

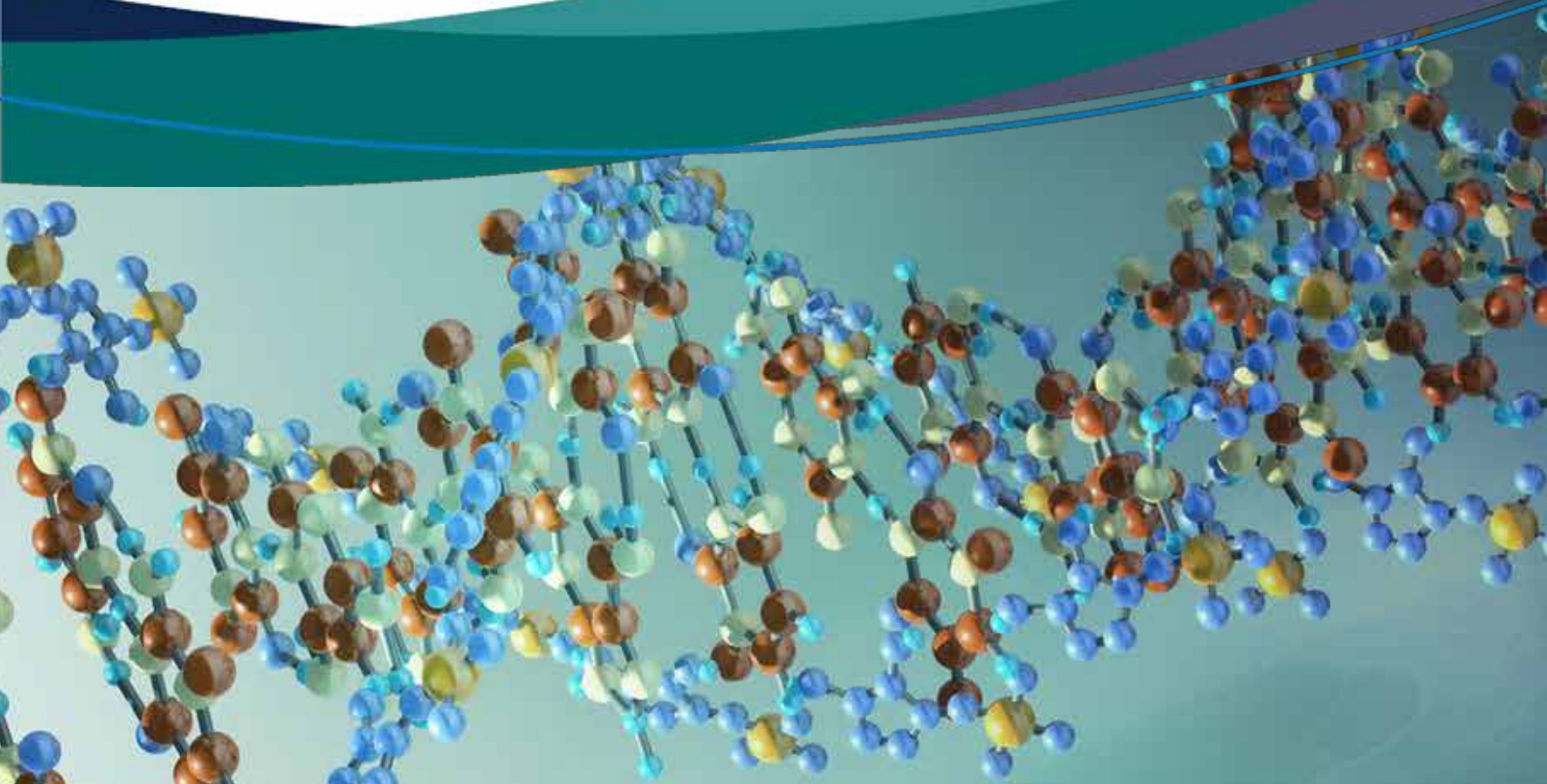


Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Nomenclature of Biological Medicines

Version 1.0, July 2017

TGA Health Safety
Regulation



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Context of this paper

1. Context

A biological medicine is a medicine that contains one or more active substances made by or derived from a biological source (such as a bacterium, yeast or mammalian cells), rather than a synthetic chemical source. Biological medicines can consist of relatively small molecules such as human insulin or large and complex molecules such as monoclonal antibodies.

A biosimilar medicine is a version of an already registered biological medicine (the reference medicine) that has demonstrated sufficient similarity to the reference medicine in physiochemical, biological and immunological characteristics, efficacy and safety such that clinically meaningful differences between the biosimilar and the reference product are not expected when used for the approved indication.

