Note from the Commissioner

It has been a bustling first quarter this year with a lot happening for the PAAB at the board and Operations levels.

We received a final report from our strategic plan session facilitators and, after review and comment from the directors, we are looking to ratify it at the AGM on April 21, 2017. The commissioner has developed an Operational plan, that looks into the future, based on that report.

We have had a busy first quarter on the review side and March saw a record review volume. We thank our clients for their continued support. On the complaints side, we have had two stage two decisions on items that were not approved by the PAAB (one carried over from last year). Both involve the same company and both have been appealed. There has been only one complaint received this year.

Internally we have revamped our financial accounting software to a new system to be able to integrate it into our customized E-file system. We have also made a major change in our personnel evaluation system as well as a review of our internal knowledge sharing system.

As part of the new plan to improve communications we have finalized a new digital, interactive

format for the code and that will be voted on April 21, 2017, at the AGM. A staff committee has been working with Innovasium to create and develop a new web-site that we continue to work on. One of our staff members has come up with a creative ide of using an adaptation of CME to help healthcare professionals learn more about, and understand what the PAAB does for them regarding the review of drug advertising.

We have started preparing for the October training workshops to be held in Montreal and Toronto.

We have been preparing for the bilateral meeting with Health Canada on April 18, 2017, during which we exchange information and discuss issues of mutual concern.

The PAAB staff has held up well through all this change and creativity. They are to be commended.

Sincerely,

Ray Chepesiuk

PAAB Commissioner

PAAB Stats

January 2017 through March 31, 2017

- Number of submissions: 1984
- Time to first response: average of 6.1 days. 1 file beyond day 10.
- Time to revision response: average 1.9 days

STAGE TWO DECISIONS

Complaint Report
Stage Two Decisions January 1 to march 31, 2017
ADVERTISER: Merck

COMPLAINANT: Amgen

SUBJECT: c16-09 Interview Article in “Biotechnology Focus” promoting Brenzys

PRECLEARANCE: No

ALLEGATIONS: Verbatim from Amgen correspondence “As an initial matter, the Interview does not fall under any of the prescribed categories of exemptions from the Code.

From Amgen's discussions with Biotechnology Focus, we understand that Biotechnology Focus will offer to conduct and publish an interview with a company representative if that company purchases a certain amount of advertising space in the publication. The interviewee provides guidance on the topic and content of the interview. Biotechnology Focus also provides the interviewee the opportunity to review and comment on the draft of the interview before it is published. Merck may not have made a direct payment to Biotechnology Focus for the Interview itself, but the Interview is tied to Merck's purchase of advertising space in the journal and Merck directs the content of the Interview.

Amgen's position is that the Interview was not independently controlled from Biotechnology Focus' perspective, and so the exception set out in Section 6.6(i) of the Code would not apply. Merck's involvement in the Interview is not limited to purchase or sponsorship of the distribution. None of the other Section 6.6 exemptions are applicable to the Interview. ·

Sections 1.1 and 1.2

The Interview is a promotional piece that is subject to PAAB 's oversight as its intended audience is health care professionals.

Section 1.1 of the Code stipulates that the Code "applies to all communications in which claims, quotations and references are made for healthcare products". Further, Section 1.2 of the Code states that "all proposed copy and illustrations for APS intended for distribution to health professionals must be submitted for PAAB review and clearance prior to use".

As noted, the Interview was published in a life sciences industry publication that targets a wide range of professionals in the life sciences sector, including health care professionals. The Interview makes several efficacy and safety claims relating to BRENZYS™, which are relevant to prescribing physicians. For example, there is a claim that there are fewer injection site reactions associated with treatment with

BRENZYS™ as compared to ENBREL®, which would be "beneficial for the patient". The Interview also indicates that there is clinical data to support the transition of patients from ENBREL® to BRENZYS™ - a claim that is understood as being directed to health care professionals:

Section 2.1 and 2.3
the Interview states that there are no safety or efficacy differences among patients who transitioned to BRENZYS™ from ENBREL®. Indeed, in advocating that BRENZYS™ receive preferential formulary listing as a biosimilar, Mr. Mader makes the following statement: "I think with BrenzysTM, we've shown that our product is as efficacious and as safe as the originator product".

