

PATENTED MEDICINE PRICES REVIEW BOARD
IN THE MATTER OF the Patent Act R.S.C. 1985, c. P-4 as amended
IN THE MATTER OF the Medicines
DIFFERIN® (adapalene)
DIFFERIN XP® (adapalene)
TACTUPUMP® (adapalene/benzoyl peroxide)
TACTUPUMP FORTE® (adapalene/benzoyl peroxide)
(Collectively, " the Adapalene Medicines")
Sold in Canada by GALDERMA CANADA Inc. (the "Respondent")

WRITTEN SUBMISSIONS OF BOARD STAFF

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PART I - SUMMARY AND ORDER SOUGHT

1. This application is about the reporting obligations of a patentee of an invention pertaining to a medicine under the *Patent Act* and *Regulations*.¹ It is also about the “merest slender thread” between a patent and a medicine that triggers those reporting obligations, as part of the test set out in the leading case, *ICN Pharmaceuticals*.²
2. Galderma Canada Inc. (“Galderma”) has failed to meet its reporting obligations. As a consequence, Board Staff is asking that the Board issue an order requiring Galderma to provide the information referred to in the Act and Regulations³ in respect of certain drug products sold in Canada by Galderma under the trade names “Differin” and “Differin XP”.
3. As part of the order, Board Staff is seeking that Galderma be required to list specific Canadian patents (collectively, the “Galderma Patents”) on the Form 1 for Differin and Differin XP, in particular:
 - a) The Form 1 for Differin (adapalene 0.1%) must list Patent No. 2,478,237 (the “’237 Patent”), Canadian Patent No. 2,656,451 (the “’451 Patent”), and Canadian Patent 2,466,321 (“the ‘321 Patent”); and
 - b) The Form 1 for Differin XP (adapalene 0.3%) must list the ‘451 Patent and the ‘321 Patent.
4. A copy of a draft order sought by Board Staff is attached as **Appendix A** to these submissions.
5. Board Staff’s position is founded on the basic characteristics of the medicine in question (the retinoid, adapalene), the rational connection of the Galderma Patents to that medicine, and the three-part test in *ICN*. Galderma concedes that two of the three branches of the *ICN*

¹ RSC 1985, c P-4 as amended (the “Act”), Book of Authorities at Tab 1, and *Patented Medicine Regulations* SOR/94-688 (the “Regulations”), Book of Authorities at Tab 2.

² *ICN Pharmaceuticals Inc v Canada (Patented Medicine Prices Review Board)*, [1997] 1 FC 32, 1996 CarswellNat 2602 at paras 47, 50 [*ICN*], Book of Authorities at Tab 3.

³ More specifically, pursuant to section 81 of the Act, requiring to Galderma provide the information referred to in section 80 of the Act and in sections 3 and 4 of the Regulations.

test are met, since Galderma is a patentee in respect of the Galderma Patents, and the adapalene medicines are being sold by Galderma in any market in Canada. The main dispute concerns whether there is a rational connection between the Galderma Patents and the medicine adapalene. In this respect, as further discussed below, *ICN* underscores that “the nexus can be one of the merest slender thread”.⁴

6. The importance of ensuring patentees meet their self-reporting obligations cannot be understated. The ability of the Patented Medicine Prices Review Board (“PMPRB”) to fulfill its consumer protection mandate depends on patentees meeting their reporting obligations. This can be seen by considering the practical implications of the position advanced by Galderma in relation to the Galderma Patents.

7. The three Galderma Patents are as follows:

- a) The ‘237 Patent was laid open on May 12, 2009 and was allowed to lapse by Galderma on March 14, 2016. The ‘237 Patent is entitled “Use of Adapalene for the Treatment of Dermatological Disorders”. The Claims in the ‘237 Patent make reference to the use of adapalene in a pharmaceutical composition at 0.3% by weight.
- b) The ‘451 Patent was laid open on January 27, 2015 and will expire on July 11, 2027. The ‘451 Patent is entitled “Composition Comprising a Retinoid and Benzoyl Peroxide”. As discussed below, Claims 9-11 and 17-19 specifically contemplate the use of adapalene in the composition.
- c) The '321 Patent was laid open on November 8, 2011, and will expire on December 9, 2022. The ‘321 Patent is entitled "Gel Comprising at least a Retinoid and Benzoyl Peroxide". It, like the '451 Patent, describes a combination product containing both a retinoid, such as adapalene, and benzoyl peroxide.⁵

⁴ *ICN*, *supra* note 2 at paras 46, 60, Book of Authorities at Tab 3.

⁵ The ‘321 Patent was not referenced in Board Staff’s Notice of Application, but was included in affidavit evidence provided by Galderma, notably at Exhibit E to the Affidavit of Trent Mayers (the ‘321 Patent Document), sworn

8. Galderma contends that it is not required to list the Galderma Patents in respect of Differin, and is not required to list the '451 and '321 Patents in respect of Differin XP. As explained below, the implication of this position is that, according to Galderma, the PMPRB has no authority over the pricing of Differin after December of 2009 (when an earlier adapalene-related patent expired), and no authority over the pricing of Differin XP after March 14, 2016 (when the '237 Patent lapsed). Thus, even though Galderma rectified other self-reporting deficiencies after this application was commenced,⁶ Board Staff finds it necessary to continue to request a failure-to-file order.

9. In summary, Board Staff's position in relation to the Galderma Patents and the medicine adapalene is that:

- a) The '237 Patent pertains to adapalene. Differin (adapalene 0.1%) and Differin XP (adapalene 0.3%) are simply two different strengths or concentrations of the identical active therapeutic agent, adapalene. The concentration difference does not affect the chemical structure or the mechanism of action of the adapalene. There is, at the very least, a slender thread connecting the '237 Patent and adapalene (i.e., Differin).
- b) The '451 Patent pertains to adapalene. The combination product disclosed in the '451 Patent comprises adapalene together with benzoyl peroxide. Although the two substances are combined in a gel vehicle, the adapalene maintains its distinct individual chemical structure and mechanism of action. Thus, the '451 Patent is

August 12, 2016, Application Record Vol. II at p 557. Board Staff considers that the '321 Patent, like the '451 Patent pertains to the medicine adapalene, and is recommending to the Board that it be included in the order sought.

⁶ The Notice of Application set out Board Staff's position that Galderma was required to report both the '237 Patent as well as the '451 patent on the Form 1 for two other adapalene medicines sold by Galderma under the trade names, "TactuPump" and "TactuPump Forte".

In response, Galderma amended the Form 1 for TactuPump Forte to list the '451 Patent as well as the '237 Patent. The Form 1 for TactuPump has only been amended to include the '451 Patent.

While Board Staff disagrees with Galderma and believes that the '327 Patent should be listed on the Form 1 for TactuPump, Board Staff is not pressing that allegation in these proceedings as the '451 Patent which Galderma has now listed on the Form 1 for TactuPump has a later expiry date than the '237 Patent.

Accordingly, although reference will be made to TactuPump and TactuPump Forte, Board Staff no longer requires an order from the Board with respect to those drug products.

connected to adapalene (i.e., Differin and Differin XP) by, at the very least, a slender thread.⁷

- c) The '321 Patent also pertains to adapalene. As with the '451 Patent, the combination product disclosed in the '321 Patent comprises a retinoid such as adapalene together with benzoyl peroxide. Once again, the adapalene in the contemplated composition maintains its distinct individual chemical structure and mechanism of action. There is, accordingly, at the very least, a slender thread connecting the '321 Patent and adapalene (i.e., Differin and Differin XP).

⁷ Galderma's arguments about synergy between adapalene and benzoyl peroxide are not relevant to the rational connection test. Galderma is not arguing that the adapalene and benzoyl peroxide combine chemically together to form a new medicine. Rather, Galderma is arguing that they act together to create an effect that is greater than if the adapalene and benzoyl peroxide were to be applied separately. This is irrelevant to the issue of whether the '451 Patent pertains to any of the medicines in the Galderma products. In any event, Galderma has provided no scientifically credible evidence of synergistic effect between adapalene and benzoyl peroxide in the combination product described in the '451 Patent.

PART II - BACKGROUND OF THIS APPLICATION

A. The Adapalene Medicines and *Acne Vulgaris*

10. Galderma is the developer of adapalene⁸ - a synthetic retinoid active therapeutic agent. Retinoids are a class of chemical compounds that are derivatives of vitamin A.⁹ The chemical structure of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthanoic acid.¹⁰ Adapalene is approved for the treatment of *acne vulgaris*.¹¹

11. For the purposes of this application, the relevant adapalene-containing drug products, all of which are produced and marketed in Canada by Galderma are:

- a) Differin Gel (adapalene 0.1% - Drug Identification Number (“DIN”) 2148749)
- b) Differin Cream (adapalene 0.1% - DIN 2231592)
- c) Differin XP Gel (adapalene 0.3% - DIN 2274000)
- d) TactuPump¹² Gel (adapalene 0.1% plus benzoyl peroxide 2.5% - DIN 2365871)
- e) TactuPump Forte Gel (adapalene gel 0.3% plus benzoyl peroxide 2.5% - DIN 2446235).¹³

12. *Acne vulgaris* is an inflammatory skin condition that manifests as pimples, whiteheads, or blackheads (comedones). Key causative factors include blockage of the hair follicle leading to formation of comedones, proliferation of the *Propionibacterium acnes* bacteria, increased sebum production and inflammation.¹⁴ In terms of prevalence, acne is estimated to affect over

⁸ Transcript of Cross-Examination of Sandrine Segura, August 31, 2016 at p 27, Application Record Vol. III at p 650.

