EXPLANATORY STATEMENT

Therapeutic Goods Act 1989

Therapeutic Goods Order No. 98 *Microbiological Standards for Medicines 2018*

The *Therapeutic Goods Act 1989* (the Act) provides for the establishment and maintenance of a national system of controls for the quality, safety, efficacy and timely availability of therapeutic goods that are used, or exported from, Australia.

Therapeutic Goods Order No. 98 Microbiological Standards for Medicines 2018 (TGO 98) is an order made by the delegate of the Minister for Health under section 10 of the Act. The purpose of TGO 98 is to succeed the existing *Therapeutic Goods Order No. 77 Microbiological Standards for Medicines* (TGO 77), which was registered on 29 September 2008 and commenced on 1 January 2010, as TGO 77 will sunset on 1 October 2018 under the provisions of the *Legislation Act 2003*.

TGO 98 commences on 1 October 2018.

BACKGROUND

The Australian Government is responsible for regulating the quality of therapeutic goods, including medicines. In respect of therapeutic goods other than medical devices, this is principally achieved by specifying ministerial standards for the goods which may relate to a range of matters (e.g. the quality of the goods and the procedures to be carried out in their manufacture), and otherwise by applying default standards specified in the international pharmacopoeias that are defined in the Act.

Subsection 10(1) of the Act relevantly provides that the Minister may, by legislative instrument, make an order determining that matters specified in the order constitute a standard for therapeutic goods or a class of therapeutic goods identified in the order. Offence and civil penalties may apply if therapeutic goods (other than medical devices) that do not comply with an applicable standard are imported, exported or supplied. The Secretary may, however, consent in writing to the import, supply or export of such goods notwithstanding their non-compliance (sections 14 and 14A of the Act refer).

Without limiting the generality of subsection 10(1), subsection 10(2) relevantly provides that an order establishing a standard for therapeutic goods may be specified by reference to a variety of matters including the quality of the goods, the procedures to be undertaken in their manufacture or a monograph in the British or European Pharmacopoeia or in the United States Pharmacopeia-National Formulary. In addition, an order may require matters relating to the standard to be determined in accordance with particular tests.

TGO 98 will apply to most medicines (other than a small number of exemptions), and specifies important minimum microbiological requirements with which medicines must comply throughout their shelf life.

The medicines that are exempt from TGO 98 under the Order are:

- export only medicines;
- medicines that are imported into Australia for use in the treatment of the importer or their immediate family in accordance with item 1 of Schedule 5 to the Therapeutic Goods Regulations 1990;
- starting materials for use in the manufacture of other medicines; and
- medicines that have not yet reached the final stage of their manufacture.

In particular, TGO 98 specifies the testing requirements for sterile medicines in relation to sterility testing and bacterial endotoxin testing, the requirements relating to efficacy of antimicrobial preservation for aqueous multidose medicines and requirements relating to the microbiological attributes for non-sterile medicines.

For example, the effect of the Order's requirements in relation to sterility testing and bacterial endotoxin testing for sterile medicines is that such a medicine must comply with a test for sterility and (if applicable) a bacterial endotoxin test, in one of the default standards defined in the Act (i.e. either the British Pharmacopoeia, the European Pharmacopoeia or the United States Pharmacopeia-National Formulary).

TGO 98 also specifies the acceptance criteria with which complementary medicine oral dosage forms that contain raw material of animal, vegetal or mineral origin must comply.

While minor updates and changes to improve clarity have been made in TGO 98 in comparison with TGO 77, the new Order is principally intended to provide continuity in relation to the requirements for the microbiological quality of medicines, and does not substantially alter the existing technical requirements of TGO 77 or introduce new such requirements. A minor amendment is made to section 8 of the Order (Efficacy of antimicrobial preservation of a multidose medicine), to clarify the multidose medicines to which that section is intended to apply (principally, these are aqueous multidose medicines).

