



Australian Government

**Department of Health,
Disability and Ageing**

Complying with quality standards for tablets, capsules and pills

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TGA Health Safety
Regulation



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Introduction

This guidance is to help sponsors and manufacturers of medicines understand the role of the Therapeutic Goods Order No. 101 - *Standard for tablets, capsules and pills* (TGO 101, the Order) in ensuring that these types of therapeutic goods are of appropriate quality.

Transition period

The requirements that applied to tablets and capsules under Therapeutic Goods Order No. 78 *Standard for tablets and capsules* (TGO 78) have been adopted into TGO 101. This means that, generally, a transition period is not needed for these medicines. Sponsors can elect to move to alternative testing requirements, where this is permitted under the Order, at any time. Details on how to request this type of change are provided later in this document.

The TGO 101 requirements that apply to pills commence on 31 March 2021. Pills were not subject to TGO 78. The delayed commencement allows sponsors two years to update their manufacturing documentation and ensure that their goods will comply with the new requirements by the end of March 2021.

A two-year transition period has also been specified in relation to section 16 of the Order. This allows sponsors time to review the manufacturing documentation for their medicines and update them in line with the requirements for elemental impurities and residual solvents in tablets and capsules.

All tablets, capsules and pills subject to the Order and [released for supply](#) after 30 March 2021 must comply with TGO 101.



Note

TGA can take regulatory action as necessary against medicines found to be unsafe with respect to elemental and solvent impurities, regardless of the transition period.

How to use this guidance

This guidance is not provided as a legal interpretation of TGO 101. It includes clarification on, and information relating to, mandatory requirements. It also includes additional information to assist medicine sponsors in meeting their obligations and best practice recommendations.

The information in this guidance may also assist other stakeholders to understand how sponsors and manufacturers assure that medicines that are tablets, capsules or pills are of good quality.

When the words '**must**' or '**required**' are used, a legal requirement is being described.

**Note**

Compliance with TGO 101 is not necessarily sufficient to demonstrate quality, safety or efficacy for the purposes of registering or listing a medicine. Additional requirements may be applied, for example, as conditions of listing or conditions of registration.

In some instances, compliance with TGO 101 may not be sufficient to establish the safe use of medicines. Sponsors will need to further consider the intended patient population, size of the recommended daily dose, etc. to ensure that their medicines are safe for the purpose for which they are to be used.

Consideration must also be given to any other relevant standards.

Using the Order

Medicines that must comply with the Order

Discrete oral dosage forms

TGO 101 applies to three types of discrete oral dosage forms: tablets, capsules and pills. Assuring the quality of medicines manufactured in this way is important to ensure that they deliver their intended therapeutic effect and to provide a measure of continuing consistency in performance over time.

Various categories of tablets are recognised dosage forms in Australian approved terminology for therapeutic goods. These include coated and uncoated tablets, effervescent tablets and modified release tablets. Compressed lozenges, which are designed to dissolve or disintegrate in the mouth, are considered to be tablets.

Capsules can be hard or soft; the contents may be present as powders or liquids. Release of the active ingredients from capsules can also be modified in several ways, for example, enteric capsules.

Pills differ from tablets as they are manufactured using wet massing, piping and moulding. They can be coated, but usually contain only certain limited excipient ingredients and are typically manufactured and supplied as part of traditional medicine paradigms.

Release vs expiry specifications

Medicines must comply with TGO 101 throughout their shelf-lives. Sponsors may choose to apply release specifications that have tighter limits than the requirements of the Order. Such an approach can assist in compliance of a medicine at the end of its agreed shelf-life.

Medicines that are not subject to the Order

Other discrete dosage forms

Other discrete dosage forms for oral administration, such as soft lozenges and pastilles, are not required to comply with this Order. Medicines supplied in these dosage forms must comply with any relevant default standard, as recognised in the *Therapeutic Goods Act 1989* (the Act). These

default standards are relevant monographs in the European Pharmacopoeia (EP), the British Pharmacopoeia (BP) and the United States Pharmacopoeia – National Formulary (USP).