⁹ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 8, Application Record Vol. I at p 95.

¹⁰ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 9, Application Record Vol. I at p 95.

¹¹ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 8, Application Record Vol. I at p 95.

¹² TactuPump was previously known as Tactuo in Canada, and is known as Epiduo outside of Canada: see Transcript of Cross-Examination of Trent Mayers, August 31, 2016 at p 7, Application Record, Vol. III at p 761; Transcript of Cross-Examination of Sandrine Segura, August, 31, 2016 at pp 23, 25, Application Record Vol. III at pp 646, 648.

¹³ Affidavit of Trent Mayers, sworn August 12, 2016 at para 4, Application Record Vol. II at p 444.

¹⁴ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 8, Application Record Vol. I at p 95.

80% of adolescents at some point in their lives, and can persist into adulthood. It affects over 20% of adults over 30.¹⁵

13. Adapalene is believed to work in the treatment of acne by unblocking the hair follicle (thereby reducing comedones), and by reducing inflammation.¹⁶

14. Galderma has been selling adapalene-containing drug products in Canada since 1996.¹⁷ During that time period, Galderma's adapalene-containing product line has grown to encompass the five previously mentioned DINs.

15. Adapalene has a well-established place in acne therapy.¹⁸ Another commonly used active therapeutic agent in the treatment of acne is benzoyl peroxide.¹⁹

16. Benzoyl peroxide is an organic compound consisting of two benzoyl groups bridged by a peroxide link. It is an antibacterial agent that kills *Propionibacterium acnes* through the release of free oxygen radicals. It also inhibits comedone formation. Benzoyl peroxide is not a compound that was developed by Galderma, though Galderma, in addition to many other pharmaceutical companies, does sell products containing benzoyl peroxide, both on its own and as a component of certain combination drug products.²⁰

17. Adapalene and benzoyl peroxide can be used: (a) separately in monotherapy; (b) in combination therapy (e.g., adapalene in the evening and benzoyl peroxide in the morning); or,

¹⁵ Affidavit of Dr. Jerry Tan, sworn August 5, 2016 at p 5, V.a, Application Record Vol. II at p 329.

¹⁶ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 8, Application Record Vol. I at p 95; see also Exhibit B to Affidavit of Dr. Vincent Ho (Differin and Differin XP Product Monograph), sworn June 13, 2016, Application Record Vol. I at p 156.

¹⁷ Affidavit of John Cook, sworn June 13, 2016 at para 6, Application Record Vol. I at p 23; Transcript of Cross-Examination of John Cook, August 31, 2016 at pp 23-24, Application Record Vol. III at pp 713-714; Transcript of Cross-Examination of Trent Mayers, August 31, 2016 at p 9, Application Record Vol. III at p 763.

¹⁸ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 17, Application Record Vol. I at p 606.

¹⁹ Transcript of Cross-Examination of Trent Mayers, August 31, 2016 at p 9, Application Record Vol. III at p 763.

²⁰ Transcript of Cross-Examination of Sandrine Segura, August 31, 2016 at p 27, Application Record Vol. III at p 650; Affidavit of Sandrine Segura, sworn August 16, 2016 at para 8, Application Record Vol. II at p 594; Transcript of Cross-Examination of Trent Mayers, August 31, 2016 at p 10, Application Record Vol. III at p 764.

(c) since the introduction of TactuPump and TactuPump Forte, in a single fixed-dose combination product.²¹

18. It should be noted that there is a broad range of topical products for the treatment of acne, including different retinoids other than adapalene.²²

Differin and Differin XP

19. Differin contains 0.1% adapalene and is approved for the topical treatment of acne.²³ Galderma has sold Differin in Canada under two DINs: as a gel (DIN 02148749) since 1996, and as a cream (DIN 02231592) since 1998.²⁴

20. Differin XP (sold under DIN 2274000) is a line extension of Differin.²⁵ It contains a higher concentration of adapalene - 0.3% compared to the 0.1% in Differin. Like Differin, Differin XP is indicated for the treatment of acne.²⁶ Galderma has sold Differin XP in Canada since 2007.²⁷

21. Differin Gel, Differin Cream and Differin XP Gel all contain the same active therapeutic agent – adapalene. All three drug products are subject to the same product monograph, and are approved for the same indications and clinical use.²⁸ Apart from the vehicle, the only differences in these products are that Differin XP has a higher concentration of adapalene (0.3% as opposed to 0.1% for Differin Gel and Differin Cream).²⁹

²¹ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at paras 21, 23, 24, see also Figure 1, Application Record Vol. II at pp 607-610.

²² Affidavit of Dr. Charles W. Lynde, sworn August 10, 2016 at para 19, Application Record Vol. II at p 373; Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at paras 23-24, Application Record Vol. II at pp 608-610; Affidavit of Dr. Jerry Tan, sworn August 5, 2016 at pp 7-9, Application Record Vol. II at pp 331-333.

²³ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 11, Application Record Vol. I at p 95.

²⁴ Affidavit of John Cook, sworn June 13, 2016 at para 6, see also para 11, Application Record Vol. I at p 23: Galderma also produces Differin as a lotion (DIN 2376660), but since it has never sold it in Canada, it has never filed any information regarding that product.

²⁵ Affidavit of John Cook, sworn June 13, 2016 at para 14, Application Record, Vol. I at p 24.

²⁶ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 14, Application Record Vol. I at p 96.

²⁷ Affidavit of John Cook, sworn June 13, 2016 at para 14, Application Record Vol. I at p 24.

²⁸ Exhibit B to Affidavit of Dr. Vincent Ho (Differin and Differin XP Product Monograph), sworn June 13, 2016, Application Record Vol. I at pp 140, 142.

²⁹ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at paras 14, 18, Application Record Vol. I at p 96. Differin Gel and Differin Cream have the same concentration of adapalene (0.1%) but contain different vehicles (gel versus

22. As explained by Board Staff's expert witness, dermatologist Dr. Vincent Ho, a topical medication consists of one or more active ingredients and a vehicle.³⁰ The function of the vehicle is to carry the active ingredient(s). The vehicle may be a lotion, cream, ointment, gel or suspension. The therapeutic effect, however, is provided by the active therapeutic agent.³¹

TactuPump and TactuPump Forte

23. TactuPump is a topical gel which contains both adapalene (0.1%) and benzoyl peroxide (2.5%). It is indicated for the treatment of acne.³² TactuPump Forte is a topical gel composed of adapalene (0.3%) and benzoyl peroxide (2.5%). It is indicated for the treatment of acne.³³ Galderma began selling TactuPump in Canada in 2011 and selling TactuPump Forte in 2016.³⁴

24. TactuPump and TactuPump Forte have the same active ingredients, but different concentrations of those active ingredients.³⁵ They can both be described as "combination products", or "fixed-dose combination products".³⁶

B. Adapalene Medicines and the Anatomical Therapeutic Classification (ATC) System

25. The World Health Organization's Anatomical Therapeutic Chemical ("ATC") classification system is instructive in showing the close relationship between the different variants of the medicine adapalene. The ATC classification system is used for the classification of pharmaceutical products into different groups according to the organ or system on which they

cream). Also, the vehicle in Differin XP contains poloxamer 124, whereas the vehicle in Differin Gel contains poloxamer 182: see Exhibit B to Affidavit of Dr. Vincent Ho (Differin and Differin XP Product Monograph), sworn June 13, 2016, Application Record Vol. I at p 151.

³⁰ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 21, Application Record Vol. I at p 97.

³¹ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 22, Application Record Vol. I at p 98.

³² Exhibit C to Affidavit of Dr. Vincent Ho (TactuPump and TactuPump Forte Product Monograph), sworn June 13, 2016, Application Record Vol. I at p 167.

³³ Exhibit C to Affidavit of Dr. Vincent Ho (TactuPump and TactuPump Forte Product Monograph), sworn June 13, 2016, Application Record Vol. I at p 167.

³⁴ Affidavit of Trent Mayers, sworn August 12, 2016 at para 4(iii), (iv), Application Record Vol. II at p 444.

³⁵ Affidavit of Sandrine Segura, sworn August 16, 2016 at para 6(c), (d), Application Record Vol. II at p 593.

³⁶ Affidavit of Sandrine Segura, sworn August 16, 2016 at paras 15, 31, Application Record Vol. II at pp 596, 601.

act and their therapeutic, pharmacological and chemical properties.³⁷ There are five levels of classification: “[t]he third ATC level groups pharmaceutical products according to their therapeutic indications, the fourth ATC level normally takes into consideration the mode of action and the fifth level defines the narrowest classes, including active substances taken individually”.³⁸

26. The Board’s *Compendium of Policies, Guidelines and Procedures* (“Guidelines”) refer to the ATC classification system as a useful tool for comparison purposes and, in particular, for establishing comparable dosage regimes.³⁹ The Guidelines state that Board usually begins with the fourth level of classification but may in some instances refer to the fifth level.⁴⁰

27. As indicated on Health Canada’s website, the ATC classification for adapalene (Differin and Differin XP) is as follows [emphasis added]:

D: Dermatologicals

D10: Anti-acne preparations

D10A: Anti-acne preparations for topical use

D10AD: Retinoids for topical use in acne

D10AD03: Adapalene⁴¹

28. In this case, both the fourth level of classification, retinoids, and the fifth level of classification, adapalene, reinforce that adapalene is the medicine.

³⁷ *AstraZeneca AB et al v European Commission* (2010), T-321/05, General Court (Sixth Chamber, Extended Composition) at para 154, Book of Authorities at Tab 5.

³⁸ *Ibid*, Book of Authorities at Tab 5.

