Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Guidance on Therapeutic Goods Order No. 78
Standard for Tablets and Capsules

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This guidance document is intended to provide a plain English explanation of various requirements of Therapeutic Goods Order (TGO) No. 78 *Standard for Tablets and Capsules* (TGO 78) and their application, thereby assisting sponsors to achieve compliance. This document does not form part of the Order.

General

The requirements of the Order apply to a medicine that comes within the operation of Part 3-1 of the *Therapeutic Goods Act 1989* (the Act), which provides for the application of standards to therapeutic goods.

Such standards may relate to any matter relevant to the quality, safety or efficacy of a medicine and, generally, a medicine must not be imported, exported or supplied if it does not conform to an applicable standard.

Paragraph (b) of subsection 10(2) of the Act states that an Order establishing a standard for therapeutic goods may require that a matter relating to the standard be determined in accordance with a particular test.

Responsibility for compliance with the requirements of the Order rests with the sponsor of the medicine to which the Order applies.

Explanation of sections

Section 1 Name of Order

This section states the legal title of the Order.

Section 2 Commencement

This section states when the Order will commence to have effect.

This is specified as the day following the day on which the Order is registered on the Federal Register of Legislative Instruments (FRLI) <http://www.frli.gov.au>, which is the official repository of Commonwealth legislative instruments and is where the authoritative text of TGO 78 can be located.

TGO 78 was registered on the FRLI on 6 November 2008 and therefore took effect on 7 November 2008.

Following commencement of the Order, a transition period for products to achieve compliance will be allowed. Transition arrangements are given in the following section.

Section 3 Transition Arrangements

This section provides the date by which medicines must comply with TGO 78. This date is 1 November 2010.

Until 1 November 2010, sponsors have the choice of complying with either TGO 78, or its predecessor – Therapeutic Goods Order No. 56 *General standard for tablets, pills and capsules* (TGO 56).

The same transition timeframe applies to both current and new medicines.

Sponsors should consult the guidelines for prescription medicines, over-the-counter (OTC) medicines, registered complementary medicines and listed medicines for information about making quality changes that are consequent upon the requirements of a new Therapeutic Goods Order.

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Stock that is released for supply/sale by a sponsor on and after 1 November 2010 will be subject to the Order. Stock that has been released for sale/supply (e.g. to warehouses, retailers and consumers) prior to 1 November 2010 in accordance with TGO 56 will not be subject to this Order.

Section 4 Introduction

This section states the purpose of the Order.

Standards, including this Order, apply throughout the shelf-life of the medicine.

To ensure compliance with the Order, a prudent manufacturer will apply release specifications that are more exacting than those included in the Order.

Section 5 Interpretation

This section provides definitions of terms used in the Order and, where relevant, directs the reader to meanings given in the Act or Regulations. Readers should check the current compilation of the Act or Regulations.

Any term not defined in the Order has its usual English meaning.

The British Pharmacopoeia (BP) is defined in the Act, as is the process for the adoption of new editions, additions or amendments. When the definition of the British Pharmacopoeia is amended under subsection 3(1) of the Act the new definition will apply in this Order.

The definitions of 'capsule' and 'tablet' include the definitions of the BP for the various types of capsules and tablets, but do not include pills.

The United States Pharmacopeia-National Formulary is not yet defined in the Act. Until the definition of this pharmacopoeia is included in the Act, the Order specifies the United States Pharmacopeia (31st edition) - National Formulary (26th edition).

This Section also advises that where a pharmacopoeia renames or renumbers a test, then the Order incorporates that renamed or renumbered test.

Section 6 Application

This section describes which medicines are subject to the Order. The Order applies to tablets and capsules intended for oral administration for human use that come within the operation of the Act.

The Order applies to listed medicines, registered medicines, and medicines that are not required to be listed or registered, unless exempt from the Order.

