abbvie

8 September 2017
Reg ref: 50-biological-medicines-naming-convention-8sep17

Therapeutic Goods Administration
Medicines Authorisation Branch
PO Box 100
WODEN ACT 2606

Re: Consultation: Nomenclature of Biological Medicines

Dear Sir / Madam,

AbbVie Pty Ltd would like to thank the TGA for the opportunity to review and comment on the consultation document entitled, *Nomenclature of Biological Medicines*.

Should you have any queries regarding this submission, please do not hesitate to contact me directly on [redacted] or via email at [redacted].

Yours sincerely
ABBVIE PTY LTD

[redacted]

AbbVie Pty Ltd
ABN 48 156 384 262

Level 7, 241 O'Riordan St
Mascot NSW 2020
Australia

+61 2 9035 8698 (OFFICE)
+61 2 9035 8741 (FAX)
abbvie.com

TGA Consultation:
Nomenclature of Biological Medicines

Submission prepared:

AUSTRALIA

8 September 2017

AbbVie Pty Ltd is pleased to have the opportunity to share its views on the Therapeutic Goods Administration's (TGA) Consultation on the Nomenclature of Biological Medicine and we appreciate the TGA's consideration of this submission. AbbVie is a global, research-based biopharmaceutical company formed in 2013 following separation from Abbott Laboratories. AbbVie's mission is to use its expertise, dedicated people and unique approach to innovation to develop and market advanced therapies that address some of the world's most complex and serious diseases. AbbVie is a global leader in biopharmaceutical innovation and has extensive experience in discovering, developing and manufacturing biologic therapies to treat complex diseases.

AbbVie recognises the Australian Government's commitment to competition in the multi-brand market for biological medicines which will generate savings and further support the sustainability of the Pharmaceutical Benefits Scheme. AbbVie support the entry of biosimilars that have been shown, with robust evidence including clinical trials, to be as safe and efficacious as the innovator biologic medicines. Access to safe and effective medicines is important to patients, those who care for them and to AbbVie. In this context we note that that biosimilars approved by the TGA will have similar physicochemical, biological, immunological, efficacy and safety characteristics.[1]

AbbVie is highly supportive of the submission made to this consultation process by Medicines Australia (MA). In agreement with MA, AbbVie encourages the TGA to implement unique suffixes as implementation of this naming protocol will positive address the Key Outcomes stated in the Consultation Paper.

Given AbbVie's strong support of MA's position, we consider it is useful to restate our understanding of the key points of MA's position. MA:

1. Supports distinguishable non-proprietary names for all biological products (i.e. biosimilars and originators);
2. Considers that distinguishable non-proprietary names for biologics are important because they:
    a. Recognise that biosimilars are not identical to reference molecules and therefore should be separately and uniquely identifiable;
    b. Facilitate physician and patient choice;
    c. Ensure accurate attribution of adverse events to the correct product;
    d. Enhance pharmacovigilance.
3. Considers that distinguishable non-proprietary names will support key stakeholders to develop further confidence in the evolving biologics and biosimilars market
4. Argues that the distinguishable name should comprise
    a. common "core name" typically the international non-proprietary name; and

[1] Australian Government. Therapeutic Goods Administration, Regulation of biosimilar medicines Accessed at: https://www.tga.gov.au/publication/evaluation-biosimilars. Accessed on: 14.8.17.

   b. a suffix identifier connected by a hyphen.
5. Supports, in principle, the retrospective application of the described suffix convention to existing biologic non-proprietary names through an orderly process.
6. Acknowledges the benefits of a harmonised approach which aligns with either the WHO or FDA approaches in terms of the unique suffix.

Building on this position, AbbVie wishes to highlight that in our view unique non-proprietary names will:

- Strengthen the pharmacovigilance system for biologic and biosimilar medicines by improving the precision of medication identification in both the reporting of adverse events and traceability through the supply chain which will reduce the risk that reports are misattributed and incorrectly pooled to all manufactures;

- Positively respond to numerous requests by key clinical and patient organisations for the implementation of unique names to support traceability and pharmacovigilance and thereby further support physician and patient confidence in this emerging area; and

- Further support the Australian Government's commitment to transparency in healthcare medicines regulation[2] and through that commitment ensure clarity in fully applying the regulatory determination to the naming protocol for biologic medicines.