³⁹ (July 2016), Patented Medicine Prices Review Board, C.8, online: <<http://www.pmprb-cepmb.gc.ca/view.asp?ccid=492>>, Book of Authorities at Tab 14.

⁴⁰ *Ibid*, C.8.2, Book of Authorities at Tab 14.

⁴¹ Confirmed by Galderma’s undertaking response, dated September 18, 2016: see Email from David Woodfield dated September 18, 2016 re: errors in transcripts, undertakings and proposed Agreed Statement of Facts, Application Record Vol. IV at p 1295. Galderma had agreed to undertake to verify this code: see Transcript of Cross-Examination of Sandrine Segura, August 31, 2016 at pp 29-30, Application Record Vol. III at pp 652-653; see also Letter from David Wilson dated September 15, 2016 re: undertakings, Application Record Vol. IV at p 1289.

29. The fourth and fifth levels of the ATC classification for TactuPump as well as TactuPump Forte further confirm that adapalene is the defining medicine as it relates to the combination products containing adapalene and benzoyl peroxide. The full ATC classification is as follows [emphasis added]:

D: Dermatologicals

D10: Anti-acne preparations

D10A: Anti-acne preparations for topical use

D10AD: Retinoids for topical use in acne

D10AD53: Adapalene combinations⁴²

30. The ATC classification system shows that the combination product of adapalene and benzoyl peroxide (D10AD53) is a sub-group of the ATC class for adapalene (D10AD03). In other words, adapalene, and the combination of adapalene and benzoyl peroxide, are closely interconnected.

C. Adapalene and Clinical Treatment Considerations

31. This case is about the rational connection between the Galderma Patents and adapalene, not about clinical treatment aspects associated with adapalene products. However, as context, Board Staff provided basic information regarding the clinical use of adapalene through Dr. Ho.

32. Dr. Ho observed that, when treating acne, clinicians have a range of topical products to choose from. A clinician will choose to prescribe a given product depending on the patient's acne type, severity and, tolerability and preference.⁴³

⁴² Confirmed by Galderma via email on September 18, 2016: see Email from David Woodfield dated September 18, 2016 re: errors in transcripts, undertakings and proposed Agreed Statement of Facts, Application Record Vol. IV at p 1295. Galderma had agreed to undertake to verify this code: see Transcript of Cross-Examination of Sandrine Segura, August 31, 2016 at pp 29-30, Application Record Vol. III at pp 652-653; see also Letter from David Wilson dated September 15, 2016 re: undertakings, Application Record Vol. IV at p 1289.

⁴³ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at Figure 1, Application Record Vol. II at p 609.

33. Retinoids, such as adapalene, as well as other compounds, including benzoyl peroxide and some antibiotics, are regularly used in the treatment of acne. Combination therapy of individual products (e.g adapalene and benzoyl peroxide, or an antibiotic and benzoyl peroxide) may also be prescribed.⁴⁴ In addition, with the introduction of the fixed-dose combination of adapalene and benzoyl peroxide (i.e., TactuPump and TactuPump Forte), clinicians have the option of prescribing the combination product. The American Academy of Dermatology guidelines of care for acne do not endorse fixed dose combination products as superior to a combination regimen of single products (for instance, adapalene and benzoyl peroxide used as separate components). Rather, they are treated as interchangeable or as alternative treatment modalities.⁴⁵

34. The treatment algorithm reproduced below from Dr. Ho's affidavit illustrates the various options available on the treatment spectrum.⁴⁶

⁴⁴ Exhibit C to Affidavit of Dr. Vincent Ho (TactuPump and TactuPump Forte Product Monograph), sworn June 13, 2016 at pp 9-10, Application Record Vol. I at pp 173-174.

⁴⁵ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 23, Application Record Vol. II at p 608.

⁴⁶ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at Figure 1, see also para 23, Application Record Vol. II at p 609, see also p 608.

	Mild	Moderate	Severe
1st Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone	Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

*Treatment algorithm from the Guidelines for the management of acne vulgaris in adolescents and young adults. The double asterisks (**) indicate that the drug may be prescribed as a fixed combination product or as separate component. BP, Benzoyl peroxide. (emphasis added)*

D. The Patents at Issue

The '237 Patent

35. The '237 Patent is entitled "Use of Adapalene for the Treatment of Dermatological Disorders" [emphasis added].

36. The first paragraph of the description states that the invention relates to the use of 6-[3-{1-adamantyl)-4-methoxyphenyl]-2-naphthanoic acid (i.e. adapalene)⁴⁷ in pharmaceutical compositions, in particular dermatological compositions.

37. The patent itself has seven claims. Claims 1-6 relate to the use of adapalene for the treatment of certain dermatological conditions, including acne. These Claims incorporate reference to a pharmaceutical composition comprises 0.3% adapalene by weight. Claim 7 relates to a pharmaceutical composition comprising, among other things, adapalene.

38. The '237 Patent was issued on May 12, 2009. The '237 Patent lapsed on March 14, 2016.⁴⁸

The '451 Patent

39. The '451 Patent is entitled "Composition Comprising a Retinoid and Benzoyl Peroxide." The '451 Patent discloses, among other things, that a retinoid is part of the composition, and in particular that: "adapalene and also its salts will be preferred"; the "preferred retinoid concentrations are between 0.0001 and 20% by weight relative to the total weight of the composition"; and "the compositions according to the invention are particularly suitable to the treatment, in a preventative and/or curative manner, of *acne vulgaris*."

40. The '451 Patent was issued on January 27, 2015, and expires on July 11, 2027.

The '321 Patent

41. The '321 Patent is entitled "Gel Comprising at least a Retinoid and Benzoyl Peroxide". It, like the '451 Patent, describes a combination product containing both a retinoid, such as adapalene, and benzoyl peroxide.

⁴⁷ Exhibit D to Affidavit of Trent Mayers (the '237 Patent Document), sworn August 12, 2016 at p 1, Application Record Vol. II at p 539.

⁴⁸ Transcript of Cross-Examination of Trent Mayers, August 31, 2016 at pp 24-25, Application Record Vol. III at pp 778-779. Mr. Mayers was unable to explain why the '237 Patent was allowed to lapse well before its expiry date. However, it is noteworthy that a U.S. patent case which found a patent similar to the Canadian '237 Patent to be invalid for obviousness. See *Galderma Laboratories, LP v Tolmar, Inc* (2013), Appeal No 2013-1034, Fed Cir (US), Book of Authorities at Tab 6.

42. Although the '321 Patent was not referenced in the Notice of Application issued earlier this year, Board Staff submits it does indeed pertain to Differin and Differin XP, as further explained below.

43. The '321 Patent was issued on November 8, 2011, and expires on December 9, 2022, about five years before the expiry of the '451 Patent.

E. Self-Reporting Obligations

44. The PMPRB's ability to fulfill its consumer protection mandate is dependent on a system of self-reporting derived from a combination of provisions in the Act and in the Regulations.

45. Subsection 80(1) of the Act requires the patentee of an invention pertaining to a medicine to provide specific information concerning that medicine:

80.(1) A patentee of an invention pertaining to a medicine shall, as required by and in accordance with the regulations, provide the Board with such information and documents as the regulations may specify respecting:

(a) the identity of the medicine;

(b) the price at which the medicine is being or has been sold in any market in Canada and elsewhere;

(c) the costs of making and marketing the medicine, where that information is available to the patentee in Canada or is within the knowledge or control of the patentee;

(d) the factors referred to in section 85; and

(e) any other related matters.⁴⁹ [emphasis added]

⁴⁹ See also, s. 81(1), and s. 88(1), which provide that:

81(1) The Board may, by order, require a patentee or former patentee of an invention pertaining to a medicine to provide the Board with information and documents respecting

(a) in the case of a patentee, any of the matters referred to in paragraphs 80(1)(a) to (e);

(b) in the case of a former patentee, any of the matters referred to in paragraphs 80(2)(a) to (e); and

(c) such other related matters as the Board may require.

46. For the purposes of patented medicines under the PMPRB's jurisdiction, as opposed to patents generally, the term "patentee" is cast in s. 79(1) in the following broad language:

"patentee", in respect of an invention pertaining to a medicine, means the person for the time being entitled to the benefit of the patent for that invention and includes, where any other person is entitled to exercise any rights in relation to that patent other than under a licence continued by subsection 11(1) of the Patent Act Amendment Act, 1992, that other person in respect of those rights.⁵⁰ [emphasis added]

47. Section 79(2) further amplifies the scope of the "patentee" definition by providing that:

79.(2) For the purposes of subsection (1) and sections 80 to 101, an invention pertains to a medicine if the invention is intended or capable of being used for medicine or for the preparation or production of medicine. [emphasis added]

48. The above provisions are the jurisdiction-conferring provisions that engage the PMPRB's consumer protection mandate, notably, with respect to the pricing of patented medicines in subsection 83(1) of the Act.⁵¹

49. As contemplated by s. 80 and s. 88(1) of the Act, and as provided for in s. 101, sections 3 and 4 of the Regulations spell out the reporting obligations of patentees of patented medicines

88 (1) A patentee of an invention pertaining to a medicine shall, as required by and in accordance with the regulations, or as the Board may, by order, require, provide the Board with such information and documents as the regulations or the order may specify respecting

- (a) the identity of the licensees in Canada of the patentee;
- (b) the revenue of the patentee, and details of the source of the revenue, whether direct or indirect, from sales of medicine in Canada; and
- (c) the expenditures made by the patentee in Canada on research and development relating to medicine.

⁵⁰ Contrast this much broader definition to the more limited "patentee" definition in section 2 of the Act: "patentee" means the person for the time being entitled to the benefit of a patent.