It is Amgen's understanding, however, that BRENZYS™ was authorized for use in Canada based on a single clinical trial that compared BRENZYS™ to ENBREL® in separate study arms. Further, Amgen is not aware of any peer-reviewed, published and Health Canada-approved data in existence to support transitioning of patients to BRENZYS™. The particular safety and efficacy claims made in the Interview (and any associated supporting data) that reference ENBREL® are not incorporated in the Product Monograph. These claims are not accurate, complete or clear, nor presented in a manner that accurate interprets valid and representative research findings.

The Interview emphasizes only the positive features of BRENZYS™, and makes no mention of any negative findings or safety issues. As discussed above, the efficacy and safety claims that appear throughout the Interview are not balanced by any discussion of negative findings. In response to the interview question "What are the strongest concerns you've heard about biosimilars?", Mr. Mader responded by lauding Merck's commitment to patient safety and stating that there is no difference in terms of safety between BRENZYS™ and ENBREL®.

Further, the Interview devotes a fair amount of attention on the issue of preferential listing of biosimilars on provincial and private insurance formularies. Mr. Mader appears to imply that the decision to preferentially list . a biosimilar is primarily based on an assessment of costs, without providing any context as to whether safety concerns relating to biosimilars might also play a role in the listing decision making process. Rather than balancing the positive features of BRENZYS™ in the Interview and acknowledging specific safety concerns relating to biosimilars and how they may have been mitigated, as required by the Code, Mr. Mader instead describes how Merck has undertaken efforts to educate its stakeholders on the safety of its products.

Sections 5.10, 5.11 and 5.12

Section 5.10 of the Code requires that any claims making direct or indirect therapeutic comparisons between drug products must not mislead and be supported by reliable current clinical data. As described above in this letter, Amgen is of the position that Merck's claims in the Interview that the safety and efficacy of BRENZYS™ supports transitioning patients from ENBREL® to BRENZYS™ is not supported by any peer reviewed, published and Health Canada-approved data. Nor is there any such data in the product monograph to support Merck's claim that there are fewer injection site reactions associated with BRENZYS™ as compared to ENBREL®.

Section 5.11 and 5.12 of the Code also require that claims must be made in the context of the study conclusions and that in no circumstances would extrapolation of a claim beyond the actual conditions of the supporting study be acceptable. The data used by Merck to make the above mentioned statement regarding fewer injection site reactions is based on a study published in the journal Annals of the Rheumatic Diseases, 1 Emery P, et al. Ann Rheum Dis 2015;0: 1-7. doi: 10.1 136/annrheumdis-2015-207588 which was analyzed in the European Medicines Agency's ("EMA") 2015 Assessment report of the EMA Marketing Authorization application for BENEPALI™ (the brand name that BRENZYS™ is marketed under in the European Union).2 The EMA concluded that the data comparing injection site

reactions occurring after administration of ENBREL® with corresponding reactions related to BENEPALI™ had no clinical significance.

This is not the first instance in which Merck has disseminated advertising material for BRENZYS™ that is non-compliant with the Code. We respectfully refer you to our correspondence from September 23, 2016 in which we submitted a complaint to Merck directly (with a copy to PAAB) that its September 12, 2016 press release violated the Food and Drugs Act and Regulations because it constituted an impermissible promotional communication. Health Canada accepted the complaint and opened a case for further follow up under reference number 2016-058562. Merck's communications for BRENZYS™ demonstrate a troubling pattern of non-compliance and we will be submitting our concerns to Health Canada's attention once again as well."

DECISION: Health Canada was consulted and confirmed that they considered the item to be advertising under the Food and Drugs Act and that there were alleged misleading statements in violation of section 9 of the Act.

Amgen provided confidential information about the publishing policy of "Biotechnology Focus" from the publishers they obtained from the publisher. There was no publicly available written policy at the time. The Publisher refuted the statement.

The interview was with a Merck employee who could have tempered his comments and also Merck had a chance for review of the APS. This APS was one of a series of three APS that drew complaints from five industry manufacturers so a pattern of activity was suspected. PAAB preclearance review is designed to avoid violations of the PAAB Code.