INCORPORATION

TGO 98 adopts each of the British Pharmacopoeia (BP), European Pharmacopoeia (EP) and the United States Pharmacopeia-National Formulary (USP), and section 4 of TGO 98 defines these pharmacopoeia as having the same meaning as in the Act. The definitions of the pharmacopoeia in subsection 3(1) of the Act refer to the publications of each as in effect immediately before the commencement of the relevant definition, and to any subsequent amendments or editions (the definition of 'default standard' in subsection 3(1) also points – in effect - to a monograph of any of those three pharmacopoeia, as defined). So the intention was that, by including those definitions, TGO 98 would (when read alongside the Act), make the intended manner of incorporation clear.

However, it has been identified that at the time of its making, incorporating these documents as in force from time to time in TGO 98 was precluded by subsection 14(2) of the *Legislation Act 2003*. As such, it is important to note that these pharmacopoeia are adopted in TGO 98 by reference to the editions of each in place at the time of TGO 98's commencement.

For the BP this will mean the British Pharmacopoeia 2018, as at 1 January 2018; for the EP – the European Pharmacopoeia (Ph.Eur.) 9th Edition, incorporating Supplement 9.5; and for the

USP – The United States Pharmacopeia-National Formulary, incorporating the First Supplement to USP 41-NF 36, dated 1 August 2018).

In relation to how to access these pharmacopoeia, unfortunately these publications are not available for free (a range of prices may apply depending on whether a person wishes to take out a subscription (and if so how many users would be involved), or purchase a particular edition). However, it is expected that the persons most affected by their adoption – in this case, medicines sponsors and manufacturers – would be aware of their terms and have access to them. As important international benchmarks for the safety and quality of therapeutic goods, it would not be feasible from a regulatory perspective (particularly in relation to such an important area as ensuring that medicines are free from microorganisms that might cause harm) to not adopt such benchmarks because they are not available for free.

It should also be noted that the National Library's Trove online system (https://trove.nla.gov.au/) allows users to identify libraries in Australia that are open to the public where (in most cases, earlier) editions of these pharmacopoeia may be viewed (for example, the University of Tasmania or the University of Western Australia in relation to the BP). Members of the public may also approach any library that participates in inter-library loans to request an inter-library loan with such university libraries, to obtain a photocopy of a particular part or monograph for personal study or research (but not for commercial purposes), at a usual cost of $16.50 per request (enquiries should be made with local libraries, State libraries and the National Library).

CONSULTATION

The TGA undertook consultation on the proposal to remake TGO 77 without substantially altering the arrangements for microbiological standards for medicines that were in place under that instrument, with the proposal available on the TGA web site (www.tga.gov.au) for public comment between 6 February and 6 March 2018. Eight submissions were received, with most supporting the action on the basis that TGO 77 continued to be efficient and effective. One submission disagreed with the proposal, and several requested a small number of technical modifications. Some of those were not able to be implemented in TGO 98 for microbiological safety reasons. However, a request to exclude multidose low water activity preparations from the need to comply with requirements relating to preservative efficacy was considered not to raise safety concerns and was reflected in TGO 98.

Consistent with Government best practice regulation requirements for sunsetting legislative instruments, the Department, after the consultation outlined above, has assessed TGO 77 as having operated effectively and efficiently since it came into force in January 2010, and it continues to do so. As such, a regulation impact statement is not required for its successor instrument, TGO 98.

Details of TGO 98 are set out in Attachment A.

TGO 98 is compatible with the human rights and freedoms recognised or declared under section 3 of the *Human Rights (Parliamentary Scrutiny) Act 2011*. A full statement of compatibility is set out in Attachment B.

This Order is a disallowable legislative instrument, and commences on 1 October 2018.

ATTACHMENT A

Details of Therapeutic Goods Order No. 98 *Microbiological Standards for Medicines 2018*

Section 1 Name

This section provides that the name of this Order is Therapeutic Goods Order No. 98 *Microbiological Standards for Medicines 2018.*

Section 2 Commencement

This section provides that this Order commences on 1 October 2018.