Goods not required to be on the ARTG

TGO 101 applies to medicines that are registered or listed on the Australian Register of Therapeutic Goods (ARTG). Some medicines can be supplied in Australia without being on the ARTG. These include medicines that are compounded for supply to particular patients by registered health professionals. Tablets, capsules and pills manufactured in this way do not have to comply with the requirements of the Order. These medicines must comply with the default standards identified in the Act.

Other exempt medicines

Therapeutic goods, which are tablets, capsules or pills, entered on the ARTG as ‘export only’ medicines do not have to comply with TGO 101.

Some active ingredients used in tablets, capsules or pills cannot be measured in a way that is meaningful for the limits specified in TGO 101. These include radiopharmaceuticals where the effectiveness of the medicine is not measured by the amount of active ingredient present. These types of medicines are exempt from the Order.

Exempt medicines are described in section 7 of TGO 101.

Structure of TGO 101

Part 1 of the Order outlines its scope and application, including commencement dates and definitions of key terms.

Part 2 of the Order contains the requirements for tablets and capsules. Divisions within this Part describe the differences between applying an applicable monograph’s requirements and the Australian specific requirements.

If an applicable monograph (there can be more than one) does exist, the sponsor can elect to comply with the applicable monograph in line with the requirements in Division 2 of Part 2. Alternatively, the sponsor can elect to comply with Division 3 – Australian specific requirements. In the absence of an applicable monograph, a medicine must comply with the requirements in Division 3.

Part 3 of the Order contains the requirements for pills, where ‘pill’ is defined in section 4 of Part 1.

Tablets, capsules and pills manufactured for supply in Australia may also be supplied in other countries. TGO 101 recognises:

- monographs in the BP, EP and USP as equivalent default standards and
- that not all medicines have applicable monographs in these pharmacopoeia.

The alternative sets of requirements included in the Order allow flexibility for sponsors to decide with which set of requirements their medicine must comply.

If a medicine that is a tablet or capsule is subject to an individual monograph in the EP, BP or USP, the medicine’s sponsor can choose to comply with any one of those, in conjunction with any specific requirements prescribed in the Order. Alternatively, the sponsor could choose to comply with the Australian specific requirements set out in TGO 101. Meeting any one of these sets of requirements demonstrates compliance with TGO 101.



Variations to BP/EP/USP monographs

In some instances, TGO 101 will require **additional** tests to those set out in the relevant individual BP/EP/USP monograph.

In other instances, TGO 101 will allow **fewer or different** tests from those set out in the relevant individual BP/EP/USP monograph.

‘Applicable monographs’

The BP, EP and USP each differentiate between general monographs (or chapters) and monographs for specific ingredients or finished goods. Each pharmacopoeia explains in the General Notices that individual or specific monographs must be read in conjunction with the general monographs or chapters. This relationship is recognised in the definition of ‘standard’ in section 3 of the Act. The definition also states that these monographs and chapters must be read and applied with consideration of the General Notices section of the relevant pharmacopoeia.

TGO 101 identifies relevant individual or specific monographs as ‘applicable monographs’. In accordance with the Act, this means that the applicable monographs include any relevant requirements in the general monographs or chapters of that pharmacopoeia. The exact nature of that relationship should be confirmed by reading the relevant General Notices.

Monographs for dietary supplements in the USP are considered to be applicable monographs for the purposes of TGO 101.

Medicines that do not have an applicable monograph in the EP, BP or USP must meet, at a minimum, the Australian specific requirements in TGO 101.

Dissolution testing

Compliance with dissolution requirements is mandatory for:

- A registered tablet or capsule citing compliance with an applicable monograph, where that monograph includes a dissolution requirement
- A registered tablet or capsule citing compliance with an applicable monograph where:
 - that monograph does NOT include a dissolution requirement, BUT
 - another relevant default standard DOES include a dissolution test for an active ingredient present in the medicine.

In this case, a suitable dissolution test for the tablet or capsule is required.