⁵¹ **83(1)** Where the Board finds that a patentee of an invention pertaining to a medicine is selling the medicine in any market in Canada at a price that, in the Board's opinion, is excessive, the Board may, by order, direct the patentee to cause the maximum price at which the patentee sells the medicine in that market to be reduced to such level as the Board considers not to be excessive and as is specified in the order.

in more detail, including the Form 1 and Form 2 information required to be filed with the PMPRB.⁵²

50. The fundamental importance of these self-reporting obligations was underscored by the Board in *ratio-Salbutamol HFA*,⁵³ a decision that was upheld by the Federal Court of Appeal in 2015.⁵⁴

The Board's ability to fulfil its mandate under sections 83 and 85 of the Act to monitor the prices of patented medicines and make remedial orders in response to incidences of excessive pricing is dependent on a system of self-reporting.

F. Board Staff's Application and Status of Galderma's Filings

51. The history of Galderma's filings with respect to the adapalene related products is addressed in **Appendix B**.

52. Following correspondence with the Board, Galderma declined to accede to PMPRB jurisdiction with respect to Differin in respect of the Patent '451.⁵⁵ In February of 2016, Board Staff issued the Notice of Application.⁵⁶

53. Initially, Board Staff took the position that Galderma had failed to meet its reporting obligations in relation to Differin, Differin XP, TactuPump and TactuPump Forte in connection with both the '237 and '451 Patents.⁵⁷ In its response to the Notice of Application, Galderma conceded that the Board has jurisdiction over TactuPump Forte under both of these patents, and that it has jurisdiction over TactuPump under the '451 Patent.⁵⁸

⁵² An overview of these requirements are set out in the PMPRB publication, the Patentee's Guide to Reporting.

⁵³ PMPRB-08-D3-ratio-Salbutamol HFA (2011) at para 51, Book of Authorities at Tab 7.

⁵⁴ *Canada (Attorney General) v Sandoz Canada Inc*, 2015 FCA 249, Book of Authorities at Tab 8. Leave to appeal to the Supreme Court of Canada was discontinued on September 8, 2016, Docket No 36798, Book of Authorities at Tab 8A.

⁵⁵ Affidavit of John Cook, sworn June 13, 2016 at para 22, Application Record Vol. I at p 25.

⁵⁶ Affidavit of John Cook, sworn June 13, 2016 at para 22, Application Record Vol. I at p 25.

⁵⁷ Notice of Application at para 1, Application Record Vol. I at p 7.

⁵⁸ Galderma's Response to Notice of Application, April 22, 2016 at para 18, Application Record Vol. I at p 17.

54. Galderma had also listed the '321 Patent on the Form 1 for both TactuPump and TactuPump Forte,⁵⁹ and referenced this patent in the affidavit of Trent Mayers.⁶⁰

55. Since that time, Galderma has amended the Form 1 for TactuPump Forte to list the '451 Patent as well as the '237 Patent.⁶¹ The Form 1 for TactuPump has only been amended to include the '451 Patent. While Board Staff disagrees with Galderma, and believes that the '327 Patent should be listed on the Form 1 for TactuPump, Board Staff will not pursue that allegation in these proceedings as the '451 Patent which Galderma has now listed on the Form 1 for TactuPump expires in 2027,⁶² while the '237 Patent lapsed on March 14, 2016.⁶³

⁵⁹ Appendix B.

⁶⁰ Affidavit of Trent Mayers, sworn August 12, 2016 at para 6(v), Application Record Vol. II at p 445.

⁶¹ Appendix B.

⁶² Board Staff Reply to Galderma's Response, May 12, 2016 at para 5, Application Record, Vol. I at pp 19-20; Affidavit of Trent Mayers, sworn August 12, 2016 at para 6(iii), Application Record, Vol. I at p 445.

⁶³ Board Staff Reply to Galderma's Response, May 12, 2016 at para 5, Application Record, Vol. I at pp 19-20; Affidavit of Trent Mayers, sworn August 12, 2016 at para 6(iii), Application Record, Vol. I at p 445.

PART III - LAW AND ARGUMENT

A. The Three-Part Test in *ICN*

56. In the seminal *ICN* decision, the Federal Court of Appeal laid out the following three-part test that must be satisfied in order to conclude that the Board has jurisdiction over a medicine:⁶⁴

- 1) Is the party in question a patentee of an invention?

This first part of the *ICN* test is not in dispute in this proceeding, since Galderma admits it is the patentee in respect of the Galderma Patents.⁶⁵

- 2) Does the invention pertain to a medicine? In particular, does the pharmaceutical end-product qualify as a medicine, and is there a rational connection between the invention and the medicine?

This is the only live issue in this proceeding, which turns on whether Board Staff can show the “merest slender thread” connecting the Galderma Patents to the medicine adapalene, notably, in Differin and Differin XP.

- 3) Is the medicine being sold in any market in Canada?

The third part of the *ICN* test is not at issue. It is not disputed that Galderma has sold the adapalene products (notably, Differin and Differin XP) in Canada.⁶⁶

57. This three part test is rooted in the language of the Act, and in Parliament’s intent in establishing and empowering the PMPRB with a mandate to protect consumers from excessively priced patented medicines.

⁶⁴ *ICN*, *supra* note 2 at paras 47, 50, Book of Authorities at Tab 3.

⁶⁵ Galderma’s Response to Notice of Application, April 22, 2016 at paras 1, 14, Application Record Vol. I at pp 12, 16; Transcript of Cross-Examination of Trent Mayers, August 31, 2016 at pp 18-19, Application Record Vol. III at pp 772-773; Affidavit of Trent Mayers, sworn August 12, 2016 at para 2, Application Record Vol. II at p 443.

⁶⁶ Galderma’s Response to Notice of Application, April 22, 2016 at paras 1, 3, 10, 14, Application Record Vol. I at pp 12, 14-16.

B. The Patents Pertain to the Adapalene Medicines

When Does a Patent Pertain? Jurisprudence on the Slender Thread Test

58. As set out above, s. 80(1) of the Act requires the patentee of an invention *pertaining to* a *medicine* to provide specific information concerning that medicine.⁶⁷ In a similar vein, s. 79(2) underscores the breadth of the PMPRB’s jurisdiction by using the concept of an invention that “*pertains to*” a medicine.⁶⁸

59. The Court of Appeal in *ICN* held that the term “*medicine*”, which is not defined in the Act, is to be construed broadly and in its ordinary sense, as that term is used in the vernacular.⁶⁹

60. The Court of Appeal categorically rejected the restrictive definition argued by the drug company, ICN, which would confine the concept of “*medicine*” to the specific drug product in respect of which a Notice of Compliance (“NOC”) is issued and a DIN assigned by Health Canada.⁷⁰ Indeed, the Court of Appeal held it was a “red herring” to focus on the drug product in respect of which an NOC is granted and the label applied to that product in the trade, as opposed to the active ingredient.⁷¹ The issue, the Court of Appeal held, is whether the active ingredient is intended or capable of being used as a medicine, irrespective of whether the end product is referred to by its trade name or its active ingredient.⁷²

61. The Court of Appeal expressed support for the following broad working definition of “*medicine*” adopted by the Board at the time:

⁶⁷ For convenience, s. 80(1) is repeated in part below:

80.(1) A patentee of an invention pertaining to a medicine shall, as required by and in accordance with the regulations, provide the Board with such information and documents as the regulations may specify respecting:
...[emphasis added]

⁶⁸ Again, for convenience, s. 79(2) is repeated below:

79.(2) For the purposes of subsection (1) and sections 80 to 101, an invention pertains to a medicine if the invention is intended or capable of being used for medicine or for the preparation or production of medicine.
[emphasis added]

⁶⁹ *ICN*, *supra* note 2 at paras 51-54, Book of Authorities at Tab 3.

⁷⁰ *Ibid* at paras 52-53, Book of Authorities at Tab 3.

⁷¹ *Ibid* at para 65, Book of Authorities at Tab 3.

⁷² *Ibid* at para 65, Book of Authorities at Tab 3.

Any substance or mixture of substances made by any means, whether produced biologically, chemically, or otherwise, that is applied or administered in vivo in humans or in animals to aid in diagnosis, treatment, mitigation or prevention of disease, symptoms, disorders, abnormal physical states, or modifying organic functions in humans and or animals, however administered.

62. In addition, the Court of Appeal provided important guidance on the meaning and effect of the word “pertaining”, in the phrase, “an invention *pertaining* to a medicine”. The Court of Appeal held that the use of the word “pertaining”, or similarly the word “pertains”, evinces a clear intention that the nexus between the patent and the medicine is of “broad import”. As the Court Court of Appeal emphasized, “the nexus can be one of the merest slender thread” [emphasis added].

63. More specifically, the Court of Appeal ruled, among other things, that:

- a) It is unnecessary to go beyond the face of a patent when establishing the required nexus, recognizing that the Board does not have the experience or expertise to engage in patent claims constructions.⁷³
- b) It is sufficient that an invention is intended to be or capable of being used for a medicine for it to pertain to that medicine.⁷⁴

64. *ICN* expressly linked the concept that the rational connection between an invention and a medicine need only be “the merest slender thread” to what was intended by Parliament to allow the PMPRB to fulfill its consumer-protection mandate, holding that:

Requiring a stronger nexus would provide a window of opportunity for pharmaceutical companies to avoid the jurisdiction of the Board, and would limit the ability of the Board to protect Canadian consumers from excessive pricing.⁷⁵

65. In *ICN*, the Federal Court of Appeal found that the slender thread was made out, since the patent at issue outlined an enzymatic process which was intended to produce the medicine,

⁷³ *Ibid* at paras 46, 61, Book of Authorities at Tab 3.