The active substances of biological medicines are larger and more complex than those of non-biological medicines. Their complexity, as well as the biologically based methods of producing biological medicines, may result in some degree of structural variability when different manufacturing processes are used, or potentially between batches of the same substance produced by the same manufacturing process. The active substance of a biosimilar and that of its reference medicine are manufactured to be highly similar and are assessed by the TGA to ensure this is the case. Part of TGA's role is to assess the differences where they exist so that patients are not exposed to a product with unexpected clinical consequences.

In a wider context, government is committed to implementing a biosimilar medicines uptake policy. Biosimilar medicines provide an opportunity to reduce the cost to Government of subsidising biological medicines. The Government is committed to supporting a viable and competitive market for biological medicines in Australia. The Biosimilar Awareness Initiative was announced in May 2015. The aim of the Initiative is to support awareness of, and confidence in, the use of biosimilar medicines for healthcare professionals and consumers. Recognising prescriber and patient choice of brand of medicine, new policies to encourage uptake of biosimilar medicines were announced in the 2017-18 Budget for:

- encouraging prescribing of a biosimilar brand for treatment naïve patients, and continued biosimilar prescribing once a patient is commenced on it; and
- providing for a lower authority level for prescribing biosimilar brands (eg, streamlined authority required) while maintaining an existing higher level authority for the reference biological brands (eg, written authority).

Alongside these specific biosimilar uptake measures, the Government has indicated it will pursue approaches to e-prescribing software that support default prescribing by active ingredient name (eg, International Non-proprietary Name or similar naming methodology). The interaction between default ingredient name prescribing and specific biosimilar uptake drivers will be refined during development of the associated software changes. The Government has also indicated it is pursuing software changes to support provision of information back to prescribers where appropriate.

Your input is sought

Comments that address any or all of the issues discussed in the Consultation Paper are invited from interested parties. Submissions must be lodged using the online consultation submission form to upload your submission in either pdf or word format. Alternatively, hardcopy submissions with a printed coversheet may be mailed to:

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

For accessibility reasons, please email responses in a word or rich text format (RTF) format.

Closing date for comments is COB 8 September 2017

2. The issue

As with all medicines, there is a need to be able to capture accurate information about a medicine that is associated with an adverse event. Hence, there needs to be mechanisms to collect sufficient details of the implicated medicine to allow an investigation into the adverse event to be conducted without confusion about exactly which medicine was involved. A unique product name, or combination of details that together give the required specificity, would meet the objective. In addition, where there is a possibility that a particular batch, or batches, of a medicine is implicated in an adverse event then retrieval of the batch number(s) of the product is an important piece of information for the investigation of the adverse event.

Internationally there are different approaches to the naming of biological medicines. These include:

- in Europe, use of the International non-proprietary name (INN), unmodified, supported by 2D-barcoding requirements
- United States Food and Drug Administration's (US FDA) plan to have a four letter suffix added to the non-proprietary name of all biological medicines, not just biosimilars
- "BSn" biosimilar identifier by Japan's PMDA.

In addition, the World Health Organisation (WHO) has indicated it intends to review its earlier proposal to the use of a Biological Qualifier (BQ) in connection with the INN.

In Australia, active ingredients of biological medicines on the ARTG, including biosimilars, use the Australian Approved Biological Name, which is the INN if one is available. There is currently no requirement for the name of the medicine to include any sort of specific identifier suffix, nor is there a requirement for the packaging to carry a bar code.

Given international developments for naming of biological medicines, the TGA is now consulting on whether there is a need in Australia for additional naming requirements.

3. Scope of this paper

In this paper, the scope is restricted to biological medicines. Biological medicines are therapeutic goods that are derived from biological sources and regulated as prescription medicines by the Therapeutic Goods Administration (TGA). They include proteins and polysaccharides such as:

- Products of the fermentation of recombinant cell-lines;
- Medicines derived from the fluids and tissue of humans (where specified in the [Therapeutic Goods \[Things that are not Biologicals\] Determination No. 1 of 2011](#)) and animals
- Bacterially-derived proteins;
- Animal-derived polysaccharides like heparin.

Biological medicines do not include antibiotics and small peptides or molecules <2500 Da. Also, while vaccines are also biological medicines they are not in scope for this paper.

Biological medicines are distinct from '[biologicals](#)' which are human cell and tissue products.

4. Outcomes sought

From a regulatory perspective any changes to the current situation regarding naming, tracking or pharmacovigilance reporting for biological medicines would need to result in an improved ability to monitor the incidence of adverse reactions that might occur through use of the biological medicine. In particular, in amending the naming conventions for biological medicines we would need to be confident that the approach:

- is necessary to provide 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

5. Background

Australian approach

Current approach to the identification and naming of biological medicines in Australia

All prescription medicines supplied in Australia are required to have the name of the medicine and the active ingredient displayed prominently on the main label. The name of the medicine is the name appearing on the product's certificate of registration and is usually referred to as the product's trade name. Other information required to be displayed on the main label of the medicine includes the dosage form, the strength and the AUST R number. The packaging must include the contact details of the Australian sponsor.

