Australian Government
Department of Health
Therapeutic Goods Administration

Guidance for TGO 101

Standard for tablets, capsules and pills

Version 1.0, December 2018

TGA Health Safety Regulation

Contents

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 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 1 April 2020. Pills were not subject to TGO 78. The delayed commencement allows sponsors time to update their manufacturing documentation and ensure that their goods will comply with the new requirements by the end of March 2020.

All medicines that are tablets, capsules or pills, that are subject to the Order and are released for supply after 31 March 2020, must comply with TGO 101.

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.

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; for example, coated tablets, uncoated tablets, effervescent tablets, modified release tablets, etc. 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 and capsules as they are manufactured using wet massing, piping and moulding techniques, not compression. 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

TGO 101 applies throughout the shelf-life of the medicine. 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 the default standards 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 Pharmacopeia – National Formulary (USP).

Goods not required to be on the ARTG

TGO 101 only 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.

Exempt medicines

Therapeutic goods which are tablets, capsules or pills but are 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

TGO 101 recognises that tablets, capsules and pills supplied in Australia may also be supplied in other countries. The Order allows for better alignment in meeting quality requirements in multiple jurisdictions, by increased harmonisation with quality standards recognised by comparable overseas regulators, where this is appropriate. 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, capsule or pill 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 follow 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 that 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.

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 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 the Australian specific requirements in TGO 101.

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

Requirements for pills are different to those for tablets and capsules. These are described in Part 3 of TGO 101.

The following table summarises the requirements for 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 monograph	8(1)(a)	90-110% Vitamins, minerals, enzymes, probiotics comply with Schedule 2	8(1)(b) 15	As per 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	28
Microbiological assay	As per monograph	8(1)(a)	Yes, for antibiotics	15(3)	No		No		No	
Dissolution **not required for chewable, effervescent or dispersible goods**	As per monograph, or if any other monograph with the active ingredient(s) requires it	8(1)(a) 12	Yes, when any monograph with the active ingredient(s) requires it. Must be performed for modified release goods.	18	As per monograph, but must be performed for modified release goods	8(1)(a) 18(2)	No, but must be performed for modified release goods.	18(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 (section 10, 16)									
Disintegration	As per monograph	8(1)(a)	Yes, unless a dissolution test is performed	19	As per monograph	8(1)(a)	Yes, unless a dissolution test is performed	19	Yes	27
Dispersion	As per monograph	8(1)(a)	Yes, for dispersible goods only	20	As per monograph	8(1)(a)	Yes, for dispersible goods only	20	No	
Uniformity of dosage units	As per monograph	8(1)(a)	Yes	21	As per monograph, or uniformity of mass/weight	8(1)(a)	Yes, or uniformity of mass	21	Yes	26
Uniformity of weight/mass	As per monograph	8(1)(a)	No		Yes, instead of uniformity of dosage units	8(2)	Yes, instead of uniformity of content	21	Yes	26
Solvents	As per monograph	8(1)(a)	Yes	Sched 1	As per monograph	8(1)(a)	Yes	17	Yes	25
Heavy metals	As per monograph	8(1)(a) 11	Yes, from applicable monograph if one exists. Otherwise schedule 1	17	As per monograph	8(1)(a) 11	Yes, from applicable monograph if one exists. Otherwise schedule 1	17	Yes	29

‘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 may be necessary to ensure that certain medicines are safe and effective.

Appropriate limits will be determined during the premarket evaluation process and agreed before the medicine is approved for registration on the ARTG.

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.

Once approved, a medicine must comply with its marketing authorisation.

Impurity limits

Medicines that adopt the requirements of an applicable monograph, as required by TGO 101, must comply with the impurity tests set out in that pharmacopoeia. Impurity limits are usually found within the general monographs of the pharmacopoeias.

For consistency, limits for residual solvents and heavy metals are similarly applied as part of the Australian specific requirements.

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.

Elemental impurities

In some instances, in recognition of particular risks associated with certain medicines, specific limits for impurities are included within an individual monograph in the BP/EP/USP. These will apply in place of the usual limits in the general monograph.

To ensure consistency, any specific limits on elemental impurities that are found in *any* applicable monograph are automatically adopted in the Order, no matter which requirements the sponsor chooses to follow.

For example:

- A sponsor making a fish oil capsule chooses to follow the Australian specific requirements within TGO 101 rather than an applicable monograph.
- There is an applicable monograph in the USP, i.e. for ‘Fish Oil Containing Omega-3 Acids Capsules’ that includes specific limits for contaminants.
- The sponsor must comply with those specific limits, instead of the Australian specific requirements for impurities stated in TGO 101.

Limits for arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb)

The elements arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb) are human toxicants that have limited or no use in the manufacture of medicines. Because of their unique nature, these four elements should be evaluated during the medicine development phase. A risk assessment should be performed that considers all potential sources of elemental impurities, particularly in

the context of the routes of administration for the medicine. The outcome of the risk assessment will determine if additional controls are required, which may in some cases include testing for these elements. It is not expected that all finished goods will require testing for these elemental impurities; testing only needs to be applied to the finished goods when the risk assessment identifies it as the appropriate control to ensure that the limits will be met.

How is compliance determined?

Not all of the specified tests 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.

In some instances, a sponsor can establish through a risk based assessment that a particular test doesn't have to be performed to demonstrate compliance with a requirement. 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 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.

Conversely, compliance with the standard doesn't mean that the TGA cannot determine that additional testing, or tighter limits on nominated tests, is required.

Updating agreed testing specifications

Sponsors can decide to 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 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.

Dissolution testing

Compliance with dissolution requirements is required for

- A registered tablet or capsule that is citing compliance with an applicable monograph where that monograph includes a dissolution requirement
- Any modified-release tablet or capsule
- Any tablet or hard capsule that contains 100 micrograms or more of folic acid
- Any registered medicine where the medicine contains an active ingredient which requires a test for dissolution as part of a specific or individual monograph in the BP, EP or USP for a tablet or capsule that contains that active ingredient.

Sponsors of listed medicines are not required to demonstrate compliance with dissolution tests, with the exception modified release dosage units or those containing folic acid (as above). However, they should consider using dissolution testing to confirm the appropriate release of active ingredients, or components, where a relevant test is provided in a specific or individual monograph of the BP, EP or USP.

Pills - testing methods

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.

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

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 2 pills should deviate from the limit of weight variation, and none should deviate from twice the limit.

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 2 pills should deviate from the limit of weight variation, and none should deviate from twice of 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 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.

Disintegration

Take 6 pills, select a basket with pore size as given in the table below.

Pill diameter	Pore diameter of sieve
less than 2.5 mm	0.42 mm
2.5 - 3.5 mm	1.0 mm
more than 3.5 mm	2.0 mm

Carry out the test as described under the Determination of Disintegration (0921) using a disk. Small honeyed pills, water-honeyed pills and watered pills should be completely disintegrated within 1 hour, while concentrated pills and pasted pills within 2 hours.

If the pills adhere to the disk and hinder the determination, repeat the test on another 6 pills without a disk.

No disk is needed for dripping pills. Dripping pills should be completely disintegrated within 30 minutes, while the coated dripping pills within 1 hour.

All the pills should pass through the sieve within the specified time. If the only residue present comprises softened masses which do not have a hard core, the pills are considered to comply with the requirements.

Version history

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