- Any modified-release tablet or capsule,
 - Delayed release dosage forms, such as gastro-resistant soft gel capsules, may use disintegration testing or equivalent to demonstrate appropriate release of active ingredients.
- Tablets and capsules registered or listed on the ARTG claiming modified-release properties.
- Any tablet or hard capsule that contains 100 micrograms or more of folic acid
- Each active ingredient in a registered medicine:
 - citing compliance with the Australian specific requirements and;

- where the active ingredient is subject to a test for dissolution as part of a specific or individual monograph in the BP, EP or USP for a tablet or capsule. The Order notes that a 'suitable' test is required in these circumstances. This allows, with appropriate justification, for some deviation from pharmacopoeial methodology if necessary.

Listed medicines are not required to demonstrate compliance with dissolution tests, with the exception of dosage units described as modified release or those containing folic acid.

The Order notes situations where a 'suitable' dissolution test may be appropriate. This allows, with appropriate justification, for some deviation from pharmacopoeial methodology and may, in some instances, require no dissolution test. Capsules containing liquids and modified release dosage forms such as gastro-resistant capsules would not typically require a test for dissolution.

Registered and listed medicines

Some requirements for medicines listed on the ARTG are different to those applied to registered medicines. These are set out in TGO 101.

The following table summarises the requirements and sections of the Order that apply to these different types of medicines.

	Registered tablet or capsule following a monograph		Registered tablet or capsule following Aust. requirements		Listed tablet or capsule following a monograph		Listed tablet or capsule following Aust. requirements		Pills	
Assay	As per applicable monograph	8(1)(a)	90-110% Vitamins, minerals, enzymes, probiotics comply with Schedule 2	8(1)(b) 14	As per applicable monograph	8(1)(a)	90-120% Vitamins, minerals, enzymes, probiotics comply with Schedule 2	8(1)(b) 15	90-120% Vitamins, minerals, enzymes, probiotics comply with Schedule 2	27
Microbiological assay of antibiotics *	As per applicable monograph	8(1)(a)	Yes, for antibiotics to estimate potency	14(3)	No		No		No	
Dissolution not required for chewable, effervescent or dispersible goods	As per applicable monograph, OR if any other relevant monograph for tab/capsule with the active ingredient(s) requires it	8(1)(a) 11	Yes, when any relevant monograph with the active ingredient(s) requires it, and for modified release goods.	17	As per applicable monograph	8(1)(a) 17(2)	Yes, for modified release goods.	17(2)	No	
Folic acid dissolution	Complies with USP<2040>, unless the good is chewable, dispersible or effervescent, or contains less than 100 micrograms of folic acid (sections 10, 15)									
Disintegration	As per applicable monograph	8(1)(a)	Yes, unless a dissolution test is performed	18(2)	As per applicable monograph	8(1)(a)	Yes, unless a dissolution test is performed	18	Yes	26
Dispersion	As per applicable monograph	8(1)(a)	Yes, for dispersible goods only	19	As per applicable monograph	8(1)(a)	Yes, for dispersible goods only	19	No	
Uniformity of dosage units	As per applicable monograph	8(1)(a)	Yes	20	As per applicable monograph, or uniformity of mass/weight	8(1)(a)	Yes, or uniformity of mass	20	Yes	25
Uniformity of weight/mass	As per applicable monograph	8(1)(a)	No		Yes, instead of uniformity of dosage units	12	Yes, unless a uniformity of dosage unit test is performed	20	Yes	25
Solvents	As per applicable monograph	8(1)(a)	Yes	16	As per applicable monograph	8(1)(a)	Yes	16	Yes (water)	24
Heavy metals	As per applicable monograph	8(1)(a)	Yes	16	As per applicable monograph	8(1)(a)	Yes	16	Yes	28

* Microbiological assay only applies to antibiotics whose efficacy is assessed by a potency assay. It does not relate to microbiological contamination or the requirements of Microbiological Standards for Medicines. See BP Appendix XIV A or Ph. Eur. Method 2.7.2

‘Minimum’ quality standards

TGO 101 sets out requirements which together comprise the ‘minimum quality standard’ for tablets, capsules and pills supplied in Australia. In some instances tighter limits or additional requirements may be necessary to ensure that certain medicines are safe and effective.