Active ingredients in biological medicines supplied in Australia must be identified using the Australian Approved Biological Name. This name is invariably an INN and is supplied by the INN committee of the WHO. In the absence of an INN, an appropriate name would be agreed between the sponsor of the new medicine and the TGA during the medicine registration process.

In 2013, the TGA published the *Guideline for the Evaluation of Similar Biological Medicinal Products (SBMPs)* which reflected the expected policy of the WHO. The WHO's INN policy was not published and consequently, in 2014, the TGA published an interim policy of simply assigning the reference product's Approved Biological Name to all biosimilars.

In July 2015, the WHO published the [Biological Qualifier Scheme Proposal](#) to assign a four consonant suffix code to all biological medicines, but it has not been implemented. So, when the current version of the TGA guideline, now renamed [Regulation of Biosimilars](#), was published in December 2015, it reaffirmed the interim measure that biosimilars would simply bear the Approved Biological Name associated with the reference product.

Current approach to the reporting of adverse events of biological medicines in Australia.

Once a medicine is approved, the TGA conducts product vigilance to monitor and evaluate the safety and efficacy profile of medicine. Pharmacovigilance is important because new information regarding the safety and efficacy continually emerges throughout a medicine's life-cycle, and systems are required for capturing and analysing this information.

One aspect of pharmacovigilance in Australia is adverse event reporting. An adverse event is any untoward medical occurrence in a patient, consumer or a clinical investigation subject administered with a medicine, which does not necessarily need to have a causal relationship with the medicine. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicine, whether or not considered caused by the medicine. The TGA currently receives around 18 000 adverse event reports for medicines each year.

In Australia, reporting of adverse events is mandatory for sponsors. Adverse event reporting is voluntary for health professionals and consumers, however the TGA continually encourages reporting from these groups.

With regards to the pharmacovigilance of biological medicines, concerns have been raised that currently unknown adverse events may arise from switching between reference medicine and biosimilar products or immune-mediated reactions that have not been observed for the innovator medicine. To date, these concerns have largely not been evident despite some studies having been undertaken for particular biological medicines/biosimilars to detect such reactions. Theoretically, such concerns could also apply as a result of variability between batches of the same biological medicine but, again, evidence is lacking to support this view. Further, any significant changes to the production methods of the active ingredient used in a biological medicine require assessment by TGA before the product can be released for supply in Australia. Manufacturers are required to validate any such changes to limit the opportunity for unexpected changes to clinical outcomes in patients.

Currently, TGA's adverse event reporting system gives prominence to reporting of a medicine's non-proprietary name, with or without the trade name or batch number, although all three are encouraged to be reported for all medicines. Normal TGA practice is to follow up with the reporter to obtain any missing information so that the actual medicine, and batch number where relevant, can be specifically identified.

Current approach to barcoding of prescription medicines in Australia

TGA does not currently mandate the use of bar codes on medicines' labels although it is common for linear bar codes to be present on products. These codes usually describe the product, but not

the batch number, and are usually used for inventory management purposes but not for pharmacovigilance purposes.

Some biological medicines supplied in Australia are currently required to be supplied with an information-rich barcode. For example, the National Blood Authority (NBA) is implementing a requirement for plasma and recombinant products supplied under the national blood arrangements to be compliant with the internationally recognised GS1 data matrix. The GS1 data matrix contains the global trade identification number (GTIN), expiry and batch number. The transition for this change commenced in 2015 and is scheduled to be complete by January 2018. For more details see the [National Blood Authority Australia](#).

Increasingly, medical software systems are allowing for the reading and electronic management of prescription medicines, including prescribing and dispensing in hospital and non-hospital settings. Proposals are also being developed to allow for the 'My Health' records of individuals to contain details of the medicines they are using.

International approaches to naming of biological medicines

FDA's approach to the identification and naming of biological medicines

In January 2017, the US Food and Drug Administration issued Guidance for Industry, [Non-proprietary Naming of Biological Products](#). The guidance outlines their intention to assign four-letter suffixes (different to the proposed WHO BQ scheme) to all biological medicines (including therapeutic protein products, vaccines, allergenic products and blood derivatives but not blood components or biological products/medicines that also meet the definition of devices) both prospectively and retrospectively to aid in pharmacovigilance, safe use and promotion of appropriate practices, and improve patients' perceptions of biological products. The FDA is continuing to consider:

- the process for implementation of this naming convention for previously licensed products
- the appropriate suffix format for products/medicines that may be substituted without the intervention of a prescribing health care provider (ie. pharmacy substitutable products).

