5 June 2015

The Hon. Sussan Ley
Minister for Health
Commonwealth of Australia
Canberra ACT
AUSTRALIA

Dear Minister

Re: **PROPOSED POLICY ON BIOSIMILARS 'SUBSTITUTION'**

I am an Australian citizen writing to you from Scotland, where I am currently living. In the field of biosimilars, Australia has had a reputation of being at the forefront of adopting/enforcing world best practice. Recently news has come to me of growing concerns, amongst an international community of those dedicated to the safe use of biosimilars, that Australia is not only moving away from best practice but seemingly about to set itself on a path that will put patients at unnecessary risk.

First, allow me to introduce myself. My name is Stephen Murby and, inter alia, I am: a biosimilars spokesperson for the International Alliance of Patients' Organizations (IAPO) headquartered in London; a member of the International Advisory Board of the Alliance for Safe Biologic Medicines (ASBM) headquartered in Virginia, USA; a Consumer Health Forum of Australia (CHF) Board Special Representative; a CHF Honorary Life Member; and a former CHF Director, Treasurer and Chair.

I have a special interest in biosimilars from the patient perspective and have been working with IAPO and others over the past few years in developing and disseminating biosimilars information and resources to patient organisations around the world. Most recently, I spoke in September at the Biosimilars Global Congress 2014 Europe on 'Latest Development Revolutionizing the World of Biosimilars'.

Of particular concern are the recent developments in Australia in respect to the policy concerning the ability of pharmacists to substitute one biosimilar for another. My understanding is that there are some proposed amendments to legislation which would give the Pharmaceutical Benefits Advisory Committee (PBAC) the role of providing advice to the Minister on pharmacy-level substitution of biosimilar medicines and that PBAC has outlined its approach to this issue. I understand that PBAC has stated that its "default position" would be to advise that a biosimilar is suitable for substitution by a pharmacist "where the data is supportive of this conclusion" and that a relevant consideration is "the absence of data to suggest significant differences in clinical effectiveness or safety compared with the originator product."

If this is the case, then such would be an enormously retrograde step for Australia. One which is completely out-of-kilter with world best practice and which has the potential to reduce the standards of safe use of biosimilars for patients. If for no other reason than PBAC is not a medicines regulator.

PBAC's status alone, however, is not the principal cause for concern. The Therapeutic Goods Administration (TGA) has also begun to communicate a retreat from its previously high levels of patient safety priorities in respect of biosimilars. These two developments combined can only lead to an unnecessary and unacceptable increased risk of adverse outcomes for Australian patients.

(Automatic) Substitution

Before addressing my concerns around the TGA and PBAC, I would like to make some observations about automatic substitution in general and, by implication, substitution at the pharmacy level in particular.

Decisions about automatic substitution are not made by the EMA (the regulator responsible for biosimilars across Europe) but are left to individual members states (once a biosimilar has been approved). To date 15 European nations have prohibited automatic substitution. The FDA can designate a biosimilar as interchangeable, however, the decision on automatic substitution is a State by State decision: with more and more States moving to prohibit automatic substitution. A similar situation exists in Canada.

In 2010 the Norwegian Medicines Agency approved the automatic substitution of a particular biosimilar. In 2011 a Court in Oslo made a ruling to strike the biosimilar from the previously approved automatic substitution status based on the determination that *biosimilars are not generically equivalent only similar*.

At the heart of this matter is the real and genuine concern that clinical efficacy, demonstrated by extrapolation, is not sufficient to meet appropriate patient safety standards in terms of pharmacy-level substitution. It is hard to see a way around conducting rigorous Phase III Clinical Trials for the registration of a prospective biosimilar for safe use across a particular national genome.

The human genome is not the same across the world, each nation or each sub-population. In short, there are significant differences between the genomes of human individuals.

Biologic and biosimilar manufacturers alike may make their own independent manufacturing changes which can result in differences being introduced that affect the drug products.

Unintended deviations in manufacturing processes can lead to product 'drift'. Different patterns of product drift and evolution could contribute, over time, to clinically meaningful differences among both biologics and biosimilars (i.e. 'divergence').