Code Section 1. The item is considered advertising that should have been submitted to the PAAB for review within section 1 Scope. The combination of the following elements have contributed to rendering the article/interview promotional:

- While the different graphs and illustrations may appear to provide general information about biosimilars, the various conditions which may be treated, the costs involved, the steps towards demonstrating biosimilarity, etc., the answers provided by the interviewee mainly emphasizes on the specific product Brenzys, its efficacy and safety profile compared to the originator biologic, its specific unique features (recent manufacturing technologies, button-free & latex-free injector) and the work accomplished by Merck to obtain approval of Brenzys.
- Contrary to Merck Canada's assertion in its January 10, 2017, response letter, the primary objective of the article/interview does not appear to have been for discussion of a topic of public interest. The content of the interview mostly presents Brenzys in a favourable light and contributes to leaving the impression that biosimilars, and mainly Brenzys, have only positive aspects, features and characteristics.
- While the magazine is mainly targeting a wide range of professionals in the life sciences sector including healthcare professionals, the target audience is unlimited in scope as any person can access articles on the Web site (www.biotechnologyfocus.ca). Access to such articles by secondary audiences is likely to be considered as an attempt to promote or advertise.
- While the article/interview was not sponsored by Merck Canada, Merck Canada was given the opportunity to comment, revise and edit the content prior to publication in order to ensure consistency with the answers actually provided during the interview. In light of this editing privilege, it would have been expected that Merck Canada would have realized that the article/interview was mostly product-focused, was describing facts in an unbalanced manner and had the potential to be considered of a promotional nature.

There is a target audience of health professionals.

Code section 2.1
I agree with Amgen.

“Section 2.1 of the Code requires that all advertising be "accurate, complete and clear and designed to promote credibility and trust". Section 2.3 further states that "APS must be presented in a manner that accurately interprets valid and representative research findings." In Amgen' s opinion, the Interview is non-compliant with these sections of the Code in multiple respects.

As mentioned above, the Interview states that there are no safety or efficacy differences among patients who transitioned to BRENZYS™ from ENBREL®. Indeed, in advocating that BRENZYS™ receive preferential formulary listing as a biosimilar, Mr. Mader makes the following statement: "I think with BrenzysTM, we've shown that our product is as efficacious and as safe as the originator product".

It is Amgen's understanding, however, that BRENZYS™ was authorized for use in Canada based on a single clinical trial that compared BRENZYS™ to ENBREL® in separate study arms. Further, Amgen is not aware of any peer-reviewed, published and Health Canada-approved data in existence to support transitioning of patients to BRENZYS™. The particular safety and efficacy claims made in the Interview (and any associated supporting data) that reference ENBREL® are not incorporated in the Product Monograph. These claims are not accurate, complete or clear, nor presented in a manner that accurate interprets valid and representative research findings.”

Section 3.1 of the Code requires that "Claims and/or quotations in Advertising/Promotion Systems (APS) must be consistent with, and within the limitations of, the Health Canada Terms of Market Authorization" .

I agree with Amgen. “As discussed above, the Interview makes several statements to encourage the transition from BRENZYS™ to ENBREL® that appear to be made on the basis that both drugs are equally safe. Data that would support such a claim does not appear in the Product Monograph and these statements are therefore not consistent with the Health Canada Terms of Marketing Authorization.”

Section 3.5 of the Code specifies that "APS containing claims or quotations that emphasize only positive features of a pharmaceutical product while ignoring significant negative findings are not acceptable."

I agree with Amgen. “The Interview emphasizes only the positive features of BRENZYS™, and makes no mention of any negative findings or safety issues. As discussed above, the efficacy and safety claims that appear throughout the Interview are not balanced by any discussion of negative findings. In response to the interview question "What are the strongest concerns you've heard about biosimilars?", Mr. Mader responded by lauding Merck's commitment to patient safety and stating that there is no difference in terms of safety between BRENZYS™ and ENBREL®.”

Sections 5.10, 5.11 and 5.12
I agree with Amgen.
“Section 5.10 of the Code requires that any claims making direct or indirect therapeutic comparisons between drug products must not mislead and be supported by reliable current clinical data. As described above in this letter, Amgen is of the position that Merck's claims in the Interview that the safety and efficacy of BRENZYS™ supports transitioning patients from ENBREL® to BRENZYS™ is not supported by any peer reviewed, published and Health Canada-approved data. Nor is there any such data in the product monograph to support Merck's claim that there are fewer injection site reactions associated with BRENZYS™ as compared to ENBREL®.