⁷⁴ *Ibid* at paras 63, 65, Book of Authorities at Tab 3.

⁷⁵ *Ibid* at paras 46, 60, Book of Authorities at Tab 3.

i.e., the active ingredient, ribavirin. Evidence that this patent could not be used to make commercial quantities of ribavirin did not affect the finding of a slender thread between the patent and the medicine. It was sufficient, the Court of Appeal held, if the patent is intended or capable of being used for a medicine.⁷⁶ Likewise, the Court of Appeal held it was a “red herring” to focus on the trade name of the medicine (in that instance, Virazole). The medicine was the active ingredient, ribavirin, not the trade-name, Virazole.

66. The reasoning in *ICN* was applied by the Board, as upheld by the Federal Court, in *Nicoderm*,⁷⁷ a case dealing with a nicotine patch. The Board held that the slender thread was made out between the patent in question and the nicotine patch, even though there was no scientific certainty as to whether nicotine in solution was capable of forming crystalline hydrates, as claimed in the patent.⁷⁸

67. The ‘dicing and slicing’ of provisions conferring jurisdiction on the PMPRB through narrow and restrictive interpretations was also emphatically rejected by the Supreme Court of Canada in *Celgene Corp v Canada (Attorney General)*,⁷⁹ in relation to the third branch of the *ICN* three-part test:

In rejecting the technical commercial law definition, the Board was guided by the consumer protection goals of its mandate, concluding that Celgene’s approach would undercut these objectives by preventing the Board from protecting Canadian purchasers of Thalomid and other foreign-sold SAP patented medicines.

The Board’s interpretive choice is supported by the legislative history.⁸⁰

⁷⁶ *Ibid* at para 63, Book of Authorities at Tab 3.

⁷⁷ PMPRB-99-D6-NICODERM (2000) [PMPRB-99-D6], Book of Authorities at Tab 9, *aff’d Hoechst Marion Roussel Canada Inc v Canada (Attorney General)*, 2005 FC 1552 at para 117, [2006] 3 FCR 536, Book of Authorities at Tab 10.

⁷⁸ PMPRB-99-D6, *supra* note 77 at p 14, Book of Authorities at Tab 9.

⁷⁹ 2011 SCC 1, [2011] 1 SCR 3, Book of Authorities at Tab 11.

⁸⁰ *Ibid* at paras 25-26, Book of Authorities at Tab 11.

The '237 Patent Pertains to Differin

68. Galderma concedes that the '237 patent pertains to Differin XP (0.3% adapalene), and has filed the required Form 1 and Form 2 information accordingly.⁸¹ However, contrary to Galderma's assertions, the '237 Patent also pertains Differin (0.1% adapalene).

69. Board Staff's position is supported by the following:

- a) The very name of the '237 Patent, "Use of Adapalene for the Treatment of Dermatological Disorders",⁸² is suggestive of a rational connection, or at least a slender thread, between the '237 Patent and adapalene 0.1%.
- b) The chemical structure of adapalene is identical to that referred to in the abstract of the '237 Patent, and in Claims 1, 2, 3, 6 and 7 of that patent, namely, 6-[3-{1-adamantyl)-4-methoxyphenyl]-2-naphthanoic acid.⁸³
- c) The 0.3% adapalene formulation is merely a line extension of the adapalene 0.1% formulation by virtue of simply being a different concentration of the same active therapeutic agent.⁸⁴
- d) The 0.3% adapalene formulation (Differin XP) and the 0.1% formulation (Differin) are subject to the same product monograph, and share, according to that same product monograph, the same basic indication, namely, the treatment of *acne vulgaris*.⁸⁵

⁸¹ Galderma Response to Notice of Application of Board Staff, April 22, 2016 at paras 16(b), 17, Application Record, Vol. I at pp 16-17.

⁸² Exhibit F to Affidavit of John Cook (the '237 Patent Document), sworn June 13, 2016, Application Record, Vol. I at p 44.

⁸³ Exhibit F to Affidavit of John Cook (the '237 Patent Document), sworn June 13, 2016, Application Record, Vol. I at p 45; see also Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 9, Application Record, Vol. I at p 95.

⁸⁴ Affidavit of John Cook, sworn June 13, 2016 at para 14, Application Record, Vol. I at p 24.

⁸⁵ Exhibit B to Affidavit of Dr. Vincent Ho (Differin and Differin XP Product Monograph), sworn June 13, 2016, Application Record, Vol. I at p 142.

70. It might be suggested that the '237 Patent does not pertain to adapalene (Differin XP) because of patent claims that reference 0.3% by weight, or 3 mg per gram,⁸⁶ whereas the Differin 0.1% adapalene formulations use a concentration of 0.1% by weight or 1 mg per gram. Such a suggestion would be contrary to the established principles in the case law reviewed above. It is very similar to the restrictive interpretation rejected in *ICN*, in which ICN attempted to define the medicine at the level of the NOC or DIN issued by Health Canada, rather than in reference to the active therapeutic ingredient.

71. Furthermore, as demonstrated by the expert evidence of Dr. Ho, the chemical structure of the adapalene, and the mechanism of action of the adapalene, are the same in Differin and Differin XP.⁸⁷ Dr. Ho's evidence is that the different concentration simply allows the clinician to tailor the medication to the patient's particular skin type to obtain optimal results.⁸⁸

72. In short, the concentration of adapalene in Differin may differ from what is referenced in the '327 Patent, but this is not sufficient to sever the rational connection between the '327 Patent and the medicine adapalene. Whether in a formulation at 0.1% concentration, or at 0.3% concentration, adapalene is adapalene.

The '451 and '321 Patents Pertain to Differin and Differin XP

73. Galderma concedes that the '451 and '321 Patents pertain to TactuPump and TactuPump Forte and this is reflected in Galderma's Form 1 current reporting for those products.⁸⁹ However, contrary to Galderma's assertions, the '451 and '321 Patents also pertain to Differin and Differin XP.

74. As previously discussed, Patent '451 is entitled "Composition Comprising a Retinoid and Benzoyl Peroxide", while the '321 Patent is entitled "Gel Comprising at least a Retinoid and Benzoyl Peroxide". Adapalene is a retinoid. Indeed, Claim 18 in Patent '451 makes explicit

⁸⁶ Exhibit F to Affidavit of John Cook (the '237 Patent Document), sworn June 13, 2016, Application Record, Vol. I at pp 61-62 (see Claims 1, 6, and 7).

⁸⁷ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 para 18, Application Record, Vol. I at p 96.

⁸⁸ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 para 18, Application Record, Vol. I at p 96; Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 23, Application Record, Vol. II at p 608.

⁸⁹ Appendix B.

reference to adapalene together with certain other compositional ingredients. The Claims in Patent '321 also make repeated references to adapalene, alongside certain other compositional ingredients.⁹⁰

75. The mention of the benzoyl peroxide in the '451 Patent does not negate the fact that the patent pertains to adapalene.⁹¹ As explained by Board Staff's expert, Dr. Ho, the adapalene and benzoyl peroxide in the combination product is stable. In other words, the combination does not lead to any change in the chemical structure and concentration of either active ingredient.⁹²

76. Galderma does not dispute this point, either through its expert or fact witnesses. On the contrary, Galderma's witness, Sandrine Segura, gave evidence that the physical and chemical stability of the adapalene/benzoyl peroxide combination was a key design criterion for Galderma.⁹³ This is because adapalene and benzoyl peroxide are difficult to combine in a single product due to the oxidizing properties and pH characteristics associated with benzoyl peroxide.⁹⁴ Moreover, the '451 Patent document states that it contains two active principles, both of which are stable in the composition due to a stabilizing vehicle. This implies that each of the active therapeutic agents has its own effect. The same is true of the '321 Patent.

77. Furthermore, the adapalene contained in the combination product has the same structure and the same mechanism of action as the adapalene in the single drug product formulation (Differin and Differin XP).⁹⁵ The chemical structure and the mechanism of action of the adapalene do not undergo change by virtue of being combined in a single, stable

⁹⁰ Exhibit E to Affidavit of Trent Mayers (the '321 Patent Document), sworn August 12, 2016, Application Record, Vol. II at pp 587-591.

⁹¹ A corollary of this logic is that the '451 Patent also pertains to benzoyl peroxide, so, for example, a prescription product sold by Galderma that contains benzoyl peroxide or a prescription drug product that contains both benzoyl peroxide and adapalene would be rationally connected to the '451 Patent as well (this is not an issue here as Galderma has admitted that the '451 Patent pertains to its benzoyl peroxide-containing prescription products TactuPump and TactuPump Forte).

⁹² Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at paras 18, 21, Application Record, Vol. I at pp 96, 97.

⁹³ Affidavit of Sandrine Segura, sworn August 16, 2016 at paras 15-29, Application Record, Vol. II at pp 596-600.

⁹⁴ Affidavit of Sandrine Segura, sworn August 16, 2016 at para 14, Application Record, Vol. II at p 596.

⁹⁵ Affidavit of Dr. Vincent Ho, sworn June 13, 2016 at para 18, Application Record, Vol. I at p 96; Affidavit of Sandrine Segura, sworn August 16, 2016 at paras 6(a)-(b), 7, Application Record, Vol. II at pp 593-594.

combination product. The Product Monograph for TactuPump and TactuPump Forte emphasizes this aspect of the combination product, stating that it:

combines two active substances, which have complementary mechanisms of action. The targets of this action are distinct with no known pharmacodynamic interactions.⁹⁶

78. Similar considerations apply to any suggestion of alleged synergistic effects associated with the combination adapalene/benzoyl peroxide product. Whether the adapalene/benzoyl peroxide product provide synergistic effects⁹⁷ compared to a combination regimen of adapalene and benzoyl peroxide used on their own, has nothing to do with whether the '451 and '321 Patents pertain to adapalene. This is because the adapalene in the adapalene/benzoyl peroxide products is chemically distinct and physically separate from the benzoyl peroxide in the combination product.

