivalent" and whether the Minister breached the duty of procedural fairness in the approval process, in particular, by not adhering to the Reconsideration Policy.

[12] As a preliminary issue, the Minister of Health moved to strike two affidavits submitted by Apotex on this application.

[13] For the reasons that follow, the application for judicial review is allowed. The affidavits sought to be admitted by the applicant are admitted in part. Although there were some irregularities in the approval process and in the application of the Reconsideration Policy, these irregularities, on their own or cumulatively, do not result in a breach of procedural fairness. With respect to the decision of the Minister, and acknowledging that deference is owed to the Minister's decision, which in such matters is delegated to and made by the Director General [DG] of the Therapeutics Products Directorate [TPD] of Health Canada, the decision is not reasonable. The interpretation advanced by the TPD to support the rejection of the ANDS does not reflect the principles of statutory interpretation. In addition, it is apparent that Apotex has been subjected to a different interpretation and treatment than other generic drug manufacturers. The questions put to the Reconsideration Panel were narrowed and avoided the key issue raised by Apotex. The Panel's recommendation for more clarity in the definitions highlights the very issue Apotex sought to have

addressed. While the position of the Minister may be preferable from a policy perspective, there must be a consistent approach to the ANDS process which cannot be achieved if the Minister may interpret the regulations differently based on the particular circumstances or chemical composition of the drug in question. The position advanced by the Minister should and could be clearly reflected in the Regulations if this is indeed what the Minister intends to be the policy.

The Regulatory scheme

[14] The respondent notes that the regulatory scheme has been accurately summarised in *Reddy-Cheminor Inc v Canada (Attorney General)*, 2003 FCT 542, 233 FTR 271 [*Reddy-Cheminor*] by Justice Layden-Stevenson, and I have, therefore, set out the relevant paragraphs (6-12):

> [6] The relevant provisions of the Regulations are attached to these reasons as Schedule "A". Reference to specific provisions will be included herein as required for ease of reference and convenience. Subsection 30(1) of the FDA authorizes the Governor-in-Council to enact regulations with respect to, among other things: the sale of any drug; the method of manufacture, preparation and testing of any drug in the interest of or for the prevention of injury to the health of the purchaser or consumer; the method of manufacture, preparation, preservation, packing, storing and testing of any new drug; the sale or the conditions of sale of any new drug and defining, for purposes of the Act, the expression "new drug". The provisions regarding new drugs are contained in Division 8, Part C of the Regulations.
>
> [7] It is common ground that drug manufacturers are prohibited from advertising or selling a new drug in Canada without obtaining a NOC. To seek a NOC, a manufacturer files a drug submission with the Minister (in practice, TPD Health Canada) pursuant to Division 8, Part C of the Regulations. Specifically, subsection C.08.002(1) provides that no person shall sell a new drug unless the manufacturer has filed a NDS or an ANDS that is satisfactory to the Minister and has obtained a NOC.
>
> [8] Subsection C.08.002(2) delineates the content requirements of a NDS. The NDS must include, among other things, detailed reports of the tests conducted to establish the safety of the new drug for the purpose and under the conditions recommended, as well as

substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended. The evidence indicates that this information is typically voluminous, ranging from 100 to 300 volumes of data.

[9] A different form of drug submission is available to manufacturers who wish to copy a marketed drug without having to provide the voluminous detailed reports and substantial data demonstrating clinical safety and effectiveness. This form of submission is known as an ANDS. The ANDS requires the use of a Canadian reference product i.e., a drug for which safety and efficacy have already been demonstrated. The Canadian reference product is typically a brand-name drug and the proposed generic copy is required to be the pharmaceutical equivalent. The generic manufacturer uses the Canadian reference product to demonstrate bioequivalence rather than making a direct assessment of the clinical safety or efficacy of the generic drug on the basis of extensive clinical studies.

[10] Specifically, subsection C.08.002.1(1) provides that a manufacturer may file an ANDS for a new drug where, in comparison with a Canadian reference product, the new drug is the pharmaceutical equivalent of the Canadian reference product. In general, the two products must be bioequivalent, the route of administration must be the same, and the conditions of use of the new drug must fall within those approved for the Canadian reference product.

[11] Subsection C.08.002.1(2) outlines the submission content requirements for an ANDS. An ANDS must include sufficient material for the Minister to assess the safety and efficacy of the new drug. This includes, but is not limited to, material to establish that the new drug is the pharmaceutical equivalent of the Canadian reference product and, where the Minister considers it necessary, material to demonstrate that the drugs are bioequivalent, including the evidence from any studies conducted to demonstrate pharmaceutical equivalence and bioequivalence. The terms "Canadian reference product" and "pharmaceutical equivalent" are defined in section C.08.001.1, which reads as follows:

Canadian reference product" means	« produit de référence canadien » Selon le cas :
(a) a drug in respect of which a notice of compliance is issued pursuant to section C.08.004	a) une drogue pour laquelle un avis de conformité a été délivré aux termes de l'article C.08.004

and which is marketed in Canada by the innovator of the drug,

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 pursuant to section C.08.004 cannot be used for that purpose because it is no longer marketed in Canada, or

b) 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, lorsqu'une drogue pour laquelle un avis de conformité a été délivré aux termes de l'article C.08.004 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 paragraph (a);

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 comparaison à une drogue visée à l'alinéa a).

"pharmaceutical equivalent" means a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients;

« équivalent pharmaceutique » S'entend d'une drogue nouvelle qui, par comparaison à une autre drogue, contient les mêmes quantités d'ingrédients médicinaux identiques, sous des formes posologiques comparables, mais pas nécessairement les mêmes ingrédients non médicinaux.

"specifications" means a detailed description of a new drug and of its ingredients and includes

« spécifications » S'entend de la description détaillée d'une drogue nouvelle et de ses ingrédients, notamment :

(a) a statement of all properties and qualities of the ingredients that are relevant to the manufacture and use of the new drug, including the identity, potency and purity of the ingredients,	a) la liste des propriétés et des qualités des ingrédients qui ont trait à la fabrication et à l'emploi de la drogue nouvelle, y compris leur identité, leur activité et leur pureté;
(My emphasis)	(Je souligne)

[12] Where a submission satisfies the requirements under Part C, Division 8, a NOC is issued pursuant to section C.08.004. The issuance of a NOC for an ANDS serves not only the function of permitting the manufacturer to sell or advertise the new drug, but also constitutes a declaration that the new drug is equivalent to the Canadian reference product and thereby assists the provinces and other interested parties in identifying the acceptability of the new drug for use as a substitute for the Canadian reference product.

Chronology of the ANDS

[15] The chronology of the steps taken to date with respect to Apotex's ANDS for Apo-Telmisartan provides the necessary background and context for these reasons

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[16] Apotex submitted an ANDS for its Apo-Telmisartan on December 16, 2010. On April 4, 2011 the TPD of Health Canada sent the Screening Deficiency Notice to Apotex and requested it to demonstrate that the medicinal ingredient in the Apo-Telmisartan tablets is identical to the medicinal ingredient in Micardis.