There are two mechanisms for a medicine to be exempt from the Order:

1. if the medicine is mentioned in Section 7 (see below); or
2. if the Secretary of the Department of Health and Ageing, or a delegate of the Secretary, grants an exemption in accordance section 14 or 14A of the Act.

Section 7 General Exemptions

This section describes the medicines that are not subject to the Order.

The standard that applies to an export only medicine is currently specified in Therapeutic Goods Order No. 70B – *Standard for export only medicine*.

Section 8 Tablet or capsule with an individual British Pharmacopoeia monograph

This section specifies that a tablet or capsule that is the subject of an individual monograph in the British Pharmacopoeia (BP) must comply with that monograph.

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There are some departures from strict compliance with the BP monograph:

- For a listed tablet or capsule, compliance with the Uniformity of Dosage Units requirements in an individual BP monograph is replaced with compliance with the BP's requirements for Uniformity of Weight (Mass).
- For a registered tablet or capsule, when an individual BP monograph does not include a dissolution test, but a United States Pharmacopeia (31st edition) monograph for the same active ingredient in a tablet or capsule does require a dissolution test, then the tablet or capsule must meet a suitable dissolution requirement.
- A tablet or capsule containing folic acid must comply with Section 9 when relevant.

Section 9 Tablet or capsule containing folic acid

This section requires tablets (other than chewable, effervescent, dispersible and modified-release tablets) and capsules (other than soft or modified-release capsules) that contain 100 micrograms or more of folic acid to demonstrate dissolution of folic acid.

The dissolution test procedures and tolerances are those specified in the United States Pharmacopeia (31st edition) – National Formulary (26th edition).

Section 10 Listed tablet or capsules without an individual British Pharmacopoeia monograph

This section specifies the requirements for a listed tablet or capsule that is not the subject of an individual British Pharmacopoeia (BP) monograph.

Subsection (a) requires that the tablet or capsule complies with the BP's requirements for uniformity of weight.

Subsection (b) sets out the requirements regarding the content of each active ingredient. The requirement is that the estimated average content is in the range 90.0 – 120.0% of the stated content (label claim) for each active ingredient and for each component of an active ingredient that is quantified on the label (e.g., hypericin in *Hypericum perforatum*). However, there are exceptions from this requirement:

> Paragraph (i) applies to an active ingredient (e.g., betacarotene) or a component in an active ingredient that is quantified on the label (e.g., iodine in *Fucus vesiculosus*) included in a group mentioned in Schedule 1. Instead of the 90.0-120.0% limits, the limits in Schedule 1 apply.
>
> Paragraph (ii) applies to the components that are quantified on the label of a multicomponent active ingredient of natural origin when the proportions of these components vary independently of each other. There must be a minimum of 90.0% of the stated content (label claim) of each component. If some components are included in Schedule 1, then the Schedule 1 limits apply to those components. For example, a natural fish oil capsule would be required to contain a minimum of 90.0% of the label claim of each of Eicosapentaenoic acid and Docosahexaenoic acid and 90.0-165.0% of the label claim of Vitamin A.
>
> Paragraph (iii) applies to a multicomponent ingredient for which no quantitative claim is made on the label for any component. For such an active ingredient (e.g., a non-standardised herbal extract) there is no quantitative limit for the content of any component of the active ingredient. Sponsors should refer to the TGA document *Guidance on the use of the term 'Quantified By Input' for Complementary Medicines* <http://www.tga.gov.au/docs/html/argcmqbi.htm> for further information.

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Paragraph (iv) applies no quantitative limit to an active ingredient that is a homoeopathic preparation.

Subsection (c) requires that a modified-release tablet or capsule complies with a suitable dissolution test.

Subsection (d) requires that, when a dissolution test is not required, the tablet or capsule complies with the BP's requirements for disintegration.

Subsection (e) requires that a dispersible tablet complies with the BP's requirement for fineness of dispersion.

Subsection (f) requires that a tablet or capsule containing folic acid complies with section 9, if relevant.