79. Finally, the rational connection (or at least, slender thread) between the '451 and '321 Patents and the adapalene medicines (including Differin and Differin XP) is also supported by the WHO's ATC classification system. As previously noted, the ATC code for adapalene and adapalene combinations is as follows [emphasis added]:

D: Dermatologicals

D10: Anti-acne preparations

D10A: Anti-acne preparations for topical use

D10AD: Retinoids for topical use in acne

D10AD03 Adapalene

D10AD53: Adapalene combinations

⁹⁶ Exhibit C to Affidavit of Dr. Vincent Ho (TactuPump and TactuPump Forte Product Monograph), sworn June 13, 2016, Application Record, Vol. I at p 179.

⁹⁷ While Board Staff considers Galderma's "synergy" arguments to be irrelevant to the issue of whether the '451 Patent pertains to adapalene (Differin and Differin XP), if the Board finds it necessary to address these additional considerations further, they are discussed in **Appendix C**. **Appendix C** also addresses points related to alleged compliance advantages of the combination product raised by Galderma in the cross-examination of Dr. Ho, which Board Staff also submits are not relevant to whether the '451 and '321 Patents pertain to adapalene (Differin and Differin XP).

80. The WHO ATC codes identify adapalene at the fourth ATC classification level, reflecting its therapeutic, pharmacological and chemical properties. The fifth ATC level defines the narrowest classes. It is at the fifth ATC level that provision is made for “adapalene combinations”.

81. In the parlance of the ATC classification system, the ‘451 and ‘321 patents involve “adapalene combinations” (i.e., combinations of adapalene and benzoyl peroxide). In this regard it is noteworthy that, from an ATC classification perspective:

- a) Adapalene combinations (D10AD53) are classified as a derivative or subset of adapalene (D10AD03);
- b) The classification of adapalene combinations is provided for at the narrowest classification level in the ATC system, the fifth level;
- c) The WHO did not see a large enough distinction between adapalene and the combination product to give the latter its own fourth-level category; and
- d) The WHO also classified the combination product as a sub-group of adapalene, not as a sub-group of benzoyl peroxide.

82. The ATC classification system is consistent with Board Staff’s position that the adapalene products are closely connected, rather than completely separate distinct products. They each have their own individual variations as it relates to the vehicle (gel versus cream), the strength (0.1% v. 0.3%) and whether they are used in combination with another substance (i.e. benzoyl peroxide). But in each case, adapalene is adapalene.

83. The Board is not bound to follow the ATC classification system in determining whether patents concerned with adapalene/benzoyl peroxides combinations are rationally connected with adapalene medicines. However, in this instance, the guidance provided by the ATC classification system is helpful and consistent with the test in *ICN* and with all of the evidence supporting Board Staff’s position that the ‘451 Patent meets the “slender thread” test with respect to adapalene-containing medicines such as Differin and Differin XP.

PART IV - CONCLUSION

84. For all of the reasons set out in these submissions, Board Staff respectfully asks that the Board issue an order substantially in the form set out in **Appendix A**.

ALL OF WHICH IS RESPECTFULLY SUBMITTED this 19th day of September, 2016.

Original signature redacted

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APPENDIX A

PATENTED MEDICINE PRICES REVIEW BOARD

IN THE MATTER OF the Patent Act R.S.C. 1985, c. P-4 as amended

IN THE MATTER OF the Medicines

DIFFERIN[®] (adapalene)

DIFFERIN XP[®] (adapalene)

TACTUPUMP[®] (adapalene/benzoyl peroxide)

TACTUPUMP FORTE[®] (adapalene/benzoyl peroxide)

(Collectively, "the Adapalene Medicines")

Sold in Canada by GALDERMA CANADA Inc. (the "Respondent")

BOARD ORDER

The Board hereby orders that:

1. Galderma Canada Inc. ("Galderma") shall, within 90 days of the date of this Order, on or before [DATE], file with the Patented Medicine Prices Review Board:
 - a. An updated Form 1 in accordance with section 3 of the *Patented Medicine Regulations*, SOR/94-688 (the "Regulations") for each of the drug products listed below and in respect of each of the Drug Information Numbers ("DIN") listed for each medicine:
 - i. Differin
 1. DIN 2148749 (0.1% adapalene gel)
 2. DIN 2231592 (0.1% adapalene cream)
 - ii. Differin XP
 1. DIN 227400 (0.3% adapalene gel).
 - b. All of the prescribed Form 2 information (the "Form 2 Information") identifying and concerning the price of each medicine, in accordance with section 4 of the Regulations, as follows:

- i. Differin (DIN 2148749) for the period of January 1, 2010 to the present and thereafter in accordance with the *Patent Act*, RSC 1985, c P-4 (the “Act”), the Regulations and any applicable instructions in the Board’s Compendium of Policies, Guidelines and Procedures;
 - ii. Differin (DIN 2231592) for the period of January 1, 2010 to the present and thereafter in accordance with the Act, the Regulations and any applicable instructions in the Board’s Compendium of Policies, Guidelines and Procedures;
 - iii. Differin XP (DIN 227400) for the period of March 15, 2016 to the present and thereafter in accordance with the Act, the Regulations and any applicable instructions in the Board’s Compendium of Policies, Guidelines and Procedures.
2. Galderma shall ensure that the updated Form 1 for the Differin drug products (DIN 2148749 and DIN 2231592) list Canadian Patent No. 2,478,237, Canadian Patent No. 2,656,451 and Canadian Patent No. 2,466,321 in section 7, “Patent Number of Reporting Patentee’s Inventions Pertaining to the Medicine”.
3. Galderma shall ensure that the updated Form 1 for the Differin XP drug product (DIN 227400) lists Canadian Patent No. 2,656,451 and Canadian Patent No. 2,466,321 in section 7, “Patent Number of Reporting Patentee’s Inventions Pertaining to the Medicine”.
4. The parties may at any time seek directions from the Board regarding any matters with respect to this Order.

Board Members: _____

Board Counsel: _____

Guillaume Couillard
Secretary of the Board

APPENDIX B - STATUS OF FILINGS BY GALDERMA IN RESPECT OF ADAPALENE-CONTAINING PRODUCTS

The issue in these proceedings is whether Galderma Canada Inc. has met its self-reporting obligations under the Act and Regulations. Accordingly, it is important that the Board hearing this application have current and accurate information with respect to Galderma's filings with the PMPRB.

Prior to the completion of the cross-examinations, counsel for Galderma and counsel for Board Staff discussed updating the record with respect to Galderma's filings, particularly given that additional information had been filed by Galderma since the issuance of Board Staff's Notice of Application.

On September 15, 2016, counsel to Board Staff circulated a draft agreed statement of facts in respect of Galderma's filings with the PMPRB. The agreed statement of facts included the summary chart set out below. Galderma did not identify any errors in the agreed statement of facts, or the summary chart, but would not consent to the filing of this information.

Given the importance of providing the Panel with accurate filing information, counsel for Board Staff will be seeking leave at the hearing to file this summary chart.

Product	DIN	Form 1 last filed/amended	Form 2 data filed with PMPRB	Patents on file as of December 2015	Patents on file as of most recent data	Status of Patents filed
Differin Gel	2148749	June 18, 2002	Jan. 1996 to Dec. 29, 2009	1,266,646	1,266,646	Expired
				1,312,075	1,312,075	Expired
Differin Cream	2231592	June 18, 2002	Jan. 1998 to Dec. 29, 2009	1,266,646	1,266,646	Expired
				1,312,075	1,312,075	Expired
Differin XP	2274000	June 2, 2015	Jan. 2007 to Mar. 16, 2016	1,266,646	1,266,646	Expired
				1,312,075	1,312,075	Expired
				2,478,237	2,478,237	Lapsed (Mar. 14, 2016)
TactuPump (formerly Tactuo)	2365871	June 27, 2016	May 2011 to June 2016 (current)	2,466,321	2,466,321	Valid
					2,656,451	Valid
TactuPump Forte	2446235	June 27, 2016	Jan. 2016 – June 2016 (current)	2,466,321	2,466,321	Valid
					2,478,237	Lapsed (Mar. 14, 2016)
					2,656,451	Valid

APPENDIX C

1. The suggestions that the combination of adapalene and benzoyl peroxide in a gel vehicle exhibits synergy beyond the individual effects of its components, or that this combination product increases patient compliance, are not relevant to the *ICN* rational connection test. Likewise, any attempts to distinguish and compartmentalize each of Galderma's adapalene-containing products based on expert opinions about clinical practice distinctions are equally irrelevant to the *ICN* test.
2. Such suggestions, which focus on the alleged clinical advantages and disadvantages of the various adapalene containing drug products, distract from the fundamental issue which the Board must decide: whether there is a "merest slender thread" thread connecting the Galderma Patents to adapalene.
3. Nevertheless, should the Board find it necessary to address these suggestions, they *also* fail on their merits. This Appendix will discuss the significant flaws in Galderma's expert evidence purporting to show synergy and increased compliance arising from the combination product, as well as clinical treatment differences between the adapalene-containing products.