[17] The letter was sent by Valerie Walker (TPD) to Mr John Hems, Director Regulatory Intelligence, Apotex and indicated:

> *"… the following Screening Deficiency Comments have been identified;*

> *1. You are requested to provide the results of an investigation to demonstrate that the medicinal ingredient in Apo-Telmisartan is identical to that in the CRP Micardis® by Boehringer Ingelheim. The focus should be on establishing that both the innovator product and Apo-Telmisartan tablets contain the same chemical form of Telmisartan. It should be noted that Telmisartan is a carboxylic acid and the drug substance is treated with excess amount of potassium hydroxide in methyl alcohol based wet granulation during the proposed drug product manufacturing process; therefore, conversion to potassium salt is likely. Meanwhile, the innovator Micardis® contains a different base sodium hydroxide in its composition according to the CPS. You are advised that in order to meet Section C.08.001.1 requirement of the Food and Drug Regulations, a subsequent – entry product must contain " identical amounts of identical medicinal ingredients" compared to Canadian Reference Product (CRP)in accordance to the TPD Policy : Interpretation of "Identical Medicinal Ingredient" 2003".*

[18] Apotex responded on May 17, 2011 and provided the results of analyses it relied on to establish that the same chemical form of Telmisartan is present in Apo-Telmisartan and in the CRP. Apotex indicated, among other information:

> *The results of the studies unequivocally demonstrated that the manufacturing process for Apo-Telmisartan tablets does not induce any chemical reactivity between the active ingredient and the potassium hydroxide used in methyl alcohol based wet granulation. The chemical species of active ingredient present in Apo-Telmisartan tablets is Telmisartan. This is pharmaceutically equivalent to the active ingredient present in the Canadian Reference Product Micardis.*

[19] On June 21, 2011, TPD sent a Screening Rejection letter indicating that the Apotex product was rejected because it did not comply with the Regulations or with the 2003 TPD Policy on Interpretation of Identical Medicinal Ingredient.

[20] The June 21 letter was sent from Andy Hus (TPD) to John Hems (Apotex) and indicated:

> *Your response to our Screening deficiency Notice dated April 4 2011 has been carefully reviewed and is considered to be incomplete and inconclusive…..*
>
> *Your response failed to include detail and discussion of the analytical techniques, sample preparation and results. In addition it is unclear from your data if your drug product or the Canadian Reference Product contains pure active pharmaceutical ingredient or a mixture of chemical species (a mixture of potassium salt / free acid or sodium salt / free acid. Therefore, the data submitted did not provide conclusive evidence that your drug product contains "identical amounts of identical medicinal ingredient" and is pharmaceutically equivalent to the Canadian Reference Product.*

[21] On August 25, 2011, Apotex requested a reconsideration of the Screening Rejection letter in accordance with the Reconsideration Policy and set out two issues of contention and its grounds for the dispute.

[22] First, Apotex objected to the Screening Rejection letter which stated that its response to the Screening Deficiency Notice was incomplete and inconclusive. Apotex responded that this was an incorrect statement: "The studies that were provided did conclusively show that the active moiety, telmisartan, is identical in the two products, and is exactly what is claimed on the label for both products."

[23] Second, Apotex objected to the conclusion set out in the Screening Rejection letter that the data provided did not provide conclusive evidence that the Apotex product contained identical amounts of identical medicinal ingredients as required by the Regulations. Apotex noted:

> *"It appears that TPDs position asserted in this case is that, not only must the generic product use, in production of the drug product, the identical active ingredient as used in the CRP and as stated on the label, but, in addition, in the final drug product, the active ingredient must be in the identical ionic associations (salt form or forms) as in*

> *the CRP, even if the active ingredient is dissolved with other ionic substances in the manufacture of the drug product. What is in contention is whether or not this interpretation of Section C.08.001 and the Policy is correct."*

[24] On September 26, 2011 TPD advised Apotex that a Reconsideration Panel would be convened and requested that Apotex forward the name of their choice for member of the Panel. Apotex also commented on the proposed names submitted by TPD and in January 2012 confirmed their agreement on the three member panel.

[25] On February 7, 2012 Apotex provided background and questions for the Panel to consider.

[26] Apotex first requested clarification from TPD on related questions and noted that the question for the Panel would depend to some extent on how TPD responds. Apotex set out the following questions for the Panel, in the absence of such clarification:

> *1. What, if any, is substantively different about the Apo-Telmisartan compared to the other examples cited in our reconsideration which led TPD to take a different decision leading to the Screening Rejection of the Apo-Telmisartan?*
>
> *2. In light of point 1 and in light of Apotex's Request for Consideration, does the Panel agree that the Apo-Telmisartan ANDS is acceptable for review?*
>
> *3. Does the Panel agree that the appropriate basis of an ANDS should be that the submitted product uses the identical active ingredient (API) to the CRP without a requirement to prove that any ionic associations between an active ingredient and one or more ionic excipients are the same between the test product and CRP?*

[27] The questions were revised following comments from the Bureau of Pharmaceutical Science [BPS] and Apotex agreed to the revised questions on February 17, 2012. Apotex also provided background information for the Panel.

[28] The preamble to the questions noted the requirements of C.08.002.1 and C.08.001.1 of the Regulations and referred to the IMI Policy 2003 (Interpretation of 'Identical Medicinal Ingredient'). The questions, as revised, were:

> *1. Is the medicinal ingredient in Apo-Telmisartan, as described in ANDS Control Number 143046, identical to the medicinal ingredient in the Canadian Reference Product, Micardis (Boehringer Ingelheim Ltd)?*
>
> *If yes*
>
> *2. Did Apotex provide sufficient information on the identicality of the medicinal ingredient to justify acceptance of the submission for review as an ANDS.*

[29] The Reconsideration Panel met on March 5, 2012. Apotex and the BPS at Health Canada had an opportunity to make comments following the presentations and questioning. The Panel then met in camera.

[30] The DG, Barbara Sabourin, was not in attendance at the hearing as she had excused herself at the start of the hearing and advised that Dr Stewart would replace her. Dr Stewart was in attendance for the entire hearing.

[31] On April 12, 2012, the DG sent a letter to Apotex indicating that she had accepted the recommendation of the Office of Science, which had reviewed the Panel's report, to uphold the decision to reject the ANDS. The Letter included the Panel's report.

