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Biologics Science Section
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

Re: Consultation: Nomenclature of biological medicines

Dear Sir or Madam,

Novartis welcomes the opportunity to review the consultation document on the naming of biological medicines for the outcomes listed below:

- provides improvements in the identification of biological medicines in the reporting of adverse events;
- aligns, as far as possible, with international practice, noting the significantly different approaches adopted by Europe and the USA;
- does not add unnecessary regulatory burden;
- supports quality use of medicines including safe prescribing and dispensing practice, and
- does not adversely impact the government's policy of increased uptake of biosimilars set out in the consultation paper.

Sandoz, a division of Novartis, is a global leader in developing and commercialising biosimilar products across the world. This experience helps to guide the comments and suggestions contained herein.

Internationally there has been much debate and discussion on the naming of biologicals. This has been precipitated by the arrival of biosimilars, but the issue applies equally to all biological drugs, as there are numerous examples of different biological medicines sharing the same non-proprietary name (e.g. somatropins, insulins).

In this letter, we provide comments on the options posed by the TGA to support evaluations of adverse events (AEs) without confusion about exactly which medicine was involved, together with the required specificity to accommodate batch to batch variability, as may be the case with biological products. Specifically, we support Option 2 which retains the status quo but includes "activities to increase public reporting of AEs with the inclusion of the product's brand name, AUST R and batch number." Further, we believe that a hybrid approach including Option 2 and elements of Option 3 would allow for a phased approach which should be the ultimate goal to achieve the outcomes listed above.

Comments on Option 1

Option 1 involves keeping the status quo where the Approved Biological Name (ABN) is used to identify the active ingredient in both the reference product and subsequent biosimilars. The current system already allows for **identification** using the ABN/INN and **differentiation** using the proprietary brand (or trade) name.

However, there is widespread acceptance for a need to adopt measures to ensure traceability that align with international naming standards by way of batch number identification. It is fairly clear that the status quo needs to change. We discuss how much and how soon, in our comments regarding the other options proposed by the TGA.

Novartis Support for Option 2

The TGA biologics naming system complies with international naming conventions and standards. ABNs are based on international non-proprietary names (INNs), which are the "default naming reference for chemical ingredients (AANs) and biological ingredients derived from human or animal materials (most ABNs)."[1]

We note that the non-proprietary name has always been intended to reflect the active ingredient as established by the conventions of World Health Organization (WHO) and country and/or regional naming agencies. The recent dialogue around biologics and/or biosimilars naming has instead suggested that the non-proprietary name is intended to facilitate the identification of a *specific drug product*. This has resulted in confusion about the use of an otherwise successful and straightforward worldwide system effectively in use for over six decades.[2]

It is important to stress that the purpose of the INN system is to inform healthcare providers about the active ingredient in the pharmaceutical product they prescribe for their patient. The brand name is always unique, proprietary[3] and is widely used as the primary means for identification of a specific product by both patients and physicians[4]. Brand names are designed for easy recognition and pronunciation when compared to the non-proprietary name. All brand names are vetted by the TGA to ensure that they will not be easily confused with other brand names.

The question of whether biosimilars should share an INN is departing from its intended purpose of facilitating the identification of pharmaceutical substances. It is essential to acknowledge that the most common identifier of any biological (or pharmaceutical) medicine is the brand name, and that is the one identifier that is also most commonly tracked. Therefore, we do not support amending non-proprietary names for the purposes of tracking and tracing.

Traceability of a pharmaceutical product is a related, but separate aspect from identity, and must be managed using additional measures e.g., batch number, bar coding for ordering, prescribing, dispensing, record keeping and pharmacovigilance practices, and as part of an integrated and validated system.

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[1] TGA. Guidance on TGA approved terminology for medicines. Accessed August 21, 2017 at https://www.tga.gov.au/sites/default/files/tga-approved-terminology-medicines.pdf

[2] WHO. Guidance on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances. Accessed August 22, 2017 at: http://www.who.int/medicines/services/inn/FINAL_WHO_PHARM_S_NOM_1570_web.pdf?ua=1

[3] [3] Guideline on the acceptability of names for human medicinal products processed through the centralized procedure. 22 May 2014 EMA/CHMP/287710/2014-Rev. 6
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167844.pdf (accessed 05 Sept 2017)
Best Practices in Developing Proprietary Names for drugs. FDA Draft Guidance (May 2014)
https://www.fda.gov/downloads/drugs/guidances/ucm398997.pdf (accessed 05 Sept 2017)