A. No Evidence of Synergy between Adapalene and Benzoyl Peroxide in the Combination Product

4. Even if synergy is relevant to the issues being heard in this application, which Board Staff denies, Galderma has provided no reliable scientific evidence that there is a "synergistic effect" between the active ingredients, adapalene and benzoyl peroxide, in the combination product.
5. A synergistic effect means that the two active therapeutic ingredients have a therapeutic effect that is greater than the effect resulting from the addition of the effects obtained by each of the two active principles taken separately.⁹⁸
6. As was stated succinctly by Dr. Vincent Ho in his cross-examination, "[i]f you claim synergy, you have to demonstrate it."⁹⁹ Galderma has not done so.

⁹⁸ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at p 52, Application Record Vol IV at p 1196.

7. Dr. Jerry Tan and Dr. Charles Lynde, the dermatologists retained by Galderma to give evidence in this application, both claim in their respective affidavits that scientific studies have shown the synergistic effect of the adapalene-benzoyl peroxide combination product. However, Dr. Ho highlighted serious reliability issues with respect to the studies on which Dr. Tan and Dr. Lynde base their conclusions. A literature review in the journal *Lancet*, by Williams et al has similarly questioned these types of studies, noting that they are “methodologically flawed” and compromised by “significant potential conflicts of interest”.¹⁰⁰

8. First, and most importantly, “[t]he three clinical trials conducted for Galderma and relied on by Dr. Tan and Dr. Lynde (the “Galderma Studies”) do not compare, on a head-to-head basis, the composition comprising both adapalene and benzoyl peroxide against adapalene and benzoyl peroxide applied separately.”¹⁰¹ Rather, those trials were designed to simply demonstrate whether the combination product has a higher efficacy than the use of adapalene alone, or benzoyl peroxide alone.¹⁰² A trial properly testing for synergy would compare the vehicle (applied in the morning) and the combination product (applied in the evening), versus benzoyl peroxide (applied in the morning) and adapalene (applied in the evening).¹⁰³ However, as Dr. Tan and Dr. Lynde admitted, no such trial has ever been done.¹⁰⁴ Galderma’s other witnesses were unable to point to such a head-to-head study either.¹⁰⁵

⁹⁹ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at p 70, Application Record Vol IV at p 1214.

¹⁰⁰ Exhibit A of Affidavit of Dr. Vincent Ho (Williams et al article, “Acne Vulgaris”), sworn August 22, 2016, cited at para 21, Application Record Vol. II at p 617; see also Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at p 80 (on re-examination), Application Record Vol. IV at p 1224, in which Dr. Ho quotes and comments on the article.

¹⁰¹ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 11, Application Record Vol. II at pp 604-605.

¹⁰² Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 11, Application Record Vol. II at pp 604-605.

¹⁰³ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 10, Application Record Vol. II at p 604.

¹⁰⁴ Transcript of Cross-Examination of Dr. Jerry Tan, September 1, 2016 at p 46, Application Record Vol. III at p 878; Transcript of Cross-Examination of Dr. Charles W. Lynde, September 1, 2016 at pp 26-27, Application Record Vol. IV at pp 1015, 1017.

¹⁰⁵ Transcript of Cross-Examination of Leithe Holowaty, September 2, 2016 at p 17, Application Record Vol. IV at p 1056; Transcript of Cross-Examination of Trent Mayers, August 31, 2016 at pp 14-15, Application Record Vol. III at pp 768-769. When questioning Mr. Mayers on that issue, Board Staff counsel asked him to undertake to verify whether such a study was ever conducted; Galderma counsel said he would take it under advisement but subsequently refused to answer: see Email from David Woodfield dated September 18, 2016 re: errors in transcripts, undertakings and proposed Agreed Statement of Facts, Application Record Vol. IV at p 1295.

9. In an attempt to fill this gap and purport to show synergies in the combination product, Tan et al. conducted a pooled analysis combining the results from three studies (the Galderma Studies) that compared the combination product to the individual products used on their own. As Dr. Ho pointed out, such a pooled analysis must be treated with caution, as it “ignores characteristics or differences of the individual studies being pooled and can sometimes yield spurious results”.¹⁰⁶ In Dr. Ho’s opinion, Tan et al failed to interpret the results of their pooled analysis with the requisite caution and rigour.

10. Tan et al’s analysis is flawed in another way: it defined synergistic efficacy as net efficacy of the combination exceeding sum of net efficacy of each active component. Net efficacy of each active ingredient was determined by subtracting out the efficacy of the vehicle. As pointed out by Dr. Ho, this is a questionable approach because, among other things, it would mean that the efficacy of adapalene is only 4%-6%, which is hardly worthy of its widespread use in acne therapy.¹⁰⁷

11. Dr. Ho’s concern that the Galderma studies were not designed to measure synergy is supported by the Board’s own jurisprudence. In *Dovobet*, the Board found that “the only reliable evidence that would establish greater clinical effectiveness than a combination therapy involving the active ingredients of the combination medicine would be a properly structured and administered (presumably double-blind, head-to-head, statistically sound) trial.”¹⁰⁸ In this case, as Dr. Ho pointed out, no such evidence has been submitted.

12. Dr. Ho was pressed in cross-examination by Galderma’s counsel, who suggested it was just Dr. Ho’s opinion that Galderma had failed to support its synergy claims, and that Dr. Ho’s position was not supported by anything in writing.¹⁰⁹ In response, Dr. Ho pointed to the Opinion issued in 2012 by the Government of France Transparency Committee with respect to the adapalene combination product sold under the name Epiduo (known as Tactupump in Canada),

¹⁰⁶ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 9, Application Record Vol. II at p 604.

¹⁰⁷ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 17, Application Record Vol. II at p 606.

¹⁰⁸ PMPRB-04-D2-DOVOBET (2006) at pp 17-18, Book of Authorities at Tab 12; see also PMPRB-07-D2-PENLAC (2011) at paras 40-41, Book of Authorities at Tab 13.

¹⁰⁹ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 46, 61-62, Application Record Vol. IV at pp 1190, 1205-1206.

which considered inclusion of Epiduo on the list of medicines refundable by French National Health Insurance and approved for hospital use.¹¹⁰ After reviewing certain studies (including the Galderma studies purportedly pooled by Tan et al), the Transparency Committee found that “[a]s none of the studies compared the fixed-dose combination of EPIDUO gel with the two active ingredients applied separately, the synergy of the two active ingredients applied at the same time was not proven.”¹¹¹ [emphasis added]

13. It should also be noted that Dr. Tan and Dr. Lynde, and the Galderma Studies they rely on, raise significant potential conflict of interest concerns in relation to Galderma and adapalene-containing drug products. Both experts admitted in cross-examination that they have acted as speakers, investigators and consultants for Galderma, and have acted on Galderma’s advisory board.¹¹² While Dr. Tan claims that the study he conducted with respect to synergy was motivated by “academic interest and intellectual curiosity”,¹¹³ this statement must be assessed in the context of Dr. Tan having acted in the above capacities for Galderma. In addition, Dr. Tan admitted in cross-examination that his clinical research company “partner[s] with drug-company sponsors to implement and complete trials efficiently to advance

¹¹⁰ Exhibit A (for identification) to Cross-Examination of Dr. Vincent Ho (Transparency Committee Opinion on Epiduo – English version), September 2, 2016, Application Record Vol. IV at p 1243; see also Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 76-77, Application Record Vol. IV at pp 1220-1221. Board Staff counsel undertook to provide the French version to Galderma: see Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 77-78, Application Record Vol. IV at pp 1221-1222; and provided it by email to Galderma on September 2, 2016: see Email from Calina Ritchie dated September 2, 2016 attaching French (legally binding) version of Opinion re: Epiduo, by the Transparency Committee of the Haute Autorité De Santé (France), Application Record Vol. IV at p 1272.

¹¹¹ Exhibit A (for identification) to Cross-Examination of Dr. Vincent Ho (Transparency Committee Opinion on Epiduo – English version), September 2, 2016 at pp 10-11, Application Record Vol. IV at p 1243; see also Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 76-77, Application Record Vol. IV at pp 1220-1221. Board Staff counsel undertook to provide the French version to Galderma: see Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 77-78, Application Record Vol. IV at pp 1221-1222; and provided it by email to Galderma on September 2, 2016: see Email from Calina Ritchie dated September 2, 2016 attaching French (legally binding) version of Opinion re: Epiduo, by the Transparency Committee of the Haute Autorité De Santé (France), Application Record Vol. IV at p 1272.

¹¹² Transcript of Cross-Examination of Dr. Jerry Tan, September 1, 2016 at pp 7, 13-17, Application Record Vol. III at pp 839, 845-846; Transcript of Cross-Examination of Dr. Charles W. Lynde, September 1, 2016 at pp 21-22, 25, Application Record Vol. IV at pp 1005, 1007, 1013.

¹¹³ Transcript of Cross-Examination of Dr. Jerry Tan, September 1, 2016 at p 23, Application Record Vol. III at p 855.

development of their product[s]”.¹¹⁴ Moreover the Galderma Studies on which Dr. Tan and Dr. Lynde rest their synergy claims were funded by Galderma, and co-authored or wholly authored by Galderma employees.¹¹⁵

14. It is also important to highlight that no official Dermatology Association has endorsed the claim that adapalene and benzoyl peroxide exhibit synergistic activity.¹¹⁶ Indeed, the study by Williams et al, cited by Dr. Ho in his affidavit, illustrated that the trials that have purported to show such synergistic effects are problematic. Here is a relevant excerpt from the study, which was published in the journal *Lancet*, and written (in contrast to the Galderma Studies) without any declared conflict of interest:¹¹⁷

The large number of products and product combinations, and the scarcity of comparative studies, has led to disparate guidelines with few recommendations being evidence-based. Recent acne guidelines include those from the Global Alliance to Improve Outcomes in Acne, the American Academy of Dermatology/American Academy of Dermatology Association, and the European expert group on oral antibiotics in acne. Because of the paucity of evidence, these guidelines rely on the opinions of experts, many of whom declare significant potential conflicts of interest.¹¹⁸

15. These significant evidentiary concerns should lead the Board to give no weight to Galderma’s attempts to show synergy between adapalene and benzoyl peroxide.