[32] The Panel's Report responded to the first question noting that the Screening Rejection Letter of June 21, 2011 and the earlier Screening Deficiency comments had alerted Apotex to the conversion and had advised it to focus on establishing that Apo-Telmisartan contains the same chemical form of Telmisartan. The Panel then stated:

> *The Screening Rejection Letter and Screening Deficiency Comments of the Therapeutic Products directorate should have made it clear to the Sponsor that the interpretation of "Identical Medicinal Ingredient" refers to the active substance as it appears in the final product and not the starting active substance (API as per WHO) definition".*
>
> (My emphasis)

[33] Based on the Panel's earlier comments, I interpret the phrase "should have made it clear" to mean that it was, in fact, made clear to Apotex. The Panel went on to state that:

> *As a consequence of the above the Panel concludes that the Sponsor has not demonstrated that the medicinal ingredient in Apo-Telmisartan is identical to that in the Canadian Reference Product.*
>
> *However, the Panel agrees unanimously that the current Guidance (Interpretation of "Identical Medicinal Ingredient" 2003-07-03) should provide a definition in the glossary of "Medicinal Ingredient" to avoid potential misinterpretation of the guidelines. In the guidelines a clear distinction should be made between the starting active substance (API as per the WHO definition) and the "medicinal ingredient", which is defined as the active substance as it occurs in the finished product. A clear definition of the term "Medicinal Ingredient" should avoid any misinterpretation in the future.*
>
> *According to the Panel's assessment, the information provided by Apotex satisfies GMP requirements with regards to the starting*

> *active substance Telmisartan (API as per WHO definition). However, as far as the identicality of the medicinal ingredient (as defined above) is concerned, the Sponsor has not addressed this issue.*

[34] The Panel concluded with the recommendation:

> *In the Notice of 2003-07-23 regarding the Interpretation of "Identical Medicinal Ingredient" the term "medicinal ingredient" should be clearly defined as being the active substance as it appears in the finished product. This would avoid confusion for Sponsors in cases where the starting active substance (API as per WHO definition) potentially undergoes chemical changes during processing into the final dosage form.*

[35] Apotex wrote to the TPD on April 18, 2012 requesting that the TPD rescind its decision. The TPD replied that the April 12, 2012 decision was final.

Standard of Review

[36] Apotex submits that the standard of review is correctness because the issue at stake is the interpretation of the regulations, which is a matter of statutory interpretation and a legal issue.

[37] While the issue involves the interpretation of the regulations, this interpretation is inextricably bound up with the science involved and with issues that fall within the expertise of the TPD at Health Canada.

[38] In *Reddy-Cheminor* the Court conducted a standard of review analysis and concluded that the appropriate standard of review for a decision similar to the present case was that of patent unreasonableness.

[39] The Federal Court of Appeal upheld the decision in *Reddy-Cheminor* (see 2004 FCA 102, 319 NR 185) and with respect to the standard of review, noted at para 8:

> [8] Second, I agree with Layden-Stevenson J. that the pragmatic and functional analysis indicates that the decision under review is entitled to a high degree of deference. The drug approval process is a complex and technical area of public administration with a direct impact on the health of Canadians. Determining whether two products contain "identical medicinal ingredients" requires scientific understanding and regulatory experience, rather than knowledge of the law or legal principles.

[40] I also note that the applicant, in seeking to admit affidavits of experts to assist the Court, argues that the issues at stake regarding the interpretation of the regulations, past practice for approval of drugs and the science or chemistry of drug production are matters beyond the ordinary knowledge of the Court. Therefore, the applicant could not disagree with the standard of review which recognises the same reality. I do appreciate that Apotex views the key issue as more of an issue of the interpretation of the regulations – i.e. a legal issue - than an issue of mixed law and fact - but in my view, it is the latter.

[41] In the post *Dunsmuir* era (*Dunsmuir v New Brunswick*, 2008 SCC 9, [2008] 1 SCR 190) the standard of review for a decision of mixed fact and law which also requires scientific knowledge as part of the factual component is reasonableness.

[42] Apotex has also raised issues of procedural fairness regarding the approval process including whether the Reconsideration Policy was followed. Issues of procedural fairness are reviewed on the standard of correctness.

The Issues

[43] As a preliminary issue the respondent moved to strike two affidavits submitted by the applicant. The motion was heard at the same time as the application for Judicial Review.

[44] Apotex has raised issues regarding the reasonableness of the decision and procedural fairness.

Preliminary Issue - The Applicant's Affidavits

[45] The respondent moved to strike the affidavits filed by the applicant of Dr Kibbe and Ms Wehner on several grounds including that these affidavits were not before the decision maker and included argument and opinion.

[46] The respondent argues that the affidavits of Dr Kibbe and Ms Wehner are unhelpful and irrelevant and introduce extrinsic expert evidence which was not before the TPD or the Reconsideration Panel (i.e. the decision maker). In addition, the affidavits include opinions and seek to interpret the provisions of the regulations, which is one of the key issues in this judicial review.

[47] The respondent does not challenge the affidavits of Mr Sherman, the CEO of Apotex, or of Mr Goldberg, the Principal Scientist of Apotex, and submits that these affidavits provide the information about the applicant's view of the process for approval and Apotex's process for the manufacture of the drug and other information of benefit to the Court.

[48] The respondent submits that in applications for judicial review, the only material that should be considered is that which was before the decision maker (*Ochapowace First Nation (Indian Band No 71) v Canada (Attorney General)*, 2007 FC 920 at para 9, 316 FTR 19) [*Ochapowace First Nation*].

[49] The respondent also relies on *Abbott Laboratories Ltd v Canada (Attorney General)*, 2008 FCA 354 at para 37, [2009] 3 FCR 547 [*Abbott*]:

> [37] The general rule in an application for judicial review is that the record before the Federal Court should not include any documentary evidence that was not before the maker of the decision sought to be reviewed. The rationale for this rule is judicial efficiency. In an application for judicial review, unlike an originating application (such as an application for prohibition under the *NOC Regulations*), the Federal Court is not the decision maker of first instance, but rather is reviewing the decision of someone else, in this case the Minister. Judicial resources would be wasted if the parties to an application for judicial review of the Minister's decision, having failed to put their best foot forward before the Minister, could hope to provide additional evidence in the Federal Court to impugn the Minister's decision.

[50] The respondent argues that the expert affidavits do not meet the test set out in *R v Mohan*, [1994] 2 SCR 9, [1994] SCJ No 36 [*Mohan*] of relevance, necessity in assisting the trier of fact, the absence of an exclusionary rule and a properly qualified expert. The respondent does not take a position on the qualifications of the affiants as experts. The key concern is the relevance and necessity of the affidavits.

[51] In the context of a judicial review, the respondent submits that the Court focuses on the reasonableness of the decision and issues of procedural fairness which are legal issues, not technical or scientific issues. The respondent disputes Apotex's position that this expert evidence will assist

the Court in assessing the reasonableness of the decision. An opinion cannot be introduced about the reasonableness of the decision nor can a legal argument be introduced about the interpretation of the regulations, as this is the issue for the Court to address.

[52] The applicant, Apotex, responds that while the issue on the judicial review is a legal issue, i.e., a question of interpretation, it is about a scientific process and must be informed by scientific knowledge as the two are integrally linked. The parties have a sophisticated understanding of the approval process, the drug making process and the various chemical reactions, but the Court does not have that same understanding or knowledge nor is the Court familiar with the specialised terminology used. Apotex submits that the Court must consider the interpretation of "identical medical ingredient" in the Regulations and cannot do so without the additional background knowledge offered by the affiants.

[53] Apotex acknowledges that the affidavit of Ms Wehner includes her opinion on the meaning of the regulations at issue and that these parts of her affidavit should be struck, but submits that otherwise, both affidavits will inform the Court.