For example, tighter limits on assay results might be applied to active ingredients with a narrow therapeutic index; or additional tests may be included in product specifications to control synthetic impurities that pose a safety risk.

TGO 101 recognises that a medicine may have multiple applicable monographs. Even when these exist, a sponsor may choose to comply with the requirements of Division 3 – Australian specific requirements instead. If this decision is made, the sponsor should consider how the two sets of requirements align and note that the requirements in the Order take precedence over requirements in a default standard only when these are inconsistent.

Example

‘Azetipine tablets’ is a fictitious Schedule 2 medicine with an applicable monograph in the BP. This monograph includes testing and limits for two related substances.



The sponsor elects to comply with the requirements of Division 3, which does not include requirements for related substances. The general monograph for pharmaceutical preparations in the BP and EP does require consideration of purity, including related substances.

In this example, the sponsor may need to justify in their application to register the medicine why the related substance test isn’t needed to establish appropriate quality.

Sponsors of listed medicines must be aware of, and comply with, any other requirements that affect the eligibility of their medicine for listing on the ARTG.

Please refer to the relevant regulatory guidelines for further information on each medicine type.

Once approved, a medicine must comply with its marketing authorisation. A medicine supplied in contravention of its authorisation is supplied unlawfully, even if it complies with the requirements of TGO 101.

General monographs and general chapters in the default standards

Applying the requirements of an applicable monograph draws in requirements from both the specific monograph and the general monograph (or their equivalents) in the relevant pharmacopoeia.

Similarly, consideration of the general monographs of the BP or EP or the general chapters of the USP is necessary when applying the Australian specific requirements.

The requirements of the default standards apply **except** where the Order includes a conflicting requirement. Where the requirements are inconsistent, the Order takes precedence.

Impurities

Medicines that adopt the requirements of an applicable monograph, must comply with any impurity requirements set out in the relevant pharmacopoeia. These include related substances, degradants, solvents and elemental impurities. Impurity limits are usually found within the general monographs of the pharmacopoeias.

Limits for residual solvents and heavy metals are identified in the Australian specific requirements. While these may replicate the requirements in general monographs or general chapters, they have been included in the Order for clarity and consistency.

The need for testing

In many cases, existing controls on impurities in the ingredients included in the medicine and compliance with GMP requirements may be sufficient to establish compliance of the finished good with the Order. Sponsors and manufacturers may be able to justify the absence of an impurity test in finished goods specifications or the use of reduced or rotational testing.

Residual solvents

The requirements for residual solvents are identified in the Order as being those provided in Ph. Eur 5.4. This section of the EP incorporates the ICH Q3C guideline. The reference is made in this way to ensure consistency with the requirements provided in the default standards.

Elemental impurities

Where an applicable monograph is not followed, the Order specifies limits on the heavy metals lead, cadmium, arsenic and mercury. Other elemental impurities should also be considered as appropriate.

For lead, arsenic, cadmium and mercury, compliance to either USP<2232> or ICH Q3D is acceptable. Both documents provide guidance on methods for establishing maximum values for elemental impurities based on the permitted daily exposure (PDE) of each element.

How is compliance determined?

Not all of the specified tests set out in the Order must be performed on all medicines, or on all batches of a medicine.

A manufacturer does not have to perform all tests in the selected applicable monograph, or in the Australian specific requirements, before the release of every batch. The basis of the design of the medicine, together with its control strategy and validation or stability data can demonstrate that the standard will be met.

For example:

- Manufacturing documentation can show that no organic solvents are used in any step of manufacture of the medicine. In this case, routine testing for residual solvents is not expected.
- Dissolution testing may be done on a rotational basis, if it can be demonstrated through data derived from manufacturing validation studies that the medicine adheres to the dissolution requirements of the Order.

However, if a released batch of the medicine was found to contain unacceptable levels of solvent residues, or failed the relevant dissolution test, it would not comply with the Order and regulatory action could be taken.

Updating agreed testing specifications

Sponsors can update the testing specifications and limits that apply to their medicines within the confines of TGO 101.

