

Karen Whitelock  
Patient Safety  
Ad. Int. Patient Safety Country Head  
Australia and New Zealand

Novartis Pharmaceuticals Australia Pty Ltd  
ACN 004 244 160  
54 Waterloo Road  
Macquarie Park NSW 2113  
PO Box 101  
North Ryde NSW 1670  
Australia  
Tel +61 2 9805 3673  
Fax +61 2 9888 1627  
Email: karen.whitelock@novartis.com



Biovigilance Consultations  
Signal Investigation Coordinator  
Therapeutic Goods Administration  
PO Box 100  
Woden ACT 2606

16 December 2016

Dear Sir/Madam

**Consultation on the draft biovigilance guidance documents and adoption of EU Guideline EMEA/149995/2008 in Australia.**

Please find attached the response from Novartis Pharmaceuticals Pty. Ltd. ['**Novartis**'] on the 31 October 2016, Guidance on biovigilance responsibilities of sponsors of biologicals, Guidance on risk management plans for medicines and biologicals and adoption of the European Union guideline EMEA/149995/2008 in Australia.

We welcome the opportunity to provide feedback on the biovigilance guidance, ahead of their implementation. In this submission, Novartis has commented on each guidance and the specific question on whether or not EU guideline EMEA/149995/2008 should be adopted.

We note that the regulatory framework for biologicals provides the legislative basis for the regulation of human tissue and cell-derived products that are supplied in Australia. The definition of a biological is defined in Part 3-2A of the Therapeutics Goods Act 1989 (the Act) as a thing made from, or that contains, human cells or human tissues, and that is used to, treat or prevent disease, ailment, defect or injury; diagnose a condition of a person; alter the physiological processes of a person; test the susceptibility of a person to disease and replace or modify a person's body parts.

Products that fall under this definition can be regulated as biologicals under the biological regulatory framework (examples include human stem cells; tissue-based products and combined cell and tissue products), regulated as therapeutic goods, but not as biologicals (biological prescription medicines such as vaccines; labile blood and blood components or haematopoietic progenitor cells) or excluded and not regulated as biologicals (fresh viable organs, IVF, bone marrow transplants, cells and tissues made by a medical practitioner for a single patient under the care of that medical practitioner).

The Australian Regulatory Guidelines for Biologicals (ARGB) provides details of the framework which applies different levels of regulation to products based on the risk associated with their use, and is designed to be flexible enough to accommodate emerging technologies.

Biologicals that are to be included on the ARTG must be classified into one of four classes, according to their level of risk, Class 1 to Class 4.

It is noted that the Australian definition of a biological is different to the EU and FDA regulatory agencies, and represents a narrower range of products, aligning most closely to the definition of the advanced therapy medicinal products (ATMPs).

### **Guidance on biovigilance responsibilities of sponsors of biologicals**

#### Novartis position: Agree

The document provides draft guidance for sponsors of biologicals on their biovigilance responsibilities. It sets out requirements and recommendations for detecting and reporting adverse events and serious threats to public health that may arise in relation to the use of any class of products regulated by the TGA under the biologicals framework. The guidance requires companies to have a biovigilance system in place and nominate a biovigilance contact person. The reporting requirements for biological adverse events aligns with device vigilance, reporting requirements of 48 hours for serious threat to public health, 10 calendar days for serious adverse events and 30 calendar days for near serious events.

The guidance is also aligned with the TGA guidance for reporting in relation to medicines, however, uses different terminology owing to differences in the underpinning legislation for medicines and biologicals. Areas that are defined in the guidance includes, spontaneous reporting conventions, changes to benefit-risk assessment of a biological including the definition of a serious threat to public health, which includes actions taken by an overseas regulatory agency, the timeline for reporting these aligns with the serious threat to public health that is 48 hours from the sponsor awareness, rather than 72 hours for medicines.

- It is recommended that TGA specifically define that "sponsor awareness" is the date of awareness of the Australian sponsor personnel. Which is defined as Day zero for the 48 hour clock start.

Reporting requirements for post-marketing initiatives and literature reports are defined, foreign cases are not required to be reported. Sponsors are expected to perform signal detection and investigation. Data elements to be included describes that batch\lot numbers are required. Sponsors are expected to validate all serious and near serious adverse event reports.

Traceability of biologicals is described, sponsors are required to be able to trace a biological product from donor to product release. For higher risk biological products where an RMP is required, product specific conditions of registration is included that requires product traceability from the donor to the recipient. Traceability also covers the ability to locate and identify all relevant data relating to products, materials and people that may have come into contact with the biological.