[54] Apotex agrees that, generally, the only material that should be considered on judicial review is that which was before the decision maker (citing *Ochapowace First Nation*) but notes that the respondent has not objected to the Sherman or Goldberg affidavits, which were also not before the decision maker. Moreover, the respondent has filed the affidavit of Andrew Adams.

[55] In addition, Apotex argues that there are exceptions to the rule, including where matters of a scientific nature are at stake (*Alberta Wilderness Association v Canada (Minister of the Environment)*, 2009 FC 710, 349 FTR 63) [*Alberta Wilderness*] and where the affidavit will assist the decision maker (*Abbott*, above, at para 39).

[56] Apotex relies on *Association of Universities and Colleges of Canada v Canadian Copyright Licensing Agency*, 2012 FCA 22, 428 NR 297 [*Association of Universities*] which noted the exceptions to the rule and that the categories of exceptions remain open.

[57] Apotex submits that the affidavits of Dr Kibbe and Ms Wehner fall into such an exception because they provide general background that may assist the Court in understanding the issues relevant to the judicial review.

[58] In *Association of Universities*, the Court noted:

> [20] There are a few recognized exceptions to the general rule against this Court receiving evidence in an application for judicial review, and the list of exceptions may not be closed. These exceptions exist only in situations where the receipt of evidence by this Court is not inconsistent with the differing roles of the judicial review court and the administrative decision-maker (described in paragraphs 17-18, above). In fact, many of these exceptions tend to facilitate or advance the role of the judicial review court without offending the role of the administrative decision-maker. Three such exceptions are as follows:
>
> > (a) Sometimes this Court will receive an affidavit that provides general background in circumstances where that information might assist it in understanding the issues relevant to the judicial review: see, *e.g.*, *Estate of Corinne Kelley v. Canada*, 2011 FC 1335 at paragraphs 26-27; *Armstrong v. Canada (Attorney General)*, 2005

> FC 1013 at paragraphs 39-40; *Chopra v. Canada (Treasury Board)* (1999), 168 F.T.R. 273 at paragraph 9. Care must be taken to ensure that the affidavit does not go further and provide evidence relevant to the merits of the matter decided by the administrative decision-maker, invading the role of the latter as fact-finder and merits-decider. In this case, the applicants invoke this exception for much of the Juliano affidavit.
>
> (b) Sometimes affidavits are necessary to bring to the attention of the judicial review court procedural defects that cannot be found in the evidentiary record of the administrative decision-maker, so that the judicial review court can fulfil its role of reviewing for procedural unfairness: *e.g.*, *Keeprite Workers' Independent Union v. Keeprite Products Ltd.* (1980) 29 O.R. (2d) 513 (C.A.). For example, if it were discovered that one of the parties was bribing an administrative decision-maker, evidence of the bribe could be placed before this Court in support of a bias argument.
>
> (c) Sometimes an affidavit is received on judicial review in order to highlight the complete absence of evidence before the administrative decision-maker when it made a particular finding: *Keeprite*, *supra*.
>
> (Emphasis added)

[59] Apotex also submits that the affidavits meet the admissibility test as established in *Mohan*: the evidence is relevant as it provides information to assist the court in interpreting the term "identical medical ingredient"; it is necessary to provide the Court with a scientific understanding in order to determine if the Minister of Health made a reasonable decision; and, there is no exclusionary rule.

The affidavits are admitted in part

[60] I agree that in appropriate circumstances on judicial review, such as in this case, where the legal issues and scientific issues are linked, the Court may benefit from expert affidavits which were not before the decision maker in order to provide important context and knowledge not otherwise in the Court's knowledge or on the record.

[61] Parts of the affidavits of Dr Kibbe and Ms Wehner fall squarely into the exception to the general rule noted in *Association of Universities* as they provide general background that will assist in the Court understanding the issues on the judicial review.

[62] I find that the respondent has not been prejudiced by the applicant's submission of the two affidavits given that the respondent has had ample time to cross examine the affiants and has done so.

[63] Moreover, a great deal of the information included in the affidavits is repetitive of the information included in the affidavit of Mr Sherman and Mr Goldberg, neither of which was objected to. I also note that the respondent's affiant, Mr Adams, comments on passages of the affidavits in dispute. In addition, the parties have made written and oral submissions on the matters deposed to. Practically, while the respondent validly objects to the reliance on affidavits that were not part of the record before the decision maker, and the opinions expressed that focus on the issue before the Court, the content of the two affidavits has been otherwise put before the Court.

[64] However, I do not agree that the opinions expressed in the affidavits meet the exceptions as noted in *Abbott* and *Alberta Wilderness* and I am mindful of the caution in *Association of Universities*. While the opinions may indeed be relevant, they are not necessary – or at least they are no longer necessary - as similar opinions have been expressed in the written arguments and oral submissions and particular passages of these affidavits seek to buttress those positions. In addition, the opinions, and to the extent that legal argument is embedded in these opinions, focus on the issue that is before the Court.

[65] I have reviewed both affidavits and both include a significant amount of information on the approval process, the formulation of the drugs (i.e., the chemical background, which is not in dispute and is addressed in the other affidavits and the arguments) and the experience of the affiants regarding the approval process for other drugs.

[66] The respondent declined my request to identify parts of the affidavits of Dr Kibbe and Ms Wehner that would be acceptable to the respondent. I have, therefore, identified the parts of the two affidavits that express opinions, including the opinion on how the term "identical medicinal ingredient" should be interpreted, and have excluded those parts.

[67] In the affidavit of Dr Kibbe, paragraphs 23, 43-52, and 54 are struck.

[68] In the affidavit of Ms Wehner, paragraphs 16, 30, 36-42, 49, 50, 54-62, 66 and 67 (her opinion on interpretation) and 76-80 (her opinion on bioequivalence) are struck. As noted above, Apotex agreed that the paragraphs expressing her opinion should not be admitted. I also note that

paragraphs 43-48 provide information already acknowledged by the respondent that Micardis is in fact mislabelled and should be labelled as telmisartan-sodium.

Was Apotex denied Procedural Fairness?

[69] Apotex submits that it was denied procedural fairness primarily because the Reconsideration Policy was not followed: Apotex requested an informal process; the questions put to the Panel were skewed; the DG was not present at the hearing yet made the decision; and Apotex did not receive the Panel's Report and had no opportunity to make submissions on the Report prior to the DG making the decision.

[70] The respondent submits that procedural fairness requires that the party know the issues, have an opportunity to respond and receive adequate reasons for the decision and that, considering the process as a whole, these requirements were met: Apotex was provided with every opportunity to make submissions in the approval process including the Reconsideration Process; the TPD reviewed the ANDS and provided sufficient reasons for its decision; and, the TPD provided opportunities for Apotex to respond at every stage.

There was no breach of procedural fairness

[71] The Reconsideration Policy (Guidance for Industry, Reconsideration of Final Decisions Issued for Human Drug Submissions) was last updated in 2006 and is a public document. The policy applies to a range of drug submissions including ANDS and applies to all sponsors and to the TPD. It is described as a formal dispute resolution process. It sets out the roles and responsibilities

of all the parties, including the DG, the Drug Submission Sponsor, the Office of Science, and the Scientific Advisory Committee or Reconsideration Panel.