TGA

My concerns around the TGA come from recent statements in the context of: the Expert Review; the TGA's approach to the naming of biosimilars; and its announcement that it plans to review its Biosimilar Guidelines which are less than 2 years old.

(a) Expert Review

Single Trusted Regulator

In the Expert Review of Medicines and Medical Devices (January 2015), there is a proposal that when it came to biosimilars the TGA might rely on 'a single trusted overseas regulator' to 'make the call'. In itself, 'a single trusted overseas regulator'

is poor science. Choosing at least two 'trusted overseas regulators' will allow for triangulation and so dramatically improve the TGA's decision taking outcome and patient safety profile. There is no universally accepted regulatory framework for biosimilars across the industrialised world, let alone worldwide. Differences exist in subtle but significant regulatory definitions and approaches between, for example: the European Medicines Agency (EMA) the World Health Organisation (WHO); the Food and Drugs Administration (FDA); and Health Canada – to name a few.

Interchangeability

In the same discussion document cited above, the authors appear to have assumed demonstration of interchangeability between the overseas reference product and the Australian reference product as a given or at least as potentially do-able.

On 29 July 2010 Health Canada issued a clarification on the subjects of interchangeability, automatic substitution and therapeutic substitution (still current) which, inter alia, noted:

"Specialised clinical studies can be used to support therapeutic interchangeability, however, these studies are not usually done and their relevance may not be long lasting. Over time, as sponsors of the SEB [biosimilar] and the reference biologic drug [biologic] make their own independent manufacturing changes, differences could be introduced that affect the drug products. For this reason, Health Canada does not support automatic substitution of a SEB [biosimilar] for its reference biologic drug [biologic] and recommends that physicians make only well informed decisions regarding therapeutic interchange." (Refer: Biologics and Genetics Therapies Directorate: 10-116885-569)

(b) Naming of Biosimilars

The TGA retreated from its original position on naming conventions for biosimilars in which it took a world leading approach by proposing a unique name for every biosimilar. Its current position on naming conventions for biosimilars (21 January 2015 https://www.tga.gov.au/evaluation-biosimilars) is stated as:-

> *"Following recent international developments in the area of biosimilar naming the TGA will not be continuing with the previously proposed naming convention for biosimilars while a review of the policy is undertaken."*

"In the interim biosimilars will use the Australian biological name without a specific biosimilar identifier suffix, for example a biosimilar to the reference product Neupogen filgrastim would be named 'TRADENAME' filgrastim."

Compare this position with some major recent international developments in biosimilar naming:

- July 2014: WHO proposed a global standard for distinguishing biosimilars from their reference product- via a 4-letter differentiating suffix called a Biological Qualifier (BQ). A meeting on 16th June 2015 is being held to finalize this proposal.
- March 2015: U.S. FDA approved its first biosimilar, Zarxio (filgrastim-sndz); which includes a 4-letter differentiating suffix. Additional FDA naming guidance is due later this year.

The TGA's naming approach is a major shift from world best practice and goes against every indicator from physicians surveyed by ASBM in Europe, USA, Canada and Latin America.

The 2015 ABSM survey of physicians in Latin America showed that 94% of respondents considered the WHO's BQ proposal "useful" in helping their patients receive the correct medicine.

Whilst 57% of respondents referred to medicine exclusively by its non-proprietary name in a patient record (which could result in patients receiving the wrong medicine). Further, some 28% used non-proprietary name exclusively when reporting adverse events (which could result in attribution to the wrong medicine).

The ASBM fourth quarter 2013 survey of European doctors showed that 62% of physicians used brand names (not distinguishable biotech med names) when prescribing and reporting adverse events for biologic and biosimilars.

The survey also showed that 53% of respondents incorrectly thought that medicines with the same non-proprietary name were structurally identical and 61% believed that they were approved for the same indications.

The 2014 survey of Canadian doctors carried out by ASBM revealed misconceptions about biosimilars, along with physician prescribing and recording practices, highlighting the need for a distinguishable naming scheme for all biologics, including biosimilars.

Physicians overwhelmingly (79%) supported Health Canada implementing distinguishable names, with the majority (54%) identifying unique non-proprietary names as their preferred method.