Section 3 Authority

This section provides that the legislative authority for making the Order is subsection 10(1) of the *Therapeutic Goods Act 1989* (the Act).

Section 4 Interpretation

This section provides a number of definitions for terms used in this Order – in particular for example, acceptance criteria, antimicrobial preservation, CFU (colony forming units) and monograph.

This section also makes it clear that a number of important terms have the same meaning as given in the Act or the *Therapeutic Goods Regulations 1990*, for example export only medicine and herbal substance. Please note that while the terms default standards, the British Pharmacopoeia, European Pharmacopoeia, 'United States Pharmacopeia-National Formulary are also defined on this basis, the operation of subsection 14(2) of the *Legislation Act 2003* precludes the adoption of those pharmacopoeia as in force from time to time. As such, it is important to note that these pharmacopoeia are adopted in TGO 98 by reference to the editions of each in place at the time of TGO 98's commencement. For the BP this will mean the British Pharmacopoeia 2018, as at 1 January 2018; for the EP – the European Pharmacopoeia (Ph.Eur.) 9th Edition, incorporating Supplement 9.5; and for the USP – The United States Pharmacopeia-National Formulary, incorporating the First Supplement to USP 41-NF 36, dated 1 August 2018).

Section 5 Application

This section identifies the kinds of therapeutic goods for which this Order constitutes a standard. Specifically, section 5 has the effect that unless specifically exempted under section 6 of this Order (see below), this Order applies to all therapeutic goods that are medicines and that come within the operation of the Act. 'Medicine' is defined in the Order as having the same meaning as in the Act, which refers in subsection 3(1) of the Act to:

- therapeutic goods (other than biologicals) that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human; and

- any other therapeutic goods declared by the Secretary of the Department of Health, for the purpose of the definition of 'therapeutic device', not to be therapeutic devices.

Section 6 General Exemptions

This specifies a range of medicines that are not subject to this Order, being:

- export only medicines;
- medicines that are imported into Australia for use in the treatment of the importer or their immediate family in accordance with item 1 of Schedule 5 to the Therapeutic Goods Regulations 1990;
- starting materials for use in the manufacture of other medicines; and
- medicines that have not yet reached the final stage of their manufacture.

Section 7 Sterility and Bacterial Endotoxin testing

This section specifies the medicines that must comply with a Test for Sterility, and with Bacterial Endotoxin testing requirements, as well as the nature of those testing requirements for such a medicine – being, the Test for Sterility and, if applicable, the Bacterial Endotoxin Test, of a default standard. 'Default standard' has the same meaning in the Order as in the Act – relevantly, this term is defined in subsection 3(1) of the Act as, in effect, any of the British Pharmacopoeia, European Pharmacopoeia or United States Pharmacopeia-National Formulary.

Section 8 Efficacy of antimicrobial preservation of a multidose medicine

This section specifies the medicines that must comply with a test for the efficacy of antimicrobial preservation. All aqueous multidose medicines must comply with a specified test in either of the British Pharmacopoeia or European Pharmacopoeia, however an aqueous multidose medicine that is a liquid oral antacid medicine may alternatively comply with a specified test of the United States Pharmacopeia – National Formulary.

Section 9 Microbiological attributes of a non-sterile medicine

This section specifies the acceptance criteria for microbiological quality that apply to non-sterile medicines.

Subsection 9(1) specifies that a non-sterile medicine, other than those mentioned in subsection 9(2), must comply with the acceptance criteria for microbiological quality of the British Pharmacopoeia, the European Pharmacopoeia or of the United States Pharmacopeia – National Formulary, when tested using the specified methods. The acceptance criteria and testing methods in these three pharmacopoeias are comparable.