[72] The Policy provides that the DG is responsible for deciding on the process for the disposition of the Request for Reconsideration and deciding on the use and membership of the Scientific Advisory Committee or Reconsideration Panel. The DG is responsible for making the reconsideration decision.

[73] With respect to Apotex's submission that the process was not fair or was breached because the panel was convened first without reconsideration by the DG, the Policy does not provide for such a two step process. The Policy, as outlined in section 5.3, provides that the options include referral of the issues under dispute to an external panel or the review of issues by the Office or a combination of the two; some issues may be referred to a panel and other issues may be reviewed by the Office. Ultimately the DG determines the process that will be followed.

[74] Contrary to Apotex's suggestion, the Policy does not provide for two steps, rather two options. In the present case, the DG determined that the process would be that the reconsideration panel would address both questions. Moreover, Apotex's request for reconsideration on August 25, 2012 clearly states, "We request that, if TPD is not prepared to grant the request without reference to a Panel, the issue be referred to a panel on an urgent basis."

[75] The Policy also provides some examples of issues that may be appropriate for referral to an external panel and issues that "generally are not appropriate for referral to an external panel". The

latter includes matters in which regulatory policy or guidance or procedures are the dominant concern.

[76] Apotex views the issue of the interpretation of the regulations as one of regulatory policy that should not have been referred to a panel, and notes that the policy indicates that such matters are generally not appropriate. However, the DG chooses the process. Clearly it is not a hard and fast rule that interpretation issues should not be referred to a panel. As noted above, the parties take different positions on whether the issues were more a matter of science than interpretation. However, there are elements of both in the questions put to the panel. In fact, Apotex has taken the position, with respect to its affidavits, that the legal or interpretation issues are intertwined with the scientific issues and hence the need for the Court to be informed by the experts.

[77] Apotex appears to have requested and agreed to the Reconsideration Panel, and proposed members to participate.

[78] With respect to Apotex's argument that it was denied an opportunity to make submissions directly to the DG about the Panel's report prior to her decision, the policy does not provide for repeated submissions by the sponsor, or in particular, submissions on the advice given to the DG after the hearing. The policy provides for the Office of Science to review the Panel report and prepare recommendations for the DG.

[79] The Policy also provides for the decision to be sent to the sponsor prior to dissemination, but this is to ensure that identifying or proprietary information has been removed and the sponsor has

had an opportunity to ensure this has been done. It is not an opportunity to review and comment and make further submissions.

[80] The troubling issues are that the DG was not present at the hearing, yet she signed the decision, and the allegation that the Panel was told to consider the issue of the identicality of the medicinal ingredient in the finished product.

[81] With respect to the absence of the DG, Barbara Sabourin, I note that she was replaced by Dr Stewart, who participated at the hearing and heard all the submissions. Dr Stewart supported the recommendation of the Panel and the letter from Ms Sabourin indicates, "Dr Stewart has reviewed their report and accepted their recommendations as do I."

[82] Although it appears to be an irregularity, Apotex was heard by those that made the decision because Ms Sabourin acted on the advice of the Panel, the Office of Science and Dr Stewart, who was present.

The Questions for the Panel Avoided the Key Issue

[83] With respect to the allegation that the Panel was told to consider identicality at the time of the finished dosage, which was the issue the Panel should have addressed, I do not regard this as clearly a matter of procedural fairness. This is more related to the reasonableness of the decision regarding the interpretation of "identical medicinal ingredient" because the Panel did not address this issue as Apotex proposed and expected, yet the Minister relied on the advice of the Panel.

[84] Although Apotex had input into the questions, the conclusion reached by the Panel appears to assume that Apotex knew all along that identicality would be measured in the finished dosage. This approach ignores the issues that Apotex raised with the Panel, as set out in its earlier submissions and in its articulation of the questions and as highlighted in its background material for the Panel, all of which made it clear that the issue was whether the input ingredient or the finished dosage should be identical, and which included past approvals which pointed to the identicality of the input ingredient.

[85] The questions (which are set out above at Para 28) were watered down or narrowed but it should have been understood by the Panel that the questions, as worded, encompassed the real issue to be addressed, which was whether the identicality of the medicinal ingredient should be determined at the input stage or at the finished dosage stage.

[86] By focussing only on the narrow question without the background, the Panel did not assist in resolving the issue of how to interpret the provision at stake. The Panel's recommendation highlights that the issue remains to be resolved and that clarity is required.

[87] Given that Apotex was told by the TPD that conversion was likely, and Apotex knew that its non-medicinal ingredient (or base) was different than that used in Micardis, and given its experience as a generic drug maker, it would not likely have pursued its position that the medicinal ingredients were identical unless it was confident that the definition of identical medicinal ingredient focussed on the input ingredients.

Was the decision reasonable; Did the Minister err in interpreting "identical medicinal ingredient" in the definition of pharmaceutical equivalent in section C 08.001.1 of the FDA Regulations?

[88] Apotex submits that the Minister erred in interpreting the definition and in particular, the meaning of "identical medicinal ingredient" and raised several arguments in support of its position regarding the principles of statutory interpretation and regarding the inconsistency and lack of credibility of the Minister's position.

[89] The respondent submits that the decision is reasonable; the Regulations were interpreted in accordance with the principles of statutory interpretation and the purpose of the Act. The respondent submits that *Reddy-Cheminor* is analogous in several respects and significantly narrows the issues.

Is Reddy-Cheminor analogous?

[90] Apotex submits that the respondent has placed too much reliance on *Reddy-Cheminor*; the issues in that case were different and the conclusions the respondent draws cannot be applied.

[91] *Reddy-Cheminor* sought to have its submission for omeprazole reviewed by comparison to omeprazole magnesium (the CRP). Reddy-Cheminor submitted that the Minister should not assess the identical medicinal ingredient in the formulated product but should assess the medicine in the body (*in vivo*). The Minister found that the compounds were different medicinal ingredients and were not pharmaceutically equivalent.

[92] The Court held that the substance could not be evaluated following an *in vivo* metabolism. Justice Layden-Stevenson noted at para 62:

> [62] Third, Reddy does not suggest that the drugs in question contain identical medicinal ingredients but rather that the substances ultimately metabolize to become the same substance. It is that substance that has the therapeutic effect and on that basis, it argues that the two products contain the same medicinal ingredient. Reddy consistently refers to the "facts that exist here". I take that reference to mean its reliance on the Minister's approach regarding AstraZeneca's LOSEC. Reddy is not entitled to rely on the mode of approval of the Canadian reference product to remedy the deficiencies in its ANDS. Moreover, I agree with the respondent that the Minister cannot evaluate the specifications of a substance that may be produced following in vivo metabolism. The legislative requirement is to consider, as the medicinal ingredient, the ingredient contained in the drug.

[93] In the present case, telmisartan does not metabolize: it is the medicinal ingredient going in and it is the medicinal ingredient which delivers the drug to the body. Apotex submits that "the ingredient contained in the drug" or "contained in the drug product" means only the medicinal ingredient that is put in – i.e., telmisartan.