OPTION 1. STATUS QUO

In agreement with the position taken by MA, AbbVie holds the view that there are opportunities to improve upon the current naming system for biologic medicines where the Approved Biological Name (ABN) is used for both the reference product and all subsequent biosimilars.

AbbVie acknowledges the high quality and robustness of Australia's existing risk-management approach to pharmacovigilance as administered by the Therapeutic Goods Administration (TGA) and we are highly respectful of the TGA's assessment framework on biosimilarity.[3] Following through with the same logic that the evidence the TGA requires to establish biosimilarity differs from the evidence to establish bioequivalence for a generic, it is important that naming is clear and transparent in identifying biologics and biosimilars as they are by definition not identical generic medicines.[4]

[2] Papathanasiou et al. 'Transparency in drug regulation: public assessment reports in Europe and Australia. Drug Discovery Today, 2016 Nov;21(11):1806-1813.

[3] Australian Government. Therapeutic Goods Administration, Regulation of biosimilar medicines Accessed at: https://www.tga.gov.au/publication/evaluation-biosimilars. Accessed on: 14.8 17.

[4] The FDA notes that "Biological products generally consist of large, complex molecules and raise unique safety concerns related to immunogenicity." Nonproprietary Naming of Biological Products: Guidance for Industry. January 2017, Accessed at: https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf. Accessed on: 6.9.17. The EMA states that "due to their much more complex nature, biologicals pose a greater potential risk of immunogenicity compared to non-biologicals and require specific

AbbVie considers that the status quo of shared nonproprietary names falls short by not upholding this regulatory pathway and determination in applying a distinct naming protocol to biologic medicines.

AbbVie holds the position that shared nonproprietary names partially impedes the TGA's ability to ensure it can "*monitor and evaluate the safety and efficacy profile of, and manage any risks associated with, medicines and vaccines throughout their lifecycle".*[5] Noting the data quoted in MA's submission, the status quo of shared nonproprietary names may obfuscate the identity of a medicine associated with an adverse event and thereby cause the forced pooling of events. Shared nonproprietary names thus complicate efforts to ascertain the exact product responsible for a safety issue, hamper the ability for regulatory authorities to take appropriately tailored corrective action and ultimately may negatively impact health outcomes for patients. Further, the pooling of adverse events may place unnecessary burden on multiple sponsors to report and conduct investigations with resultant impacts on patients and HCPs both in terms of a time and administrative burden.

In addition, we note that a key focus of stakeholders in this emerging area is robust data and ensuring in-market traceability, particularly in a pharmacy substitution environment. The status quo falls short in maximising the robustness of the data available and thus measures to support the quality of data, including the key role played by unique names as outlined in this submission, will build rather than detract from confidence.

OPTION 2: STATUS QUO WITH ACTIVITIES THAT INCREASE PUBLIC REPORTING OF ADVERSE EVENTS WITH THE PRODUCT'S TRADE NAME, AUST R, AND BATCH NUMBER

AbbVie is supportive of additional educational measures to improve the accuracy of adverse event reporting. Encouraging adverse events to be reported with trade names, AUST R and batch numbers can improve accurate product attribution. However, we consider the measures proposed in Option 2 are inferior to Option 4 in achieving the Key Outcomes stated in the Consultation Paper (particularly with regard to ensure all event reports contain necessary information to accurately attribute reports to a single manufacturers) and may also be associated with negative unintended consequences.

We note that there are existing online learning modules developed by the TGA and NPS MedicineWise to assist healthcare professionals understand the importance of reporting adverse

consideration." European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Product- or Population-Specific Considerations II: Biological medicinal products. Accessed at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf. Accessed 6.9.17.