TGO 101 recognises that where a medicine meets the definition of an individual monograph in more than one pharmacopoeia (i.e. in the EP, BP or USP), compliance with one standard is sufficient. Similarly, the Australian specific requirements in TGO 101 are considered equivalent to an applicable monograph. Therefore, a sponsor can request that an approved medicine be varied to adopt alternative, equivalent sets of requirements within TGO 101.

These requests are considered minor variations to registered medicines and must be approved by the TGA before implementation. The same change can be made to listed medicines without approval by the TGA but must be made in line with the requirements for the Code of Good Manufacturing Practice (PIC/S Code).



Applicable monographs must be followed in full.

Sponsors cannot select tests from different monographs to create a unique testing protocol. The applicable monograph, as required by TGO 101, must be adopted in its entirety.

Best practice recommendations

Size of discrete dosage forms

The tests specified in TGO 101, and in the various pharmacopoeia referenced by the Order, are designed to ensure that medicines are of appropriate quality and are therefore safe to use and can deliver the intended therapeutic benefit.

The size and shape of tablets, capsules and pills are not regulated by any requirements within TGO 101. However, these attributes can significantly affect the safety profile of the medicine if they present a choking hazard. Swallowing difficulties can also contribute to non-compliance with treatment regimens.

The United States Food and Drug Administration (US FDA) document [Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules - Guidance for Industry](#) includes recommendations about the size of tablets and capsules. This document recommends that largest dimension of a tablet or capsule should not exceed 22mm and that capsules should not exceed a standard 00 size. Sponsors should consider the size, shape, use of coating materials and the intended patient population to minimise the risk of the dosage units presenting a choking hazard.

Sponsors should be particularly mindful of choosing solid dosage forms, particularly soft gel capsules, for medicines intended for children under five years of age. These dosage forms may present a choking hazard as this population may not have a full set of teeth, be able to adequately chew, or be able to swallow, a whole dosage unit.

Uniformity of dosage units

Listed medicines are not required to comply with requirements for uniformity of dosage units.

Section 12 in Part 2 allows listed medicines to substitute a uniformity of dosage unit requirement in an applicable monograph with a test for uniformity of weight (mass).

Similarly, section 20 in Part 2 states that the requirement of uniformity for listed medicines is item 4 in the table in Schedule 1, i.e. uniformity of weight (mass). This requirement doesn't preclude a sponsor choosing to test for uniformity of dosage units for a listed medicine. Compliance with such a test would be considered as demonstrating compliance with uniformity of weight (mass).

Testing methods for pills

The following testing procedures are provided to assist sponsors in confirming compliance of pills with the Order. Alternative methods can be used but in the case of dispute, the TGA would rely on results generated using the stated methodology.



Disintegration tests

Methodology to be used for disintegration testing is included as a requirement in the Order.

Determination of water

Should be carried using an appropriate method such as oven drying, toluene distillation, drying under reduced pressure or gas chromatography.

Uniformity of weight

Dripping pills and sugar pills

Procedure – weigh accurately 20 pills and calculate the average weight, then weigh each of them accurately. Compare the weight of each pill with the labelled or average weight. Not more than two (2) pills should deviate from the limit of weight variation, and none should deviate from twice the limit.

Other pills

Procedure – Take 10 pills as one part or, for pills weighing 1.5g or more, each pill is a part.

Weigh separately 10 parts and compare with the labelled weight of each part (labelled weight of each pill X the number of pills weighed). If there is no labelled weight, compare the weight of each pill with the average weight calculated. Not more than two (2) parts should deviate from twice the limit.

Filling variation

Procedure – Take ten packs (or vials) of pills, weigh separately the content of each pack (or vial) and compare with labelled weight.

Errata

Item 4 in the table in Schedule 1 to the Order refers to the United States Pharmacopeia - National Formulary chapter <711>. This is incorrect. The correct reference is chapter <2091>.

Version history

Version	Description of change	Author	Effective date
V0.1	Draft document for consultation	TGA	December 2018
V1.0	Original publication	TGA	1 April 2019
V1.1	Clarification to requirements in the section 'Dissolution Testing' and reformatting of the 'Minimum Quality Standards' section.	TGA	February 2020

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