Canadian physicians felt strongly about the need to retain sole prescription authority. It is not acceptable to them for a pharmacist to make an automatic substitution.

(c) TGA review of its Biosimilar guidelines

The TGA's Guidelines on the Evaluation of Biosimilars were issued in July 2013. Recently the TGA announced that it would review these guidelines because: "The understanding of biosimilar medicines is evolving and as a result the current guideline 'Evaluation of Biosimilars' may need to be updated." I am advised that the TGA plans to revise its current position on pharmacy level substitution of biosimilar medicines. The TGA, like most regulators around the world , currently considers that biosimilar medicines should only be switched under the supervision of a physician.

PBAC

My concerns around the PBAC relate to its recently announced approach to biosimilar medicines.

PBAC considered the matter of substitution by a pharmacist of biosimilars at its April 2015 meeting and has released outcomes from this "special meeting". (http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-04/2015-04-biosimilars.pdf)

PBAC advised that biosimilar products would be "a" flagged, and therefore suitable for substitution at the pharmacy level, where the data are supportive of this conclusion. PBAC considered that this would be the Committee's default position.

PBAC advised that the following would be relevant considerations in establishing that a biosimilar product could be "a" flagged with the originator product:

- *Absence of data to suggest significant differences in clinical effectiveness or safety compared with the originator product;*
- *Absence of identified populations where the risks of using the biosimilar product are disproportionately high;*
- *Availability of data to support switching between the originator product and the biosimilar product;*
- *Availability of data for treatment-naïve patients initiating on the biosimilar product;*
- *Whether the Therapeutic Goods Administration has deemed a product to be biosimilar with the originator product.*

The 'absence' or 'availability' of data being sought by PBAC on the basis of the TGA granting biosimilar registration brings into question what PBAC considers to constitute 'evidence'. Evidence in the form of Phase III clinical trials across a representative sample of the 'Australian' genome is one thing – though the extent of such a trial is a further question (should they be abridged or full scale – for example). Furthermore, proof based on the 'absence of evidence', done properly, is a high bar to reach; one that can too oft be missed – as with all such 'proofs by induction'.

When one considers this issue in the context of a possible "trusted overseas regulator" (should this be the outcome of the Expert Review), it raises the following questions:

If TGA's 'trusted overseas regulator' allows for substitution at the pharmacy level, does the TGA have criteria around 'trusted' status that includes the way in which decisions are made on substitution? Though, as already demonstrated earlier, such regulators today would be hard to find in the first place.

If the TGA bases its decision on an overseas regulator that doesn't allow for substitution by a pharmacist then there will be very little 'evidence' available in the

jurisdiction of that overseas regulator (i.e. a systemic absence) suggesting significant risks. I can only wonder whether PBAC would accept arguments along the lines that: although TGA listed a biosimilar based on a 'trusted overseas regulator' which didn't support substitution, PBAC would accept the ('absence' or ' availability') evidence from another 'trusted overseas regulator' that does allow for substitution at the pharmacy level?

There remains a great discrepancy between approaches taken by those overseas regulators who actually do allow for substitution by a pharmacist as to upon what evidence they base their decisions (e.g. clinical trials, extrapolation, pharmacovigilance, etc.).

It seems to me that PBAC's advice on substitution has done little to clarify the situation nor does it provide confidence to consumers of a rigorous and reliable approach to the registration and administration of biosimilars in Australia. Indeed, coming out with any advice ahead of a clear statement from TGA implies an undue (and unnecessary) haste – which leaves one to wonder why?

Furthermore, PBAC considered that *'where a biosimilar product could not be "a" flagged at the time of PBS listing, data should be collected to support "a" flagging at a later point*'.

This advice is of concern from the point of patient safety. First, because TGA, not PBAC, is the qualified and resourced regulator charged with making the necessary and sufficient investigation and decision taking on interchangeability and substitution (which are themselves two separate scientific concepts and medico-scientific realities both in absolute terms and in terms of the relevant genomic profile for which they are being considered). Secondly, this statement seems to be a committed 'push' by PBAC to dedicate resources to pursue proactively substitution at the pharmacy level when such should be in the responsibility and expense of the applicant (either initially or over time).