[94] The respondent submits that the Court in *Reddy-Cheminor* accepted that the different salt forms of medicinal ingredient are not identical and do not meet the requirements of "pharmaceutical equivalent" and pointed to para 25:

> [25] Reddy's position, that once ingested and metabolized all forms of omeprazole are transformed into a sulfenamide metabolite (the substance having the therapeutic effect) and therefore the medicinal ingredients in both the omeprazole (base) and omeprazole magnesium (salt) are identical, is not satisfactory to the Minister. At best, this position suggests that the drugs are therapeutically equivalent. The respondent notes that Reddy does not dispute that the base and salt are different substances.

[95] The respondent acknowledges that the issue in *Reddy-Cheminor* is not exactly the same, but that the Court rejected the argument that if the medicinal ingredients become the same substance in

the body, the two products must be considered to have the same medicinal ingredient. The respondent submits that the conclusion to be drawn from *Reddy-Cheminor* is that the comparison of the medicinal ingredient contained in the drug is required in its finished form, not in the body.

Reddy- Cheminor is distinguished

[96] In *Reddy-Cheminor* the input ingredients were different. The Court concluded that the identicality could not be evaluated after the transformation *in vivo*.

[97] I do not agree that the findings in *Reddy-Cheminor* resolve or guide the resolution of the issues in the present case which focus on the interpretation of the definitions and whether identicality is to be determined at the input stage or at the finished dosage stage.

Do the principles of statutory interpretation support the Minister's interpretation?

[98] Apotex submits that the fundamental principles of statutory interpretation must be applied; the words must be read in their entire context, in a grammatical and ordinary manner and in a manner that is in harmony with the overall statutory scheme and with the legislative purpose and with Parliament's intention (*Rizzo & Rizzo Shoes Ltd (Re)*, [1998] 1 SCR 27 at para 21, [1998] SCJ No 2).

[99] Apotex argues that the term "ingredient" ordinarily means the starting component and that when ingredients are combined to make something else, they cease being ingredients and become the compound or mixture created.

[100] Similarly the term "medicinal ingredients" in the definition of "pharmaceutical equivalent" should be given its ordinary meaning. Apotex argues that the ordinary meaning makes it plain that telmisartan is the input medicinal ingredient. While telmisartan-sodium may be formed and be in the finished dosage or tablet form of Micardis and telmisartan-potassium may be in the finished dosage or tablet form of Apo-Telmisartan, neither the sodium or the potassium is the medicinal ingredient; rather telmisartan is the medicinal ingredient in both.

[101] Apotex also notes that if the intention of the drafters/legislators had been to compare identicality of the medicinal ingredient in the finished product, the regulations should have used clear language to convey that concept, rather than refer to "ingredients".

[102] The respondent offers its preferred interpretation and submits that where there are transformations during manufacturing, pharmaceutical equivalence is best determined by comparing the finished dosage forms of the drug. Choosing its words carefully, the respondent submits that based on this interpretation, Apo-Telmisartan contains telmisartan-potassium which is different from the CRP, Micardis, which contains telmisartan-sodium and therefore, it is not an identical medicinal ingredient.

[103] The respondent's interpretation also relies on the definition of "pharmaceutical equivalent" in the Regulations, repeated here for ease of reference:

> "pharmaceutical equivalent" means a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients;

[104] The respondent suggests that "medicinal ingredients" are what is contained within the new drug and that the reference to 'comparable dosage form' suggests that pharmaceutical equivalence is to be assessed with reference to the finished dosage form of the drug.

[105] The respondent also relies on the dictionary definition of "ingredient" and submits that there are two possible meanings; the definition is broad enough to cover things used to make something or the things contained in something.

[106] The respondent concludes that when the broad scheme of the Regulations is considered, the proper interpretation is that "ingredient" refers to the thing in the finished dosage product.

"Ingredient" has an ordinary meaning

[107] I find the respondent's argument about the meaning of ingredient to be circuitous and unhelpful.

[108] It is true that an ingredient can mean the input ingredient and the thing contained in the finished product, but that should be one and the same thing. On an ordinary, non-scientific interpretation, the original ingredients remain the ingredients and are not referred to as the possible mixtures they become.

[109] The plain words are "contains identical amounts of the identical medicinal ingredients". I cannot reconcile the respondent's position that a drug can contain an ingredient (i.e., the ingredient

put in at the start) and also that the finished product can be the ingredient or that ingredients can also be other compounds created in the finished product.

[110] To use a simple example of a baking analogy, (because the respondent had also used a baking analogy), the same amount of egg whites and same amount of sugar could be the ingredients in different products, e.g. a pie and a cake. No one could argue that these two ingredients in the pie and cake are not identical, yet the egg whites and sugar in the pie create a meringue and the egg whites and sugar in the cookies create flavour and texture. If asked what the ingredients are in the pie, the answer would not be meringue, but would be sugar and egg whites.

[111] The respondent's submission suggests that the Minister may choose whether to compare the medicinal ingredient in the finished dosage form or at the input stage depending on whether transformations occur during manufacturing. Such a choice does not ensure any consistency in the approval process and puts generic drug makers seeking an ANDS at a disadvantage; it highlights the lack of clarity in the definition.

[112] The ordinary meaning of the words does not support the Minister's approach.

Should the same words in the Regulations have the same meaning?

[113] Apotex submits that relying on the principle of statutory interpretation that the same words in a statute have the same meaning and different words have different meanings, only the input medicinal ingredients can be required to be identical. Therefore, the term "medicinal ingredients"

should have the same meaning throughout the FDA and the only harmonious reading is that only the input ingredient is required to be identical.

[114] Apotex has noted several provisions of the Regulations that use the term "ingredients" to support its position that this means the input ingredient and not the finished dosage form. Apotex referred to: paragraphs C.08.002.1(3) (b) and (c) which refer to the requirement to provide both samples of ingredients of the new drug and samples of the new drug in its dosage form; subsection C.08.002(2) which requires that a submission contain a list of ingredients of the new drug, stated quantitatively, and the specifications for each of those ingredients; subsection C.08.002(4) that requires that, on request, the sponsor provide samples of the ingredients; and paragraph C.01.004(1) (c) that requires the label to show the quantitative list of medicinal ingredients.

[115] With respect to the requirement of subsection C.08.002(2) Apotex submits that it is impossible to provide a list of the ingredients stated quantitatively in the finished product. This can only be done for the input ingredients because it is impossible to test for the formation of a salt; i.e., there is no way to ascertain how much medicinal ingredient is converted to a salt. Only the telmisartan can be measured, not the salt. Even in the salt form telmisartan is the medicinal ingredient; it is not degraded or metabolised and remains as telmisartan.

[116] Apotex also notes that the other generics would not have been able to quantify how much salt exists in their finished product.

[117] Apotex argues that the interpretation advanced by TPD cannot possibly be correct as it would make compliance impossible. The only way a generic can comply with the regulations is to refer to the input ingredients which can be specified quantitatively.

[118] In Apotex's cross examination of the Health Canada affiant, Mr Adams, he agreed that the ingredients would be tested before they are incorporated into a finished dosage form and this would include both the medicinal and non-medicinal ingredients (see para 24-26).