Section 11 Registered tablet or capsule without an individual British Pharmacopoeia monograph

This section specifies the requirements for a registered tablet or capsule that is not the subject of an individual British Pharmacopoeia (BP) monograph.

Subsection (a) requires that the tablet or capsule complies with the BP's requirements for Uniformity of Dosage Units.

Subsection (b) sets out the requirements regarding the content of each active ingredient. The requirement is that the estimated average content is in the range 92.5 – 107.5% of the stated content (label claim) for each active ingredient. However, there is an exception:

Paragraph (i) applies different limits for an antibiotic active ingredient that is assayed by a microbiological method. Supplementary Chapter I L of the BP provides relevant details.

Subsection (c) specifies which tablet or capsule must comply with a dissolution test. A tablet or capsule for which there is an individual monograph for a tablet or capsule containing that active ingredient in either the BP or the United States Pharmacopeia (USP) that includes a dissolution test must show compliance with a suitable dissolution test. However, a chewable, effervescent or dispersible tablet is not required to demonstrate compliance with a dissolution test.

Subsection (d) requires that, when a dissolution test is not required, the tablet or capsule complies with the BP's requirements for disintegration.

Subsection (e) requires that a dispersible tablet complies with the BP's requirement for fineness of dispersion.

Subsection (f) requires that a tablet or capsule containing folic acid complies with section 9, if relevant.

Schedule 1 Limits for content of each active ingredient or component in a listed good that is a tablet or capsule

This Schedule specifies the limits for the content of each active ingredient or component in a listed tablet or capsule when there is no individual BP monograph. The limits apply to each active ingredient and component that is quantified on the label. The limits apply to single ingredient and multi-ingredient tablets and capsules.

Definitions for 'enzyme', 'mineral', 'mineral compound', 'probiotic', 'provitamin' and 'vitamin' are provided in section 5 of the Order.

Examples of provitamins are betacarotene, choline bitartrate and palm tocotrienols complex.

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Examples of enzymes are bromelains and papain.

Questions and answers relating to the standard for tablets and capsules

Why is the Order necessary now?

Therapeutic Goods Order No. 78 *Standard for Tablets and Capsules* (TGO 78) will replace Therapeutic Goods Order No. 56 *General standard for tablets, pills and capsules* (TGO 56) <http://www.tga.gov.au/docs/html/tgo/tgo56.htm> from 1 November 2010. TGO56 came into effect in 1996. Industry experience and progress on pharmacopoeial harmonisation have contributed to the changes introduced in TGO 78. TGO 78 also applies different requirements regarding dissolution, disintegration and uniformity of dosage units to listed (lower risk) and registered (higher risk) medicines. This reflects the risk-based regulatory model of the TGA.

TGO 78 has been made by the delegate for the Minister for Health and Ageing following consideration of advice provided by the Therapeutic Goods Committee (TGC) <http://www.tga.gov.au/docs/html/tgc.htm>. The TGC includes representatives of the manufacturers of prescription medicines, non-prescription medicines and complementary medicines, and consumers.

As TGO 78 will replace TGO 56, why is there no mention of "pills"?

Pills are generally used in traditional Chinese medicines and in homoeopathic medicines.

The TGA intends to undertake consultation to determine if a new standard for pills is required prior to the revocation of TGO 56.

As TGO 78 will replace TGO 56, where do I now find information on controls on colouring agents?

A guideline on colourings permitted in medicines for oral use was published by the TGA in 2004; see *Colourings permitted in medicines for oral use* <http://www.tga.gov.au/meds/colourings.htm>.

Is compliance with TGO 78 all I have to demonstrate to gain product approval?

No. The Order defines the general and minimum requirements for tablets and capsules. It does not anticipate every quality attribute for every medicine. For example, the shelf-life for a tablet may be controlled by the level of degradation products (which is not controlled by the Order) rather than by the loss of content of the active ingredient (a parameter which is controlled by the Order). Another example would be a requirement for uniformity of weight or content for halves of tablets when subdivision of a tablet is required by the directions for use for a registered medicine. Medicines must also comply with Therapeutic Goods Order No. 77 *Microbiological standards for medicines* <http://www.tga.gov.au/legis/tgo/tgo77.htm>.