Potential outcomes from allowing substitution of biosimilars

In the end, when it comes to biosimilars at this time in their development and release and with the low levels of awareness and/or knowledge across physicians, pharmacists and patients evident across the world (let alone Australia), PBAC's "a"

flagging position on biosimilars introduces an unnecessary and unacceptable 'risk chain' in terms of patient safety (particularly for patients taking an extant biosimilar). The two situations set out below outline how risks may occur:-

SITUATION 1:
The physician doesn't tick 'no substitution' (for whatever reason);

1. The pharmacist provides the "a" flagged biosimilar (with or without patient consent/knowledge);
2. This automatic substitution for a patient already taking the biologic in effect assumes interchangeability proven for the biosimilar in the context of the Australian genome profile (something which may be beyond the knowledge of both pharmacist and physician);
3. The pharmacist is not obliged to inform the physician of the substitution;
4. The patient experiences an adverse event (which may or may not be reported and/or recorded);
5. If the adverse event is recorded then the pharmacovigilance process may or may not be effective, depending on whether prescription drug or dispensed drug are used in the report (let alone accurate biosimilar naming issues already raised); and
6. If the adverse event is serious, severe and/or fatal then a risk chain for litigation has been clearly established.

SITUATION 2:
The physician does tick 'no substitution'

1. The pharmacist notes the 'no substitution', however, offers the "a" flagged biosimilar (either as an 'automatic' response, as per generics, or because the pharmacist considers 'biosimilar' and 'generic' as one in the same when it comes to "a" flagging);
2. The patient accepts the offer of the biosimilar (for whatever reason – trust in pharmacist, cost, etc.);
3. The pharmacist is not obliged to inform the physician of the substitution; and
4. Risk Chain steps 4 to 6 above relate.

Given these risks, it is my view that the best place to start is NOT to allow "a" flagging of biosimilars and to RELY SOLELY on the physician to prescribe either the biologic or the biosimilar as s/he sees most appropriate for the patient in context.

Concluding remarks

Currently there are over 200 biologics being prescribed to over 800 million people worldwide. Over time, a vast biosimilars market is inevitable.

Australia has 8 approved biosimilars based on 3 biologics (the first in 2010). Europe has around 20 biosimilars based on 8 biologics (the first in 2006). Canada has approved 3 biosimilars based on 3 biologics (the first in 2009). The USA recently approved its first biosimilar.

Clearly these are early days and the message is that available information is both diverse and limited. Patients must be confident of their safety and best interests when relying on the Regulator. As the number of biosimilars seeking entry to the market increases, the pressure will be on Regulators to find 'The Holy Grail of Biosimilars': *A fast track regulatory framework to bring high-quality, safe and efficacious biosimilars to the widest number of patients most cost-effectively.*

The first and foremost priority of any Regulator must be to ensure safe regulatory and approval pathways for biosimilars with strict pharmacovigilance requirements based on the populations in their own jurisdictions.

These are 'Early Days' and we do more good than harm in setting the entry barriers high now in order to ensure patient safety and to improve the prospects for the 'Holy Grail of Biosimilars' in years to come.

For your consideration.

Yours sincerely

Stephen Murby FRSA

Cc:

The Hon Catherine King MP
Shadow Minister for Health

Senator Richard di Natale
Leader, The Australian Greens

Declaration

Recently Medicines Australia contacted me and invited me to address a Health Consumer Organisation Workshop on Understanding Biological and Biosimilar Medicines – The New Frontier on Wednesday 24 June 2015 at Rydges Sydney Airport, which I have accepted. During my presentation, I will be addressing a number of topics directly related to the impact and implications of regulatory frameworks for biosimilars in the context of: the Expert Review; the TGA's approach to the naming of biosimilars; and TGA's announcement that it plans to review its Biosimilar Guidelines, which are less than 2 years old; and the, even more recent, advice issued by PBAC in respect of substitution of biosimilars at the pharmacy level ("a" flagging).The views that I will express will be my own and informed by the work done with and by IAPO, ASBM and CHF. My views will be wholly independent of any pharmaceutical industry position though it is possible that, on some issues, there may well be a concurrence of position outcome.