[119] With respect to C.08.002.2(3) (b) and (c) that require drug makers to provide both samples of the ingredients and finished dosage, Apotex submits this would be impossible if the Minister's position prevails. The salt is buried in the tablet and a sample of the ingredient - the salt which is not the medicinal ingredient - could not be provided. Only a sample of the medicinal ingredient could be provided.

[120] On cross-examination, Mr Adams, agreed that it would not be possible to provide samples of the ingredients in the finished dosage form - e.g. a tablet, because you cannot disassemble a tablet.

[121] Apotex notes that other generics would face the same impossibility, but they were not asked to comply with the interpretation that the Minister now favours.

[122] Apotex also notes that the labelling provisions of the Regulations, C.01.004 (1) (c) (iv), require that the maker of drugs sold in Canada must show on the label "a qualitative list of the medicinal ingredients of the drug…"

[123] Although Micardis and the generics previously approved are in fact telmisartan-sodium, the only medicinal ingredient listed on the label is telmisartan. Apotex submits that these drug makers have not been required to label their products as telmisartan-sodium and, therefore, the Minister of Health must have interpreted the medicinal ingredient to be the input ingredient, which is telmisartan.

[124] The respondent submits that its interpretation is in keeping with the broader scheme of the Regulations, which is relevant to issues of statutory interpretation.

[125] With respect to the use of the term medicinal ingredient in other parts of the Regulations, the Respondent agrees that C.08.002.1(3)(b), C.08.002(2) and C.08.002(4) are better understood as meaning the thing used to make the drug (i.e. the input ingredient) but that this does not preclude the term "medicinal ingredient" being used elsewhere to mean what is found in the finished dosage product such as in C.01.004(1)(c).

"Medicinal Ingredients" should have a consistent meaning in the Regulations

[126] The principle that the same words have the same meaning does not support the respondent's position that the term "medicinal ingredients" can have a different meaning in different parts of the same Regulations. That position is completely at odds with statutory interpretation.

[127] If the basic drafting conventions are relied upon along with the ordinary meaning, the reader could not arrive at the position advanced by the Minister.

[128] If different interpretations are desired, then different words should be used or exceptions should be specifically noted.

Does the purpose of the Act support the Minister's position?

[129] Apotex submits that the purpose of the Act and Regulations is to bring safe and effective drugs to the Canadian market to advance health (*AstraZeneca Canada Inc v Canada (Minister of Health)* 2006 SCC 49 at para 12, [2006] 2 SCR 560) and its product will do so.

[130] That same principle was reiterated in *Apotex Inc v Canada (Minister of Health)*, 2012 FCA 322 at para 29, 443 NR 291 [*Apotex*]:

> [29] Apotex' analysis fails to consider the purpose of the *Food and Drugs Act*, R.S.C. 1985, c. F-27 (Act) and the Regulations. That purpose has been described by the Supreme Court of Canada to be "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 S.C.R. 560, at paragraph 12). The primary responsibility of the Minister under the Act and the Regulations is to the health and welfare of Canadians.

[131] Apotex submits that the use of excipients (the non-medicinal ingredients) does not affect safety and efficacy. Moreover, after the screening stage approval of the ANDS further steps in the process would evaluate the safety and efficacy of the drug.

[132] Apotex agrees that the Minister must be able to consider the consequences of transformation and submits that comparing identical medicinal ingredients at the time of input does not deprive the Minister of doing so. If accepted at the screening stage, the Minister still has the ability to assess safety and efficacy resulting from the use of the potassium hydroxide.

[133] Apotex notes that the Minister does not review the non-medicinal ingredients at the screening stage, but these could be reviewed later, for example, for toxicity, tolerance and stability.

[134] The respondent seeks to refine Apotex's submission on the purpose of the Act and Regulations and submits that to properly interpret the Regulations, the words of Justice Dawson in the same case (*Apotex*) at para 30 must be considered:

> [30] When the Minister exercises her discretion under section C.08.004 of the Regulations to issue a NOC, she must be satisfied that the drug is safe and effective. Nothing in the wording of the Regulations compels the contrary conclusion and it would, in my view, 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.

[135] The respondent contends that Apotex's interpretation could result in a drug being declared equivalent to Micardis even where the Minister is not satisfied of its safety and effectiveness. Although there is no evidence or allegation that this is the case, the respondent submits that the use of a different salt form could have an impact on safety and the Minister should not be precluded from inquiring if there are any changes in chemical form of a medicinal ingredient during the manufacture of the drug.

[136] The respondent also points to the Identical Medicinal Ingredient [IMI] Policy which indicates that salts are not chemically the same as ionized forms of the active moiety.

[137] The respondent again offers a definition that would be suitable to the Minister, noting that, "At a minimum, the definition of 'pharmaceutical equivalent' ought to be interpreted to mean that in cases where the Minister believes a transformation occurs during the manufacture of a finished dosage form, she is able to inquire into the chemical identity of the medicinal ingredient in the finished dosage before making the identicality assessment".

[138] The respondent submits that, with this interpretation, it would be open to the Minister to use the input Active Pharmaceutical Ingredient [API] if appropriate. But in some cases, like this case, the Minister is entitled to reject an ANDS where she is not satisfied that the medicinal ingredients in the finished dosage forms are identical and such a decision is reasonable.

The Purpose of the Act does not resolve the interpretation of "identical medicinal ingredients"

[139] There is no disagreement about the purpose of the Act. However, the screening stage is, as the name implies, for screening and it is not the final step in the approval process. Nothing precludes the Minister from inquiring into the safety and effectiveness of the drug or the transformations that may occur in the manufacturing process.

[140] The issue is the interpretation of "identical medicinal ingredients" at the screening stage. The respondent raised hypotheticals about safety. Apotex's evidence is that there are no safety

concerns about the use of its non-medicinal ingredients, in particular, the excipient potassium hydroxide. Regardless, the safety and effectiveness would be assessed at the next stages of approval.

[141] I do not accept the respondent's proposition that it should be open to the Minister to take different approaches depending on the circumstances. If this is, in fact, what the Minister does or what the Minister should do, then the definitions should be changed to address the need to compare the ingredients based on the dosage forms depending on transformations that occur after the medicinal and non-medicinal ingredients are combined.

[142] The Health Canada Policy "Interpretation of Identical Medicinal Ingredient" 2003, [IMI], Section 4, Guiding Principles, provides:

> *The term identical medicinal ingredient could literally be interpreted to imply medicinal ingredients that are both physically and chemically identical. However, in the context of the Regulations, only the chemical identicality of the medicinal ingredients is taken into account while determining pharmaceutical equivalence. Pharmaceutical equivalent drug products should contain chemically identical, but not necessarily physically identical, medicinal ingredients…*
>
> *Based on the above considerations, medicinal ingredients containing the same active moiety are classified into identical or non-identical medicinal ingredients according to the following guiding principles:*
>
> *4.3 Different complexes, esters, or salts of the same active moiety are considered non-identical.*

[143] In the affidavit of Mr Adams he commented on the use of terms at para 46, noting that there is a lack of common lexicon for terms such as "medicinal ingredients", "active moieties" and "active medicinal ingredients". He stated that the IMI Policy defines "active moiety" as excluding esters or salts and that this is distinct from the medicinal ingredient, which includes esters or salts.