[5] Australian Government, Therapeutic Goods Administration, Therapeutic product vigilance. Accessed at: https://www.tga.gov.au/publication/therapeutic-product-vigilance. Accessed on: 31.8.17.

events and the operation of the pharmacovigilance system.[6] Considering some educational materials already exist and the complexities associated with adjusting normalised behaviour, further education may offer a welcome but only incremental benefit.

AbbVie holds significant concerns with the aspect of this Option that canvasses mandating tradenames and other relevant information such as batch number when adverse events are reported. A primary concern with this proposal is the clear risk that mandating tradenames in adverse event reports may lead to reluctance and/or a constraint to report these events when this information is not available. This issue is especially pertinent when observed alongside the fact that, as noted in the TGA's online learning modules, *"the documentation of adverse events associated with medicines is suboptimal".*[7] Given this context, AbbVie considers that any proposal such as this which has the potential to suppress adverse event reporting (and thus signal detection) should be avoided.

AbbVie's also considers that mandating or even just more actively seeking additional data fields is unlikely to resolve concerns regarding the accurate attribution of adverse events and is also an inferior option to applying unique non-proprietary names. To illustrate a component of this issue, AbbVie reviewed its Global Safety Database to understand how often reports currently contained batch numbers. Although the product batch number is a standard request during adverse event reporting, few case reports included an associated batch number, demonstrating that seeking to increase the requirement that certain data fields are completed is far from a wholly effective method to ensure accurate adverse event attribution.

It is also important to recognise that increased reliance on brand name reporting may lead to inaccurate attribution to originators and thereby undermine the quality of the adverse event reporting for all brands of a particular molecule. For example, in cases when a patient has been taking a medicine for an extended period of time they will often be familiar with the product's brand name and thus report adverse events using that name even though post-patent expiry on the innovator product they may have moved to taking a different brand.

This issue of over-representation of the originator brand name was identified in the example quoted by Medicines Australia regarding an Amgen Neupogen product and also in a study of the FDA's Adverse Event Reporting System (FAERS). In this study by Lietzan et al[8] of the eight products the authors analysed, in six cases the number of adverse events attributed to the originator did not

[6] Australian Government, Therapeutic Goods Administration. Adverse event reporting - online learning modules for health professionals https://www.tga.gov.au/media-release/adverse-event-reporting-online-learning-modules-health-professionals. Accessed on: 31 August 2017. Linked to NPS Medicinewise.

[7] Roughead EE, et al. Medication safety in acute care in Australia: where are we now? Part 1: a review of the extent and causes of medication problems 2002-2008. Aust New Zealand Health Policy. 2009 Aug 11;6:18.

[8] Erika Lietzan, et al., Biosimilar Naming: How do Adverse Event Reporting Data Support the Need for Distinct Nonproprietary Names for Biosimilars?, 3(6) FDLI'S Food & Drug Policy Forum, vol.3:no.6 (2013). Noting that the FDA system exhibits several similar characteristics as Australia's adverse event reporting system.

appreciably decrease following the introduction of generic brands even though the market share of the reference drug fell significantly. As only adverse events containing a 'valid trade [brand] name' were included in the analysis and assuming there was no reason to deviate from standard distribution of reports, the study demonstrated that adverse events continued to be reported against the innovator brand name out of proportion to the use of the relevant products. The authors note the analysis shows that *"adverse event reporting in practice has suffered from substantial product misattribution and gaps in information that impede traceability"*.[9] Even though this study was conducted on small molecules, it is reasonable to consider that the same principle would apply to the biologic market and given that biologic and biosimilars are not identical the significance of this misattribution is enhanced.

In summary, for the reasons outlined above, AbbVie considers that whilst some aspects of Option 2 do have merit, Option 2 may introduce a range of negative factors into the pharmacovigilance system and is inferior to Option 4.

OPTION 3: MOVE TOWARDS ADOPTING A BARCODE SYSTEM SIMILAR TO THE EU.