[4] NS Vermeer et al. Drug Safety (2013) 36:617–625

In Europe, the most mature biosimilar market, the EMA has adopted a guideline to enhance pharmacovigilance for biological medicines.[5] To ensure traceability of biological medicines throughout the supply chain, product packaging includes the product name and batch information which facilitates the inclusion of this information throughout the supply chain – from manufacturer to patient including at the time of prescribing, dispensing and patient administration.[6]
Additionally, the EMA guideline recommends that all summaries of product characteristics (SmPCs) for biological products should include "a prominent statement that the name and batch number of the administered product should be clearly recorded in the patient file" and recommends that related wording should also be included in educational material, healthcare professional communication, and promotional materials.[7]

EMA's actions have resulted in the implementation of a thoughtful and risk-based approach to biologic pharmacovigilance that does not uproot or misuse the successful international naming system. In fact, an analysis of adverse drug reaction reports in the EU revealed clear identification of more than 90% of the affected biopharmaceuticals.[8] Therefore, we strongly encourage and support TGA's continued utilisation of ABNs based on the WHO INN system.

We believe the mandated use of the AUSTR number may only provide minimal utility for traceability purposes, especially if the brand name and batch number are required to be recorded. Mandatory inclusion of the AUSTR would deviate from international pharmacovigilance practices and focus on an Australia-specific product element. As previously stated, the use of the batch number is the most important part of any AE reporting because it crosses all international jurisdictions. Additionally, the brand name is important to capture because it is an element that is reviewed and approved by the TGA and is always unique. Recording both of these elements facilitates the traceability of products throughout the supply chain. We would however, support recording of the AUSTR number if it is an optional element that does not supplant the need to record the brand name and batch number.

Hybrid Approach Option 2+3

Alternatively, we offer support for an approach that would implement a hybrid of Options 2 and 3, which would retain status quo with the inclusion of additional details to address pharmacovigilance concerns and include a move towards adopting a barcode system similar to the EU and one that is under development in the US (with a target implementation of 2-3 years).

As noted in TGA's consultation document, the benefits of Option 3 are that the bar codes contain product codes, national identification numbers, batch numbers, and expiry dates – all of which enhance the traceability of products throughout the supply chain. A bar code system would support the Government's broader e-prescribing and dispensing initiatives, linking with the My Health record to improve pharmacovigilance and quality use of medicines.

As any given product usually retains the product name following significant changes to manufacturing processes, batch traceability is an important aspect to be considered in any associated updates to risk management plans.

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[5] EMA. Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations II: Biological medicinal products, August 4, 2016. Accessed on August 21, 2017 at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf

[6] EMA. Guideline on GVP, 2016

[7] EMA. Guideline on GVP, 2016

[8] NS Vermeer et al. Drug Safety (2013) 36:617–625

As a general principle, the name and batch number of the administered product should always be clearly recorded in the patient file in order to improve traceability of biological medicines. We believe traceability needs to be fully integrated in different healthcare settings and infrastructure that may vary across products and between states, such as the infrastructure for electronic data recording and record linkage.

System-wide traceability can be achieved by following these key principles:

1) require the recording of the batch number by a healthcare professional at the time of administration,
2) adopt measures to facilitate the tracking and recording of the batch number (e.g. peel off stickers/bar codes) , and
3) ensure that electronic reporting systems include prompts for the provision of batch information, which should be further reinforced via internal and external stakeholder training on batch documentation as well as internal evaluations (including PSURs and signal detection) to evaluate brand and/or batch specific trends/patterns.

The use of tools such as sticky/tear-off labels in the product packaging should be considered to facilitate accurate recording in patient files and provision of information to patients. Additionally, the use of available bar code-scanning technology and infrastructure across health care professionals and treatment centres should also be ensured before this option is introduced.

Under this approach, we encourage the TGA to consider the following suggestions if a decision is made to implement elements of Option 3:

- Choose to use a GS1 Datamatrix code (two-dimensional (2D)): using a global standard offers a streamlined approach for manufacturers. This should be applicable to all biological medicines, not just biosimilars.
- Allow companies and healthcare practices sufficient time to implement this scheme following publication of a final guidance following necessary impact analyses, procurement of required equipment and retrofit of packaging lines as well as end user interface
- Obviate the need for a separate regulatory submission to implement the code to minimise administrative burden for both sponsors and the TGA in keeping with a risk based approach
- Ensure extensive engagement with stakeholders for feedback on draft guidelines

We note that the above largely aligns to the EMA's implementation of a bar code system, which included many discussions with stakeholders while putting the requirement in place. This type of consultation and approach was greatly appreciated by stakeholders.