Section 5.11 and 5.12 of the Code also require that claims must be made in the context of the study conclusions and that in no circumstances would extrapolation of a claim beyond the actual conditions of the supporting study be acceptable. The data used by Merck to make the above mentioned statement regarding fewer injection site reactions is based on a study published in the journal Annals of the Rheumatic

Diseases, 1which was analyzed in the European Medicines Agency's ("EMA") 2015 Assessment report of the EMA Marketing Authorization application for BENEPALI™ (the brand name that BRENZYS™ is marketed under in the European Union).2 The EMA concluded that the data comparing injection site reactions occurring after administration of ENBREL® with corresponding reactions related to BENEPALI™ had no clinical significance:

"All injection site associated AEs were generally mild and resolved within a few days. Therefore, even if the exact cause of the observed imbalance could not be established, the CHMP (Committee for Medicinal Products for Human Use) considered that it was not of clinical significance"
Emery P, et al. Ann Rheum Dis 2015;0: 1-7. doi: 10.1 136/annrheumdis-2015-207588
.
Amgen is troubled by Merck's statement in the Interview that the reduced injection site reactions "may in fact be beneficial for the patient" as it is clearly misleading and distorts the underlying study's findings. Further, Merck's statement should have at the very least been accompanied by a disclosure on the study trial size, which, in Arngen's opinion, was not sufficiently large enough to support such a general statement on the difference in safety data."

Summary and Penalty

This APS should have been submitted to the PAAB for review within the PAAB Code. There are multiple violations of the PAAB Code.

OUTCOME: Merck filed a PAAB Code s9.7 Stage Three Appeal based on their belief that the APS did not fall under the scope of advertising. A decision is pending at the time of this publication.

ADVERTISER: Merck

COMPLAINANT: A Group of four companies, Roche, Janssen, AbbVie, Takeda

SUBJECT: c17-01 Editorial Advertising "The Rise of Biosimilars" appearing in "Benefits Canada" December 2016.

PRECLEARANCE: No

ALLEGATIONS: verbatim from the complainants:
"• The Report falls within the scope of the Code, and none of the exemptions set out under section 6.6 of the Code apply to the Report.

• The Report contravenes section 2.3 of the Code in its discussion of the NOR-SWITCH clinical study.

• The Report contravenes section 2.4 of the Code, as it advocates for the transitioning of stable patients to an alternative therapy for purely financial reasons, without supporting medical justification.

• The Report contravenes section 2.6 of the Code in making sweeping and unqualified statements on the safety and efficacy of biosimilars.

• The Report contravenes section 3.1 of the Code in making multiple claims which:

o may be inferred as relating to BRENZYS (a recently approved product and a biosimilar of ENBREL® which Merck markets in collaboration with Samsung Bioepsis Co.)

o go beyond the scope of the terms of marketing approval for BRENZYS

(BRENZYS is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adults, and for reducing signs and symptoms of active ankylosing spondylitis);

o are incompatible with Health Canada's official statements on biosimilars; and

o are not supported by proper references or evidence.

• The Report contravenes sections 3.7 and 5 of the Code, as it draws improper conclusions on biosimilars as a class from limited evidence available for biosimilars of REMICADE®, namely INFLECTRA®.

• The Report contravenes section 2.1 of the Code, in mischaracterizing the way in which Health Canada will "extrapolate" indications for biosimilars.

• The Report constitutes a violation of the Food and Drug Act restrictions on Direct-to- Consumer advertising by virtue of ready access in the public domain through publication on the non-gated Benefits Canada website. Based on prior Health Canada ruling on parallel issues (Rx&D complaint to PAAB regarding advertisements sponsored by the Canadian Generic Pharmaceutical Association (CGPA) (attached), we are also referring the matter of violation respecting Direct-to-Consumer advertising directly to Health Canada for consideration in parallel.

