



Wednesday, 17 June 2015

Economics Legislation Committee

Dear Chair and Members,

**Re: National Health Amendment (Pharmaceutical Benefits) Bill**

We would like to raise our serious concerns about the potential impact on patient safety of certain provisions of the National Health Amendment (Pharmaceutical Benefits) Bill 2015 which facilitate the substitution of biosimilars for biologic medications at the pharmacy level.

We have written recently to the Minister for Health outlining our concerns about the substitution of biosimilars. We have also written to PBAC outlining our concerns. Our letter to PBAC is attached for your reference.

The specific provisions of the Bill that we are concerned about are the amendments relating to PBS listing for bioequivalent and biosimilar medicines and treating brands as Schedule equivalent. These are:

- Schedule 1, Clause 3, which provides for a brand or pharmaceutical item that is biosimilar or bioequivalent to a listed item, to be taken to have the same drug.
- Schedule 2, Clause 1, which provides for the Minister to determine, having regard to any advice from the PBAC, that a brand of pharmaceutical item is to be treated as equivalent to one or more other brands of pharmaceutical items.

These clauses would allow biosimilars to be treated in the same way as generic medications. However, a biosimilar is not a generic biological medication.<sup>i</sup> Biologic medications are extremely complex molecules grown using living organisms and it is virtually impossible to replicate them exactly. Minor variations in the manufacturing process can have a major impact on efficacy and patient safety. Consequently it cannot be assumed that a biosimilar can be used interchangeably with its biologic reference product.

We are also concerned that the legislation gives the responsibility of advising the Minister as to whether a biosimilar is to be treated as equivalent to its reference product to the PBAC. While we respect the skills of the PBAC members, its role is to evaluate products for cost-effectiveness and reimbursement. The bioequivalence of a biosimilar is an issue of quality, safety and efficacy which should be determined by the TGA which is responsible for registering pharmaceuticals in Australia. The TGA's view is that it is not currently possible 'to determine a degree of similarity, between a biosimilar and an already registered biological medicine sufficient to support a designation by the TGA of 'bioequivalence'.'<sup>ii</sup> Consequently we recommend that Clause 1 in Schedule 2 be amended to read '... having regard to advice from the TGA and the PBAC...'

We would be pleased to provide any additional information to the Committee that you may require.

Yours sincerely,

Dr Mona Marabani  
**President**  
**Australian Rheumatology Association**

### **About Us**

The Australian Rheumatology Association is the professional association of rheumatologists in Australia. Rheumatologists are specialist physicians who diagnose and treat diseases affecting joints, muscles and bones. Rheumatologists are one of only two prescriber groups who can prescribe bDMARDs under the PBS

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<sup>i</sup> Therapeutic Goods Administration <https://www.tga.gov.au/book/what-biosimilar> viewed 16 June 2015.

<sup>ii</sup> <https://www.tga.gov.au/book/labels-product-information-pi-and-consumer-medicine-information-cmi-biosimilars> viewed 16 June 2015



10 June 2015

Professor Andrew Wilson  
Chair  
Pharmaceutical Benefits Advisory Committee  
[commentspbac@health.gov.au](mailto:commentspbac@health.gov.au)

Dear Professor Wilson and PBAC members

I am writing to bring to your attention Australian Rheumatology Association's (ARA) serious concerns about the PBAC's recently published position on 'a' flagging of biosimilars. In particular we urge the PBAC not to recommend 'a' flagging for Inflectra, the biosimilar of infliximab that is being considered at the July 2015 PBAC meeting, as we are concerned that patient safety may be compromised by allowing substitution of the biosimilar for the originator product at the pharmacy level.

The ARA strongly recommends that measures be put in place to protect patient safety with respect to the usage of biosimilars in Australia;

- People already receiving a biologic medication should not be put in a position where they might be switched to the biosimilar version at the pharmacy level without the informed mutual decision and consent of the prescriber and the consumer.
- New patients or patients moving to a new biologic therapy could be started on a biosimilar.
- Biosimilar infliximab and other biologic disease modifying anti-rheumatic drugs (bDMARDs) should not be 'a' flagged by the PBAC until further clinical evidence supporting the safety and efficacy of switching between the biosimilar and its originator product is available.
- A clear naming convention for biosimilars should be adopted to facilitate tracking and reporting of adverse events.
- Enhanced post-marketing pharmacovigilance and adverse events monitoring should be put in place to monitor the clinical efficacy and safety of biosimilars in the Australian market.
- Education programs for consumers, prescribers and pharmacists in relation to biosimilars should include a strong focus on protecting patient safety and should be developed in consultation and collaboration with consumers, clinicians and other stakeholders.

The rationale for our position is as follows.