Export only tablets and capsules are subject to TGO 56 but not TGO 78. What standard applies to export only tablets and capsules during the transition period?

Export only medicines will continue to be subject to both Therapeutic Goods Order No. 70B *Standards for export only medicine* (TGO 70B) <http://www.tga.gov.au/docs/html/tgo/tgo70b.htm> and Therapeutic Goods Order No. 56 *General standard for tablets, pills and capsules* (TGO 56) <http://www.tga.gov.au/docs/html/tgo/tgo56.htm> until TGO56 is revoked on 1 November 2010. Following that date, TGO 70B only will apply.

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Manufacture of this tablet will occur in the UK. There is no individual BP monograph for this tablet. Is compliance with the BP general monograph for Tablets sufficient?

No. If there is no individual monograph in the BP, the tablet must comply with the requirements of section 10 for a listed medicine, or section 11 for a registered medicine.

Can we use our in-house assay method for the active ingredient, as our method is easier to perform than the BP method?

The method specified in the Order is only obligatory where a sponsor wishes to contest the test results obtained by an official analyst. The Order does not prevent the use of in-house methods for routine quality control purposes. For a registered medicine, the TGA will evaluate the in-house method before the medicine is approved.

The need to use USP Reference Standard tablets to confirm apparatus suitability adds expense to the dissolution testing for folic acid-containing tablets. Is this necessary?

See above.

Modern analytical techniques don't require the use of 20 tablets to determine the average content of an active ingredient. Can fewer tablets be used?

See above.

Why are there special requirements in this Order for tablets and capsules containing folic acid?

Folic acid taken by the prospective mother daily for one month before conception and during early pregnancy may reduce the risk of a baby having spina bifida/neural tube defects. In 2001 the Complementary Medicines Evaluation Committee (CMEC) recommended that there should be a legal requirement for tablets containing 100 micrograms or more of folic acid to comply with a dissolution standard. This recommendation was in response to a public health concern to ensure the effectiveness of folic acid supplements.

The requirement for tablets containing folic acid to comply with a dissolution specification was introduced in late 2003. This requirement is now included in TGO 78. The Order also extends the requirement to hard capsules that contain 100 micrograms or more of folic acid.

Is dissolution testing required for any listed tablet or capsule?

Compliance with a dissolution specification will be required for:

- A tablet or capsule that is the subject of an individual BP monograph that includes a dissolution test.
- A modified-release tablet or capsule.
- A tablet or hard capsule that contains 100 micrograms or more of folic acid.

All other listed tablets and capsules must comply with a disintegration requirement.

What is a 'component in an active ingredient that is quantified on the label', as stated in section 10(b)?

"A component in an active ingredient that is quantified on the label" could be hypericin for a tablet containing *Hypericum perforatum*, or iodine for a tablet containing *Fucus vesiculosus*, or eicosapentaenoic acid for a capsule containing natural fish oil. A component that is not quantified on the label, such as a mandatory component in Substances that may be used in Listed medicines in Australia, is not subject to the requirements of TGO 78. "Label" has the same meaning as in the Act.

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The limits in Schedule 1 for the contents of active ingredients or components in listed tablets and capsules are different to those included in TGO 56. Why?

The Order nominates a range of limits for the content of active ingredients or components in listed tablets and capsules, depending on the nature and stability of the active ingredient or component. The Order seeks to harmonise requirements with international standards where possible.

The limits for vitamins and minerals in Schedule 1 are largely consistent with the limits specified in the United States Pharmacopeia – National Formulary for dietary supplements. The experience of Australian manufacturers supports the use of the proposed limits for betacarotene, panthenol and pantothenate salts.

There are no general standards in the British Pharmacopoeia or United States Pharmacopeia – National Formulary for the content of probiotics and enzymes as active ingredients.