DECISION: PAAB will rule on the nature of and the distribution of the published Report because there appears to be intent of distribution by email to a target audience that is known to include health professionals who make decisions on what drugs doctors are encouraged to prescribe within various drug plans. PAAB has previously stated in response to questions that paid articles in Benefits Canada could be considered to be advertising if distributed to healthcare professionals. To my knowledge the PAAB has not had complaints about Benefits Canada articles in a good number of years.

The DTC website version is being referred to Health Canada as DTC.

The Report is considered to be advertising because it was a paid insertion in Benefits Canada magazine, Merck had review privilege prior to publication and the content serves to promote Brenzyz, a Merck biosimilar product. It would fall under s7.5 of the PAAB Code for review purposes as it is editorial in nature and Merck has stated they did not seek to promote Brenzys specifically.

Therefore there is a violation of S1.1 of the PAAB Code of Advertising Acceptance in that Merck did not submit this for PAAB review.

The Complainants also make allegations about the content and they state "Rather, the Report promotes Merck's biosimilar product Brenzys and includes a plethora of misleading and inaccurate statements as detailed in the Stage 1 complaint letter dated February 10, 2017."

We did not see a "plethora of misleading and inaccurate statements" in the PAAB informal review. There appears to be violations of s2.4 and 2.6 because of statements such as "They're safe." In an absolute manner. There appears to be some violation of s3.1 because of statements supported by inadequate evidence such as abstracts or statements that may go beyond the Marketing Authorization for individual products. That would be captured in a formal PAAB review and that is not the purpose of this complaint ruling.

Summary and Penalty
The PAAB has ruled that the item is an advertising/promotional system subject to review and there are alleged violations of safety and efficacy statement provisions in the PAAB code.

OUTCOME: Merck has registered a Code s9.7 Stage Three Appeal and a decision is pending at time of publication.

New PAAB Guidance Documents added to the website

Since the previous newsletter, the following guidance documents have been added to the PAAB website:

Guidance on indication and fair balance font size

This document is meant to provide you with some guidance on acceptable font size and general type legibility…

Read more

[links to]:

http://www.paab.ca/Indication_and_Fair_Balance_Font_Guidance_-_Final_Draft.pdf

If you'd like to know as soon as new documents are posted, follow us on Twitter @ThePAAB.

Training & Events

eFiles Ticket and Tagging System

The PAAB is excited to announce that the Ticket and Tagging Innovation on the eFile system is live and ready to go! You've likely noticed new buttons related to the functionality if you've logged onto the eFile system recently.

We want you to help the PAAB to continually improve the customer experience through this digital advance. There are two sorts of instances in which you'll want to create a ticket:

i. Create a ticket in order to tag issues you've encountered during the preclearance process. Tags are simply intended to create a record of issues for periodic review by the PAAB management team. Tags are NOT a communication tool for resolving issues during the live review of the file. In fact, the eFiles platform does not show client tags to the reviewers. Continue to utilize written and verbal correspondences to move files forward and to obtain clarification respectively.

ii. Create a ticket in order to submit requests for calls with reviewers (whether file specific or general questions). Moving forward, we ask that our clients submit requests for calls with reviewers through the ticketing system on the eFile system or the "General Questions For Reviewers" link accessible throughout our website (www.paab.ca). For general questions please briefly describe the question in the details box. For calls relating to a particular file, please identify the comment numbers for discussion during the call in the details box. Please note that calls will be recorded for quality assurance, training and auditing purposes. Also note that the ticket may be accessed by the client after the call in order to tag issues encountered during that call. This would help ensure that this particular call is reviewed by a PAAB manager when considering opportunities for training and improvement. Although tickets relating to call requests are visible to reviewers, the tags placed on these tickets to inform management of issues encountered during the call are not visible to the reviewer.

For more information, please visit our website, PAAB.ca or Efiles Home page, to view our client training video and Ticket and Tagging Guidance document. If you have questions regarding this new innovation, please email the PAAB office at info@paab.ca.

The PAAB Code

To see the current edition of the PAAB Code, visit our website.

Our Mission

Mission: To provide a preclearance review that fosters trustworthy healthcare communications within the regulatory framework for the benefit of all stakeholders

Vision: Trusted healthcare product communication that promotes optimal health

Values: Integrity, competency, credibility, independence, excellence, transparency

Social Media

PAAB LinkedIn Group

PAAB LinkedIn Page

PAAB Twitter

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