He also indicated that where there is no *in situ* transformation, the API is the same as the medicinal ingredient, but where there is an *in situ* transformation, this is not the case, and the medicinal ingredient is different from the API.

[144] In my view, the wording of the IMI Policy, which does not address the point at which the identicality is to be determined, the evidence of Mr Adams, and the ultimate recommendation of the Reconsideration Panel confirms that there is a lack of clarity about the precise meaning of several terms, particularly "identical medicinal ingredients". Reliance on the purpose of the Act as an aid in the interpretation of the definition does not provide helpful guidance in this case. The term requires a clear and consistent interpretation, but this has not occurred.

Is the Minister's position inconsistent?

[145] Apotex submits that the Minister has thrust an interpretation upon Apotex that it has not used in the approval of the other generic telmisartan products.

[146] Apotex notes that although the Minister has acknowledged that Micardis and the generics previously approved convert to telmisartan-sodium, the Minister continues to allow these products to be labelled as having the medicinal ingredient, telmisartan.

[147] On cross-examination of Mr Adams, he acknowledged that the CRP, Micardis, and the generics should be labelled as telmisartan-sodium and that Health Canada had raised this issue with Boehringer, the maker of Micardis, in 2008 but had not pursued the issue.

[148] He indicated:

> *I would say that we have concerns about the medicinal ingredient. We have raised it with Boehringer. We have asked them to conduct more studies to clarify what the medicinal ingredient is in the final product.*
>
> *We have- they have not engaged in that. We haven't come to a conclusion that has conclusively shown that – excuse me – that this labelling is incorrect, that it is mis-labelled.*

[149] He added, in response to more probing questions:

> *I think you are quite right it does say that we believe it to be telmisartan-sodium, so, yes, we believe it should be labelled as telmisartan-sodium.*

[150] Apotex takes the position that the Minister would not permit such mislabelling unless the Minister also agreed, as in the past, that the medicinal ingredient is the input ingredient and that it is telmisartan.

[151] Apotex also notes that the subsection 9(1) of the Act provides that no person shall label a drug in a misleading or deceptive manner including with respect to its composition.

[152] Apotex submits that it is not credible for the Minister to permit this error with Micardis and with the generics and yet assert that approving Apo-Telmisartan and requiring it to be labelled as telmisartan-potassium would create confusion in the market.

[153] Apotex also submits that none of the other generics was required to demonstrate that their products contain identical amounts of identical medicinal ingredient in the finished product. Apotex suggests that the position taken by the Minister that the other generics did not need to do so because

of a complete conversion is contradictory to the assertion of the Minister. If a complete conversion occurred there would have been no need to ask Apotex what chemical species was contained in the CRP Micardis, as was asked in the Screening Rejection Letter.

[154] Apotex argues that other generics were not required to provide quantitative amounts of the salt (and again notes it would be impossible). The cross-examination of Mr Adams indicates that they were not required to do so due to complete conversion. Apotex submits that there is no evidence of this and this answer is also inconsistent with the screening rejection letter.

[155] There is no evidence from the Minister that the salt issue was ever considered in the approval of the other generics. There is no evidence that quantification of telmisartan-sodium was required of the CRP, Micardis, or others to establish identical quantities.

[156] Apotex submits that the salt content has no effect on the medicine the patient will receive and on cross-examination, Mr Adams agreed that the medicinal ingredient in the blood would be telmisartan.

[157] With respect to the use of the term "medicinal ingredient" in other parts of the Regulations , particularly regarding labelling, the respondent submits that the labelling policy supports the interpretation that medicinal ingredient means the ingredient in the finished dosage.

[158] The respondent notes that the IMI Policy was published in 2003 after the approval of Micardis, which was in 1999. If Micardis had been approved after the 2003 Policy, it would have

been more accurate, and in accordance with the naming conventions, to label it as telmisartan-sodium. In addition, the TPD, as noted above, raised the labelling issue with the manufacturer of Micardis in 2008, but did not pursue it, noting that there were no safety concerns and that "telmisartan" was by this point recognised as a common name.

[159] The respondent submits that the overall goal of Health Canada is the safety of the drugs and scarce resources would not be well used to pursue a labelling issue with a drug manufacturer.

[160] The respondent concedes that requiring the identical medicinal ingredient in the finished product was not considered with the early entrant generics because *in situ* transformations were not considered. It is now known that a reaction takes place, and therefore identical medicinal ingredients must be compared in the finished product.

[161] The respondent submits that TPD approved "telmisartan" as the common name in 1999 and because all the other generics that also contained telmisartan-sodium were identical to Micardis, they were also permitted to simply be labelled as telmisartan.

[162] The respondent agrees that it would not be incorrect to use the common name "telmisartan-sodium" for the CRP and the generics approved to date, but due to the consumer reliance on the existing common name, it may not be practical to do so.

The Minister's Position is Inconsistent

[163] As the respondent conceded, the CRP Micardis is currently mislabelled; it is telmisartan-sodium and should be labelled accordingly as required by the Regulations and the Act. Similarly, all the generics that have been approved to date should be labelled as telmisartan-sodium.

[164] It appears that the Minister (TPD) has not been consistent in its interpretation of the Regulations, including the labelling provisions. Whether or not scarce resources should be used to pursue a labelling issue, when there are no safety concerns, is for the Minister to determine. However, this is one more example of the inconsistent approach that Apotex has been subjected to which differs from its predecessors.

The Panel's Recommendation

[165] As noted above, the Reconsideration Panel did not resolve the underlying issue about when identicality is to be determined. However, its recommendation acknowledges the "confusion" and lack of clarity. Apotex was subjected to this confusion and would not likely have pursued its ANDS if it was pre-determined or there was a clear policy that identicality in the finished product was the requirement of the Regulations.

[166] As noted in the Chronology, the Panel recommended:

> *In the Notice of 2003-07-23 regarding the Interpretation of "Identical Medicinal Ingredient" the term "medicinal ingredient" should be clearly defined as being the active substance as it appears in the finished product. This would avoid confusion for Sponsors in cases where the starting active substance (API as per WHO definition) potentially undergoes chemical changes during processing into the final dosage form.*

Conclusion

[167] For the reasons noted above, the decision of the Minister regarding the interpretation of "identical medicinal ingredient" in the definition of pharmaceutical equivalent in section C.08.001.1 of the FDA Regulations is not reasonable when assessed against the *Dunsmuir* standard. The application for judicial review is granted, with costs to the applicant

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[168] The issue of costs will be determined following the receipt of submissions by Counsel.

JUDGMENT

THIS COURT'S JUDGMENT is that the application for judicial review is granted, with costs to the applicant. The decision of the Minister not to accept the ANDS for review is, therefore, quashed and set aside and should be reconsidered.

"Catherine M. Kane"
Judge

FEDERAL COURT

SOLICITORS OF RECORD

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