***Patient safety may be compromised by allowing substitution***

Biosimilars are not generics. Biologic medications are extremely complex molecules grown using living organisms and it is virtually impossible to replicate them exactly. Consequently it cannot be assumed that a biosimilar can be used interchangeably with its biologic reference product.

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The risk of immunogenicity is an important efficacy and safety concern for all biologics, including biosimilars. Small differences in the materials, manufacturing process, distribution and route of administration of biologics can have a major impact on immunogenicity. For example a minor change in manufacturing of the biologic erythropoietin a decade ago led to a sharp increase in an incurable form of severe antibody-induced anaemia. It took years to determine and address the cause.<sup>1</sup>

The bDMARDs like infliximab used to treat auto-immune arthritis carry an increased risk of immunogenicity both because the molecules are more complex than other biologics and because they are used over long periods for chronic conditions.<sup>2</sup>

***More evidence is required to support the efficacy and safety of substitution***

There is ongoing concern that switching between a biologic and its biosimilar may increase the risk of immunogenicity.<sup>3 4 5</sup>

International approval processes for biosimilars do not require clinical data on the safety and efficacy of switching between the biologic and its biosimilar. The only exception is the FDA which requires additional evidence for biosimilars to determine interchangeability.<sup>6</sup>

In the case of infliximab, clinical evidence to support the safety of switching between the biosimilar and the originator product of infliximab in people who are well controlled on the originator product, is sparse.<sup>7 8</sup> In the absence of this data, Norway is funding a study into the safety and efficacy of switching from Remicade (infliximab originator) to the biosimilar treatment Remsima. This study is due for completion in May 2016.<sup>9</sup>

***Leading experts and regulatory authorities do not support substitution***

Regulation of biosimilars is still an evolving field. Notably, leading clinical experts and regulatory authorities do not support substitution of biosimilars for biologics at the point of dispensing. These include regulatory authorities in the UK,<sup>10</sup> Canada,<sup>11</sup> and most European countries,<sup>2</sup> as well as the American<sup>12</sup> and British Colleges of Rheumatology<sup>7</sup> and the Council of Australian Therapeutic Advisory Groups,<sup>13</sup> which provides guidance on drug use in Australian hospitals.

The PBAC's advice that it will consider 'a' flagging of biosimilars as suitable for substitution at the pharmacy level is in contrast to the weight of opinion internationally. Of particular concern is the PBAC's advice that it would consider 'absence of data to suggest significant differences in clinical effectiveness or safety' when considering 'a' flagging.<sup>14</sup> This is inappropriate as absence of evidence is not the same as evidence of absence.

'A' flagging is likely to lead to inadvertent substitution at the pharmacy level without the knowledge, understanding or agreement of the consumer and/or prescriber. While both can veto substitution, consumers may not understand that biosimilars are not generics and busy doctors may forget to prescribe by brand name or to specify that substitution is not permitted.

***Safety monitoring may be compromised***

Substitution at the pharmacy level can create confusion when reporting adverse events. Effective safety monitoring needs doctors and consumers to know exactly which medicine is being taken.

Immune reactions can also occur after a patient has been using a biologic for a long time, so if medications have been switched it can be difficult to tell which product is responsible for any adverse event.

In Thailand, a number of cases of immune reactions to a biologic medication (epoetin alfa) were recorded between 2004 and 2007. The market included a number of biosimilars of this product and hospitals and pharmacists frequently switched patients between products, often with

incomplete documentation. Despite intensive investigation, it was not clear which product or products had caused the problem.<sup>15</sup>

***Disease control may be compromised***

Achieving adequate disease control or remission for people with auto-immune forms of arthritis can be challenging and may take many attempts using different combinations and doses of various medications, including different bDMARDs. This process can take years.

Eligibility criteria for access to biologic medications on the PBS are also strict and require patients to fail other therapies before these medications can be prescribed or changed.

In rheumatology, clinical trials of biosimilars have been of new users only, with no trial of direct substitution. In the absence of data from such trials, substitution which may jeopardise hard-won disease control should not be allowed.

***A safety issue would be a major setback to the introduction of biosimilars***

Biosimilars offer the welcome potential to reduce health system costs and increase patient access to effective biologic medications. However it is essential to proceed with caution to ensure measures to encourage their uptake do not compromise patient safety in any way. Aside from the impact on individuals, if a safety issue does arise, it would be a significant set-back for the future adoption of biosimilars and hence the potential to realise the benefits they may offer.

I strongly urge you to make patient safety your top priority when considering the appropriateness of 'a' flagging of biosimilars.

***Meeting***

We also request a meeting with you and or your committee should that be convenient.

Yours sincerely

Dr Mona Marabani  
**President**  
**Australian Rheumatology Association**

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## References

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- <sup>4</sup> Cortes J et al 2014 Expert perspectives on biosimilar monoclonal antibodies in breast cancer. *Breast Cancer Res Treat* 2014; 144(2): 233–239.
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