Comments on Option 4

Many pharmaceutical products, including biologics, have shared non-proprietary names for decades[9] and we are not aware of any issues with their safe and effective use. The TGA consultation paper acknowledges that concerns around safety issues that may arise from switching between a reference medicine and a biosimilar have not been evident. As an example, in the United States approximately 77 unique drug products have shared 25 non-proprietary names for many years without any degree of

[9] WHO. List of Recommended and Proposed INNs. Accessed August 22, 2017 at: http://www.who.int/medicines/publications/druginformation/innlists/en/

confusion in pharmacovigilance.[10] It is important to note that concerns regarding the need to alter the naming conventions of biological products have only been raised after biosimilars began to be developed and commercialised, and that the organisations calling for these changes did not voice any concerns prior to that time.

Therefore, we emphatically object to Option 4 which would introduce the use of suffixes to the naming of biological medicines. We note that a suffix (-xxxx) consisting of random letters has been adopted in the US, although only applied to biosimilars thus far.[11] At this time, no information is available to confirm that the added suffix offers any enhanced benefit to the US pharmacovigilance system. In fact, evidence to the contrary exists that demonstrates no safety concerns when biologics share a non-proprietary name.[12]

As such, we believe that the introduction of suffixes to the non-proprietary names of biologics is unnecessary and may even cause more problems than it resolves. For example, changing non-proprietary names will be onerous for companies, providers (hospitals, clinics, HCPs, pharmacies), pharmacovigilance systems, databases and compendia. While the US healthcare system is larger than that in Australia, data standard organisations and drug distributors have recently commented to the US FDA that implementation of the newly devised biologics naming system will cost over $2 billion US dollars to fully implement, including hospitals, pharmacies, distributors, safety databases and government entities that purchase and distribute biologics.[13,14] These cost estimates were not available prior to the decision of the US FDA to adopt their new biologics naming convention. If the issue with the current system is the completeness and accuracy of the records, TGA risks compounding these problems by introducing a new naming system for biologics.

To revise a key component of the Australian naming convention will not necessarily create a safer system but it will increase uncertainty, create confusion and entail a significant financial burden on many stakeholders well beyond product sponsors. The TGA also notes that a suffix-based naming scheme specific to Australia may add to prescriber, dispenser and patient confusion, which would ultimately impact the government's policy of increased biosimilar uptake.

There is no reason to assume that creating a more complicated naming system will improve pharmacovigilance if the underlying problem is that existing systems are not fully utilised. As previously stated, we believe any concerns with the current system can be addressed by enhancing pharmacovigilance practices and targeting education and training on the use of existing naming convention and AE reporting systems. The creation of a new system and its implementation will necessarily require a significant and expensive effort, along with a much more substantial educational undertaking. Until the new and untested system is completely functional, the completeness and accuracy of the record keeping may be worse.

The non-proprietary name, even as revised per Option 4, will never contain the level of detail of the bar code systems, and increasingly these systems are part of the more broadly implemented Electronic

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[10] McCamish, Gallaher, Orloff. "Biosimilar by Name and Biosimilar by Nature", RPM Report, June 28, 2013. Accessed on August 21, 2017 at: https://www.pharmamedtechbi.com/publications/rpm-report/9/7/biosimilar-by-name-and-biosimilar-by-nature

[11] FDA. "Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations." Accessed August 21, 2017 at: http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm

[12] McCamish, Gallaher, Orloff, 2013

[13] Comment from the National Council for Prescription Drug Programs to OMB Control No. 0910 and Docket No. FDA-2013-D-1543, dated 7 February 2017.

[14] Comment from Wolters Kluwer Health to OMB Control No. 0910 and Docket No. FDA-2013-D-1543, dated 9 February 2017.

Medical Record (EMR), which is more automated and not dependent on handwritten records. Adopting Option 3 will ensure Australia keeps up with the advances in pharmacovigilance systems. Further, to change the current system and to add complexity by creating longer, non-standard non-proprietary naming formats is in itself a hazard to the effective use of the longstanding and successful international naming system.

While we do not see the need to make any changes to the current systems used for non-proprietary names, we appreciate TGA's recognition that any changes to the current non-proprietary naming convention should be applied equally and concurrently to all biological medicines.

Conclusion

We appreciate the opportunity to provide comments on this important topic. As described, we strongly support TGA's Option 2 to bolster the current system with increased public reporting of AEs with the inclusion of the product's brand name, and batch number in line with the EU GVP guideline on pharmacovigilance for biologics. Additionally, we also offer support for a hybrid approach of Options 2 and 3 that could be implemented in a staggered manner, which would include the implementation of a bar code system. Lastly, we have significant concerns with an approach to biologics naming that would include a change to the existing and reliable international non-proprietary naming convention.

Should you have any questions about the input provided, please feel free to contact either of the undersigned.

Sincerely,

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