EMA's approach to the identification and naming of biological medicines

While the European Medicines Agency (EMA) shares similar concerns to the US FDA in terms of the need to minimise prescribing and dispensing errors for biological medicines and to have robust pharmacovigilance systems in place to monitor on-going safety and efficacy of biological medicines, it has indicated their preference for the use of 2D barcoding on product packaging instead of suffixes added to the name of the medicine. The 2D barcoding system, initially implemented to track all medicines and control fraudulent or counterfeit medicines, will also be used for the purposes of assisting with prescribing and pharmacovigilance monitoring. The EMA has indicated that this, coupled with enforcement of reporting of pharmacovigilance, is sufficient to monitor the safety of all medicines, not just biological medicines, without recourse to alternative nomenclature requirements.

6. Options for biological medicine nomenclature,

Possible options for naming of biological medicines supplied in Australia in the context of the current international inconsistency include:

1. **Status quo.** Use the agreed Approved Biological Name to identify the active ingredient in both the reference product and all subsequent biosimilars. Unique identification of

individual products would rely on its allocated Australian registration number (AUST R) and proprietary trade name.

Your views are sought

Do you support maintaining the current system with no change? Please provide reasons to support this view, or not.

2. Status quo with activities that increase public reporting of adverse events with the inclusion of the product's trade name, AUST R and batch number. This option would focus on increasing education to healthcare professionals and the public to report all medicines, particularly biosimilars, associated with adverse events by their trade name, AUST R and with the associated batch number. Provided healthcare professionals and members of the public reported this additional information, this would allow identification of the product associated with an adverse event and is consistent with the scheme as it currently operates.

Currently the trade name is a non-mandated field on TGA's forms for reporting adverse events as a prescriber who wishes to report an adverse event in relation to a patient may not know what product was supplied to the patient by the pharmacist. Mechanisms can be put in place to enhance the reporting of product/batch specific information, for example through mandating this information as a field in the on-line reporting form. Even if the trade name is not known a prompt to provide this information when available may enhance the number of reports where this information is provided.

Education and information is available to health professionals via the [NPS website](#) on the importance of reporting adverse events and what to report to the TGA. The information could also be enhanced to include further information on the specific medicine associated with the occurrence of the adverse event, as well as the importance of reporting batch number information where possible. This would have general benefits for the scheme for all products and would enhance TGA's ability to more rapidly identify adverse events associated with quality or other batch-related issues to be identified with any product.

Your views are sought

Do you support this option? Please provide reasons to support this view, or not.

3. **Move towards adopting a barcode system similar to the EU.** The EU has mandated that most medicines supplied in the EU must have a unique identifier (a 2-dimensional barcode) placed on the packaging no later than February 2019. This bar code contains information including the product code, national identification number, batch number and expiry date. The barcode must comply with relevant standards so that it is readable throughout the EU. The barcode system allows traceability of batches of medicines from the manufacturer to individual patients as well as aiming to prevent falsified medicines entering the legal supply chain and improved pharmacovigilance. The system relies on healthcare facilities, prescribers and dispensers recording information by way of the bar code and adverse events being notified to the regulatory agency.

Your views are sought

Do you support use of a similar barcode system in Australia? Please provide reasons to support this view, or not.

What system and level of serialisation should a barcode use?

What is the impact (including financial impact) of this option on you?

4. **Introduce the use of suffixes to the naming of biological medicines.** Use of suffixes to uniquely identify all biological medicines would be consistent with the approach taken by the US FDA. The FDA Approved Biological Name is to be used as the core name, but each product would have a unique suffix associated with the FDA Approved Biological Name. This is intended to be implemented by FDA as a mandatory scheme, with or without retrospectivity. If a similar approach was implemented in Australia, consideration would need to be given to the extent of alignment with the FDA scheme as, although unlikely based on previous experience, it could be possible that a product's name and suffix has not been determined by the FDA at the time an application is made for registration of that product in Australia, resulting in different suffixes being applied to the same medicine internationally. Developing a suffix-based naming scheme specific to Australia may add to prescriber and patient confusion.

This option would make the biosimilar and reference biological brands appear as different drugs for prescribing purposes because they would be presented as distinct entries in prescribing lists and would therefore be displayed separately for the prescriber to choose from. This may undermine the scientific findings concerning their level of similarity, which could be contrary to whole of government messaging around uptake of biosimilars.

Your views are sought

Do you support this option? Please provide reasons to support this view, or not.

What is the impact (including financial impact) of this option on you?

If this option was to be implemented should Australia adopt the outcomes of the FDA scheme or develop its own scheme for adding a suffix? Please provide reasons to support your view.

If this option was to be implemented should it apply retrospectively? Please provide reasons to support this view, or not.

Your views are sought

Are there other options which should be considered? Please provide reasons to support this view, or not.

Therapeutic Goods Administration

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Reference/Publication #