AbbVie agrees with the position taken by Medicines Australia and acknowledges the benefits of the EU's track and trace system currently being implemented. The system will offer a more secure, effective and efficient medicines supply chain management, with better control on the medicine's location and greater protection against fraud and counterfeits. In a similar manner as the TGO91 reforms currently being implemented in Australia, the EU verification process has the potential to facilitate and assist pharmacists in the avoidance of dispensing errors and the elimination of counterfeit medicine, while at the same time being incorporated in improved inventory management to facilitate product recall procedures.

AbbVie highlights that it is our understanding that under the EU system currently being implemented there is no requirement within the existing Delegated Regulation to record or link unique identifiers to specific patients, nor will patient-specific information be captured or stored within the repositories system. Given this, a number of the Key Outcomes outlined in the Consultation Paper will not be addressed with adoption of this EU system.

[9] *ibid*

OPTION 4: INTRODUCE THE USE OF SUFFIXES TO THE NAMING OF BIOLOGICAL MEDICINES.

In alignment with the position taken by Medicines Australia, Abbvie supports the adoption of distinguishable nonproprietary names based on a common "core name" composed of the INN and a suffix identifier connected by a hyphen. Noting and building on the points highlighted above, particularly regarding the shortcomings of the status quo (Option 1) and education and additional reporting (Option 2), we have briefly outlined a number of the key factors that support the adoption of Option 4.

Strengthen the pharmacovigilance system by improving the precision of medication identification in the reporting of adverse events

AbbVie is strongly of the view that unique names have the capability to strengthen the pharmacovigilance system by improving the precision of adverse event reporting. This accuracy will reduce the risk that events are misattributed and incorrectly pooled to all manufacturers.[10] These pharmacovigilance considerations are particularly pertinent for complex biologic medicines as we enter into an environment where multiple products referring to the same reference molecule are likely to be approved for use. With multiple approved biosimilar products likely to be managed in a pharmacy substitution environment, postmarket safety monitoring will be more complex and all the more essential – unique names will play a key role in supporting the quality and thus overall utility of the pharmacovigilance system for biologic medicines.

To put it simply, AbbVie agrees with the FDA when it notes that distinguishable names, *"can serve as a key element to identify specific products in spontaneous adverse event reporting and to reinforce accurate product identification…used for active pharmacovigilance*" and can *"support the tracking of product-specific events over time".*[11]

Assist with the recognition that biologics are not small molecules and establish a clear mechanism for both identifying and distinguishing biologic medicines.

AbbVie encourages the TGA to acknowledge that unique names assist with the recognition that biologics are not the same as small molecule medicines, and that the regulatory framework, including the naming system, should reflect this fundamental difference. As the TGA is aware, biologics are distinct from small molecule medicines for several reasons, including:

[10] Nonproprietary Naming of Biological Products: Guidance for Industry. January 2017, Accessed at: https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf. Accessed 6.9.17.
[11] *ibid*

- Molecular size and complexity of protein structure including post-translational modifications (e.g. aspirin has 21atoms, monoclonal antibodies are commonly >20,000 atoms)[12];
- Extremely complex manufacturing processes making it impossible for different sponsors to produce exact copies of biologic medicines[13]; and
- Biologic medicines have a higher potential for immunogenicity than small molecule medicines which may result in the body developing anti-drug antibodies (ADA) which could impact efficacy.[14]

Thus, just as biologics in general are distinct from small molecules, a biosimilar is not a generic medicine and the biologics environment will be supported through ensuring clarity in applying this principle to the naming convention. AbbVie aligns with positions such as those of the Australian Rheumatology Association who noted that *"biosimilars are not generic forms of the originator and should not be considered as such. Biologics (including biosimilars) are large complex heterogeneous molecules"*.[15]

By positively responding to calls by healthcare professionals, distinct names will support confidence

Acknowledging physician confidence is a key driver to the uptake of biosimilars and the success of a competitive multi-brand biologics market, the perspectives of physicians regarding unique names is a key consideration. The adoption of unique names would positively respond to calls by clinician groups[16] to ensure both robust traceability for standard clinical monitoring as well as ensuring the pharamcogivilance system can suitably track any adverse events and thereby provide confidence that any potential safety issues could be quickly detected and ultimately mitigated.