Subsection 9(2) specifies that a complementary medicine oral dosage form containing raw material of natural (animal, vegetal or mineral) origin must comply with the acceptance criteria for microbiological quality specified in Schedule 1 of this Order, unless the medicine is a herbal medicine consisting solely of one or more herbal substances (whole, reduced or powdered) to which boiling water is added before use, in which case the medicine must comply with the acceptance criteria specified in Schedule 2.

Schedule 1 tabulates the acceptance criteria for microbiological quality that apply to a complementary medicine oral dosage form containing raw material of natural (animal, vegetal or mineral) origin.

Schedule 2 tabulates the acceptance criteria for microbiological quality that apply to a herbal medicinal product consisting solely of one or more herbal substances (whole, reduced or powdered) to which boiling water is added before use.

ATTACHMENT B

SUPPLEMENTARY MATERIAL - STATEMENT OF COMPATIBILITY WITH HUMAN RIGHTS FOR A LEGISLATIVE INSTRUMENT THAT DOES NOT RAISE ANY HUMAN RIGHTS ISSUES

Statement of Compatibility with Human Rights

Prepared in accordance with Part 3 of the *Human Rights (Parliamentary Scrutiny) Act 2011*.

Therapeutic Goods Order No. 98 *Microbiological Standards for Medicines 2018*

This legislative instrument is compatible with the human rights and freedoms recognised or declared in the international instruments listed in section 3 of the *Human Rights (Parliamentary Scrutiny) Act 2011*.

Overview of the Legislative Instrument

Therapeutic Goods Order No. 98 Microbiological Standards for Medicines 2018 (TGO 98) is an order made by the delegate of the Minister for Health under section 10 of the Act, and is designed to succeed the existing Therapeutic Goods Order No. 77 *Microbiological Standards for Medicines* which was registered on 29 September 2008 and commenced on 1 January 2010, as TGO 77 will sunset on 1 October 2018 under the provisions of the *Legislation Act 2003*.

TGO 98 applies to most medicines (other than a small number of exemptions), and specifies important minimum microbiological requirements with which medicines must comply throughout their shelf life.

The medicines that are exempt from TGO 98 under the Order are:

- export only medicines;
- medicines that are imported into Australia for use in the treatment of the importer or their immediate family in accordance with item 1 of Schedule 5 to the Therapeutic Goods Regulations 1990;
- starting materials for use in the manufacture of other medicines; and
- medicines that have not yet reached the final stage of their manufacture.

In particular, TGO 98 specifies the testing requirements for sterile medicines in relation to sterility testing and bacterial endotoxin testing, the requirements relating to efficacy of antimicrobial preservation for aqueous multidose medicines and requirements relating to the microbiological attributes for non-sterile medicines.

For example, the effect of the Order's requirements in relation to sterility testing and bacterial endotoxin testing for sterile medicines is that such a medicine must comply with a test for sterility and (if applicable) a bacterial endotoxin test, in one of the default standards defined in the Act (i.e. either the British Pharmacopoeia, the European Pharmacopoeia or the United States Pharmacopeia-National Formulary).

TGO 98 also specifies the acceptance criteria with which complementary medicine oral dosage forms that contain raw material of animal, vegetal or mineral origin must comply.

While minor updates and changes to improve clarity have been made in TGO 98 in comparison with TGO 77, the new Order is principally intended to provide continuity in

relation to the requirements for the microbiological quality of medicines, and does not substantially alter the existing technical requirements of TGO 77 or introduce new such requirements.

A minor amendment is made to section 8 of the Order (Efficacy of antimicrobial preservation of a multidose medicine), to clarify the multidose medicines to which that section is intended to apply (principally, these are aqueous multidose medicines).

Human rights implications

As this legislative instrument does not introduce any measures other than those outlined above (and is principally designed to specify microbiological standards of a technical nature for medicines), it does not engage any of the applicable rights or freedoms.

Conclusion

This legislative instrument is compatible with human rights as it does not raise any human rights issues.

Jane Cook, delegate of the Minister for Health