¹¹⁴ Transcript of Cross-Examination of Dr. Jerry Tan, September 1, 2016 at p 16, Application Record Vol. III at p 848; Exhibit B to Transcript of Cross-Examination of Dr. Jerry Tan (Documents printed from Windsor Clinical Research Inc, Website), September 1, 2016, Application Record Vol. III at p 890.

¹¹⁵ Transcript of Cross-Examination of Dr. Jerry Tan, September 1, 2016 at pp 26-31, Application Record Vol. III at pp 858-863: see p 858 (re: Thiboutot et al study), pp 859-861 (re: Stein Gold et al study), pp 861-862 (re: Gollnick et al study), and pp 863 (re: Osman-Ponchet et al study, Bouvresse et al study, and Sevin et al study).

¹¹⁶ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 21, Application Record Vol. II at p 607.

¹¹⁷ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at p 80, Application Record Vol. IV at p 1224.

¹¹⁸ Exhibit A to Affidavit of Dr. Vincent Ho (Williams et al article, “Acne vulgaris”), sworn August 22, 2016, Application Record Vol. II at p 615.

B. No Evidence that the Combination Product Increases Compliance

13. The evidence presented by Galderma in the context of this application also fails to establish that the combination product results in increased patient compliance as compared to two separate applications of adapalene and benzoyl peroxide.

14. While increased compliance was briefly alluded to in Ms. Sandrine Segura's affidavit,¹¹⁹ she did not provide any studies or other evidence upon which this assertion was based. Neither Dr. Lynde, nor Dr. Tan, address this subject in their affidavits.

15. Dr. Ho, however, squarely addressed the issue of compliance in his evidence and indicated that there are no clear advantages or disadvantages in a single daily application versus two separate applications in a combination regimen.¹²⁰ Dr. Ho explained that this is because compliance cannot be assessed in a unidimensional manner.¹²¹ Additional factors that can impact compliance include convenience, tolerance, flexibility, as well as the cost effectiveness of the product.¹²² As Dr. Ho stated, in reference to the combination product and patient adherence: "So if you irritate someone early on, you may actually decrease compliance because they're going to stop using it".¹²³

16. Dr. Ho also testified that studies commenting on the possibility of suggesting greater compliance with the combination products must be viewed in the context of being sponsored studies that were not specifically about compliance; in other words as editorial, rather than evidence-based comments.¹²⁴

17. Thus, not only has Galderma failed to establish that reliable scientific evidence showing increased compliance purportedly brought about by its combination product exists, but it has

¹¹⁹ Affidavit of Sandrine Segura, sworn August 16, 2016 at para 15(d), Application Record Vol. II at p 596.

¹²⁰ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 24, Application Record Vol. II at pp 609-610.

¹²¹ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 37, 42-43, Application Record Vol. IV at pp 1181, 1186-1187.

¹²² Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 35, 37, 42, Application Record Vol. IV at pp 1179, 1181, 1186.

¹²³ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 42-43, Application Record Vol. IV at pp 1186-1187.

¹²⁴ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at p 36, Application Record Vol. IV at p 1180.

also ignored other relevant factors that can impact compliance. Galderma has not been able to establish that the combination product leads to increased adherence compared to two separate applications.¹²⁵

C. Clinical Practice Distinctions Exaggerated by Galderma

18. The affidavits of Galderma's experts (Dr. Tan, Dr. Lynde and Ms. Holowaty) overstate the distinctions between the various adapalene-containing products.¹²⁶ The evidence of Dr. Tan and Dr. Lynde, in particular, is based on flawed arguments asserting synergy and greater efficacy of certain products, which are irrelevant to the *ICN* test,¹²⁷ and contrary to the required broad interpretation of the term "medicine".¹²⁸ The approach advocated by Galderma would also mean that each separate DIN is effectively a separate medicine, which is directly contrary to *ICN*.

19. Moreover, guidelines cited by Dr. Tan and Dr. Lynde that present a positive case for the use of the combination product in clinical practice, even if assumed to be relevant, are compromised by significant potential conflict of interest concerns. For example, the Global Alliance guidelines cited by Dr. Tan and Dr. Lynde was exclusively funded by Galderma and all 21 co-authors declared competing interests involving Galderma.¹²⁹

¹²⁵ Transcript of Cross-Examination of Dr. Vincent Ho, September 2, 2016 at pp 34-47, Application Record Vol. IV at pp 1178-1191.

¹²⁶ Affidavit of Dr. Jerry Tan, sworn August 5, 2016 at pp 8-14, Application Record Vol. II at pp 332-338; Affidavit of Dr. Charles W. Lynde, sworn August 10, 2016 at paras 26-35, Application Record Vol. II at pp 376-378; Affidavit of Leithe Holowaty, sworn August 12, 2016 at p 3, Application Record Vol. II at p 436. This approach is based on flawed arguments about synergy.

¹²⁷ The fundamental issue in the *ICN* test is whether the patent pertains to the medicine. Effects of the medicine do not matter. Indeed, there is nothing in the Act that suggests that the effects of medicinal products are relevant.

¹²⁸ *ICN*, *supra* note 2 at paras 51-54, Book of Authorities at Tab 3.

¹²⁹ Transcript of Cross-Examination of Dr. Jerry Tan, September 1, 2016 at pp 7, 42, Application Record Vol. III at pp 839, 874, with respect to the Global Alliance Guidelines. In a similar vein, with respect to the Canadian guidelines (see Exhibit D (For Identification) and Exhibit E (For Identification) to the Transcript of Cross-Examination of Dr. Charles W. Lynde (First and Last Pages of "Canadian clinical practice guideline"), September 1, 2016, Application Record Vol. IV at pp 1038-1039), the lead authors were Dr. Tan and Dr. Lynde and 9 out of the 11 co-authors declared competing interests involving Galderma: see Transcript of Cross-Examination of Dr. Charles W. Lynde, September 1, 2016 at p 23, Application Record Vol. IV at p 1009. Dr. Tan and Dr. Lynde also cited European guidelines (see Exhibit H to the Transcript of Cross-Examination of Dr. Jerry Tan ("Methods Report re: European Evidence-based (S3) Guidelines"), September 1, 2016, that failed to address significant competing interests: see Transcript of Cross-Examination of Dr. Jerry Tan, September 1, 2016 at pp 43, 53-54, Application Record Vol. III at pp 875, 885-886.

20. Galderma's arguments also ignore the realities of clinical practice in the treatment of acne. As stated by Dr. Ho, "there is no topical acne product that would be considered irreplaceable, or that cannot be substituted for."¹³⁰ From the range of topical adapalene-containing products available, a clinician selects an appropriate treatment regime for a patient, depending on the patient's acne type, severity, tolerability and preference.¹³¹ The various options available are set out in the treatment algorithm from the American Academy of Dermatology guidelines that was reproduced earlier in these submissions. The guidelines give equal weighting to single agent retinoid (i.e. containing only adapalene, used in a combination regimen with benzoyl peroxide) and fixed-dose combination products (i.e. containing adapalene and benzoyl peroxide).¹³²

21. The substitutability of the adapalene-containing products is reinforced by the American Academy of Dermatology guidelines of care for acne cited by Dr. Ho, which state that "[t]here are several head-to-head studies with retinoid products. ... Overall, the limitations of the existing studies prohibit direct efficacy comparisons."¹³³

22. Finally, when assessing the competing opinions of experts regarding clinical advantages or disadvantages of certain drug products, it is important to take into account the hierarchy of levels of evidence, as the Board did in the passage below from *Penlac*:

61. The Panel considered the evidence of the witnesses and had reference to the scientific literature to resolve the differences between the witnesses called by sanofi-aventis and Board Staff. In assessing the efficacy of a medicine, scientists, clinicians and the Board look to the available evidence. There is a hierarchy of reliability in the evidence that is available concerning the efficacy and safety of medicines. The most reliable evidence comes from well-designed, randomized double-blind controlled trials (RCTs) and the least reliable evidence comes from the general knowledge of an expert clinician, with a range of forms of evidence with intermediate reliability between the top and bottom of the hierarchy.

¹³⁰ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 23, Application Record Vol. II at p 608.

¹³¹ Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 23, Application Record Vol. II at p 608.

¹³² Affidavit of Dr. Vincent Ho, sworn August 22, 2016 at para 23, Application Record Vol. II at p 608.

¹³³ Exhibit D to Affidavit of Dr. Vincent Ho (American Academy of Dermatology Acne Management Work Group Review of guidelines of care), sworn June 13, 2016, Application Record Vol. I at p 218.

62. The conclusions that can be reliably drawn from the different types of evidence concerning the efficacy or effectiveness of medicines have been the subject of discussion in scientific circles and in hearings before the Board. This is an important topic for the Board, because the Board must look at various forms of evidence in order to categorize the performance of new medicines relative to the performance of other existing medicines. The fact that expert opinions are the least reliable form of evidence does not render such evidence worthless, but such evidence is not likely to sustain a finding (for or against) clinical equivalence by the Board, and in all events the Board gives the greatest weight to the most reliable evidence available.¹³⁴ [emphasis added]

¹³⁴ PMPRB-07-D2-PENLAC (2011) at paras 61-62, Book of Authorities at Tab 13.