In this context Abbvie notes the strong support for unique names amongst key clinician groups, including the Australia Rheumatology Association which stated that *"adoption of a naming convention is essential to facilitate tracking".*[17] We also highlight the views of Australian biologics prescribing physicians as surveyed by the Alliance for Safe Biologic Medicines (ASBM). The survey showed that over three quarters of surveyed doctors (76%) believe the TGA should insist on distinct non-proprietary scientific names for all biosimilars and reference products.[18]

[12] International Alliance of Patients' Organizations (IAPO). Briefing paper on biological and biosimilar medicines. 2013. Available at: https://www.iapo.org.uk/sites/default/files/files/IAPO%20Briefing%20Paper.pdf. Accessed 31 August 2017.
[13] *ibid*
[14] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products. Accessed at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf. Accessed on 31August 2017.
[15] Australian Rheumatology Association. Position on the introduction of biosimilars for the treatment of rheumatic diseases. Accessed at: https://rheumatology.org.au/. Accessed on: 6 9 17.
[16] For example, *ibid*
[17] *ibid*.
[18] Alliance for Safe Biologic Medicines (ASBM). Australian Prescribers and Biosimilars. Kevin Olson, CEO. Industry Standard Research July, 2016. Accessed at: https://safebiologics.org/surveys/. Accessed on: 6.9.17.

We note that the Consultation Paper states that the adoption of a unique identifier *"may undermine the scientific findings concerning their* [originator and biosimilar] *level of similarity, which could be contrary to whole of government messaging around uptake of biosimilars".*[19] Rather than negatively impacting perceptions around biosimilars, through numerous positive factors including enhancing the quality of data by supporting traceability and simply reflecting the regulatory assessment of biosimilarity, AbbVie considers that the adoption of unique names will actually support clinician and patient confidence in a multi-brand biologic medicine markets.

The value of harmonisation

Abbvie encourages the TGA to consider that the benefits of global harmonisation of a unique naming system outweigh a distinct Australian naming convention. The benefits of global harmonisation are numerous and include improved convergence of international pharmacoviligence databases to assist with identification of rare adverse events, supporting patients and the quality use of medicines through reduced risk of confusion when travelling overseas and not unduly increasing the regulatory burden on product sponsors.

ADDITIONAL CONSIDERATIONS

As the clinical, regulatory and commercial environment for biologic medicines continues to evolve, AbbVie believes that there are additional elements which would work in co-ordination with Option 4 to further enhance the system and build confidence.

AbbVie is encouraged that the government has recognised the patient benefits involved with dispensing notification with *"proposals currently being developed to allow for the 'My Health' records of individuals to contain details of the medicines they are using".*[20] We further highlight that the *"Government has also indicated it is pursuing software changes to support provision of information back to prescribers where appropriate".*[21]

AbbVie is keen to work with Medicines Australia, Government and other key stakeholders to see the timely implementation of these additional measures and thereby further increase the quality and robustness of data throughout the prescribing, dispensing and monitoring systems.

CONCLUSION

AbbVie is highly supportive of the submission made to this consultation process by Medicines Australia (MA). In agreement with MA, AbbVie encourages the TGA to implement unique suffixes as this will achieve the Key Outcomes as stated in the Consultation Paper.

[19] Australian Government, Therapeutic Goods Administration, Consultation: Nomenclature of Biological Medicines, Version 1.0, July 2017.
[20] *ibid*
[21] *ibid*

As outlined, unique names will strengthen the adverse event reporting system, assist with clarity regarding biologic medicines and support clinical confidence in a multibrand biologics market. In addition, we consider that the positive outcomes associated with applying unique names will be further supported through embracing the opportunity to, where appropriate, share information (eg. dispensing notification) and thereby support optimum patient outcomes.