Do the limits in Schedule 1 include overages?

Yes. The limits stated in Schedule 1, and elsewhere in the Order, are designed to accommodate normal analytical and manufacturing variations and to allow for recognised deterioration of active ingredients. No further tolerances are applied to the limits given in the Order, including situations where manufacturing overages are employed.

Do the limits in Schedule 1 apply to registered complementary medicines?

No.

Why has the Uniformity of Dosage Units requirement been introduced for registered medicines, and which medicines have to comply with this requirement?

The test for Uniformity of Dosage Units has become an international standard. The harmonised test for Uniformity of Dosage Units has been official in the European Pharmacopoeia since July 2005, the British Pharmacopoeia (BP) since December 2005, the Japanese Pharmacopoeia since April 2006, and the United States Pharmacopeia since January 2007.

The general monographs for Tablets and Capsules in the BP allow for the Uniformity of Content and/or Uniformity of Weight tests to replace the requirements of the Uniformity of Dosage Units test where justified and authorised.

Tablets and capsules registered by the TGA prior to the revocation of TGO 56 will be considered to have justified the continuing use of Uniformity of Content and/or Uniformity of Weight tests. This takes effect by the application of TGO 78. This is consistent with the approach now in place in Europe.

However, sponsors should be aware that the European Pharmacopoeia has proposed that all tablets and capsules (including those already approved for supply) will be required to comply with the Uniformity of Dosage Units requirements after 2013. It may be prudent for sponsors to take this into account when reviewing product specifications.

Which registered tablets must comply with a dissolution specification?

If there is a dissolution test in the individual British Pharmacopoeia (BP) monograph, then the tablet must comply with that dissolution test.

If there is no dissolution test in the individual BP monograph, but there is a dissolution test in a United States Pharmacopeia (USP) monograph for a tablet or capsule containing that active ingredient, then the tablet must comply with a suitable dissolution test.

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If no individual BP monograph is applicable to the tablet, a tablet must comply with a suitable dissolution test if either the BP or the USP require a dissolution test for any tablet or capsule containing that active ingredient.

Our registered tablet was originally approved without a dissolution specification. Must it now comply with a dissolution requirement?

See above.

Sponsors have the transition period to acquire missing data or take other actions.

Which dissolution test is required for a registered tablet that is not the subject of an individual BP monograph?

In the absence of a specific method and assessment criteria in the BP, methods and assessment criteria that would be a 'suitable test' and acceptable to the Minister for Health and Ageing are those that have been validated to assure product quality. The TGA would need to be satisfied that the test method and limits selected are a suitable quality measure for the performance of the tablet *in vivo*. Compliance with the agreed test method and limits may be imposed as a Condition of Registration by the TGA.

The 'suitable test' would usually also include the three levels of testing common to the Interpretation requirements for dissolution testing in the BP and other pharmacopoeias.

My product does not meet the requirements of TGO 78. Can I request an exemption?

Subsection 6(2)(b) of the Order indicates that an exemption from the requirements of the Order can be granted by the Secretary in accordance with section 14 or 14A of the Act. Those sections of the Act relate to approvals for the supply, importation or export of a medicine that does not conform to an applicable standard, such as an Order or parts of an Order. Such approvals may be granted unconditionally or subject to conditions, and can relate to one batch or all batches of a medicine.

Where exemption from any aspect of TGO 78 is sought, the sponsor should apply in writing to the TGA, stating precisely the particular section or sections of the Order against which the exemption is sought and providing justification for the exemption. When an exemption is granted, information concerning the exemption is published in the *Commonwealth Government Notices Gazette*.

My product has an exemption from TGO 56. Is this still valid?

The letter of exemption and the *Gazette* notice would have specifically referred to TGO 56. Such an exemption cannot automatically transfer to TGO 78 and a new request for exemption will be needed. However, medicines that required an exemption from TGO 56 may not need an exemption from TGO 78.

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