- In the existing healthcare practices in Australia, it will be challenging for sponsors to meet the traceability measures to track the product down to the patient and others in the healthcare setting who have come into contact with the biological. There will need to be collaboration across sectors including hospitals, pharmacies, wholesalers and sponsor companies. TGA would need to have a collaborating and supportive role in developing traceability measures in many instances.

Periodic Safety Update Reports are required to be submitted at defined time-points for all class 4 and class 3 and some class 2 biologicals.

For Australian products marketed overseas, the sponsor is requested to assure any information in other countries is brought to the attention of the Australian sponsor. Australian products manufactured overseas are expected to receive safety data from the overseas sponsor to include in their ongoing monitoring but are not expected to report these to the TGA.

- Recommendation to clearly define in the guideline the definition of a biological in Australia to ensure which products are covered by which vigilance reporting responsibilities for sponsors.

## **Guidance on risk management plans for medicines and biologicals**

### Novartis position: Partially Agree

The document is revised guidance on risk management plans for medicines and biologicals. It has been developed from the current guidance on risk management plans for medicines. Where appropriate, reference to biologicals and biovigilance has been added, also included is a section which details the additional requirements for biologicals based on the European Union requirements for advanced therapy medicinal products. The revised guidance describes the TGA's expectations for preparation of risk management plans for Class 3 & 4 biologicals and some Class 2.

The TGA requests EU-RMPs for biologicals that are regulated under the Australian biological framework to contain additional sections describing "Specific risks of biological products" that includes discussion of risks that would not fit into other parts of the safety specifications in the EU RMP. In addition, RMP Part II Module SVII Identified and Potential Risks should be replaced with RMP modules SVII Identified and Potential Risks (ATMP version). This request is challenging from an administrative perspective as local sponsors may need to amend global EU-RMPs to adhere to the above requirements. Global sponsors would be producing EU-RMPs for biological medicinal products that aligned with the European Guideline EMA/168402/2014. It is not clear for products that meet the definition of an ATMP in the EU that the EU-RMP would contain the sections that the TGA define to be included, as the definition of a biological is not aligned there may be times when this is the case

- It is recommended that TGA accept EU-RMPs for biological products that align with guideline EMA/168402/2014 and that any additional requirements with respect to identifying risks, ATMP version of Identified and Potential Risks be detailed in an Australian Specific Annex

In keeping with the principles of good regulatory practice and practices by comparable overseas regulators, Novartis believes a framework should be developed for the submission and evaluation of updated RMPs ASAs and the accompanying ASAs. This will ensure there are transparent and consistent procedures for making decisions under the legislation.

At present, changes to an ASA outside of the Category 1 Application are generally assessed by the TGA in an informal manner. In light of other TGA reforms, in particular the TGA's proposal for expedited pathways for NCEs such as provisional approvals, we anticipate sponsors will increasingly be required to implement additional post-marketing risk management measures.

As many of these measures take time and resource to develop and implement (eg. Educational program, patient registry), a well-defined process for the evaluation of updated RMPs (and ASAs) will ensure sponsors can effectively track progress of the review and the timing of the outcome. Sponsors will be able to plan accordingly and implement RMP commitments in a timely manner, thereby reducing delays in patient access to new medicines. Similarly, it will allow the TGA to more effectively monitor compliance to RMP commitments

and allow for the more identification of safety concern of special interest that require additional monitoring and mitigation.

#### **Adoption of European Union guideline EMEA/149995/2008 in Australia**

Novartis position: It is not necessary to adopt this EU guideline.

It is understood that TGA have proposed to adopt this EU guideline as the TGA's biological definition mostly aligns with the ATMP definition that this guidelines discusses. This EU guideline discusses safety and efficacy follow-up, and risk management of Advanced Therapy Medicinal products. The TGA's draft biovigilance guideline describes requirements for the traceability of biologicals, and the TGA's draft consultation paper on risk management plans for medicines and biologicals describes RMP requirements for biologicals in enough details for implementation in the Australian environment. Therefore, it is recommended to not adopt the EU guideline EMEA/149995/2008.

TGA have not adopted all of the EU Pharmacovigilance guidelines, for example Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products, has not been adopted but reference to this guideline is made in the TGA's Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines. TGA state that certain requirements and recommendation in the TGA's pharmacovigilance requirements are consistent with those described in that EU guideline.

- It is recommended that TGA take the same approach with EU guideline EMEA/14995/2008 where this guideline is referenced in both the TGA's Biovigilance guideline and RMP requirements and not adopted wholesale.



Novartis thanks the TGA for considering its submission.

Yours sincerely,

Karen Whitelock  
Ad. Int. Patient Safety Country Head  
Novartis Patient Safety