Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Proposed quality standards for MDMA and psilocybin

Consultation outcomes paper

Version 1.0, July 2024

Contents

Purpose

This paper summarises the submissions and outcomes from the public consultation on the proposed quality standards for 3,4-methylenedioxy-N-methylamphetamine hydrochloride (MDMA) and psilocybin.

All submissions that gave permission to be published on our website are available through the 'View submitted responses' on our consultation hub.

Background

Effective from 1 July 2023, the Therapeutic Goods Administration (TGA) created entries for MDMA and psilocybin under Schedule 8 (Controlled drugs) to the Poisons Standard. This change permits the prescribing of MDMA for the treatment of post-traumatic stress disorder (PTSD) and psilocybin for treatment-resistant depression (TRD) by psychiatrists who are specifically authorised under the Authorised Prescriber (AP) scheme. Unapproved therapeutic goods accessed through these pathways have not been evaluated by us for safety, quality and efficacy.

Provisions in the *Therapeutic Goods Act 1989* (the Act) allow creation of ministerial standards known as Therapeutic Goods Orders (TGOs) to set out requirements that must be met to ensure medicines are of appropriate quality. Unless specific consent has been given under the Act, it is unlawful to supply medicines that do not comply with a relevant standard.

The introduction of Australian quality standards for MDMA and psilocybin is intended to ensure consistency of products supplied to Australian patients. Consistent quality is essential to support the known safety and efficacy of any medicine.

We developed a draft TGO for each substance with input from companies manufacturing MDMA and psilocybin for clinical trials. The proposed requirements were based on the current methodologies and testing limits used by these manufacturers, for both the active pharmaceutical ingredients (API) and finished products (in these cases, capsules). In this way, goods supplied under the AP scheme and compliant with the new standards should have safety profiles established in existing clinical trials. We then undertook a public consultation to allow manufacturers, peak health organisations, medical practitioners, pharmacists, patients and other interested stakeholders the opportunity to comment on the appropriateness of these requirements.

Public Consultation

The public consultation on the technical requirements in the draft TGOs for MDMA and psilocybin was conducted between 8 December 2023 and 31 January 2024. A total of 25 submissions were received from sponsors, manufacturers, pharmacists, health care practitioners, industry associations, patients and members of the public. The consultation asked eight questions and provided an opportunity for respondents to raise any other issues or submit additional comments in relation to the draft TGOs.

The consultation confirmed there was broad in-principle support for the draft TGOs but a number of suggestions for minor technical changes were received. Respondents recommended:

- Changes to the assay limits for active pharmaceutical ingredients (API) and finished product for both MDMA and psilocybin.
- Changes to the testing limits for impurities, heavy metals, and residual solvents.
- Employing United States Pharmacopeia (USP) or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines as an alternative to European Pharmacopoeia methods and limits.
- Including additional testing, such as loss on ignition, microbial enumeration, appearance and content uniformity.

Requests were also made to include a transition period after the new standards are registered on the Federal Register of Legislation, to provide sufficient time to develop and validate methods for testing the APIs and finished products.

There was strong support for the requirement for unlicensed compounding pharmacists to use a MDMA and psilocybin API that has been tested at an Australian GMP-licensed laboratory before use.

We have considered all the submissions, and in response, some minor amendments have been made to the draft TGOs. A summary of the responses, the rationale for our decisions and the resultant changes are outlined below.

Respondents

Public consultation on the draft TGOs allowed interested stakeholders the opportunity to comment on the proposed quality requirements.

Table 1 below summarises the number of submissions received from interested stakeholders. The largest proportion of submissions was from Australian and overseas manufacturers.

Table 1: Interested stakeholder groups.

Stakeholder group	Total	Percentage
Australian Manufacturer	4	16%
Australian testing laboratory	2	8%
Government organisation or academia	2	8%
Industry association or consultant	2	8%
Member of the public	3	12%
Other healthcare practitioner	2	8%
Overseas Manufacturer	3	12%
Patient/patient advocate	2	8%
Pharmacist or pharmacy	3	12%
Psychiatrist	0	0%
Sponsor	2	8%

Table 2 below details the locations of respondents.

Table 2: Location of respondents

Location	Total	Percentage
ACT	1	4%
NSW	8	32%
NT	1	4%
QLD	1	4%
SA	0	0%
TAS	0	0%
VIC	4	16%
WA	4	16%
Overseas	6	24%

Consultation questions on MDMA

Do you agree with the tests included in the draft standard for MDMA? If not, what changes do you propose and why?

There were 16 respondents that answered the question:

- 10 answered 'Yes" they agreed with the tests included.
- 6 answered 'No' they did not agree with the tests included.

The 6 respondents that answered 'no' proposed to specify a particular chromatographic technique, include additional testing (such as tests for nitrosamines, loss on ignition, microbial enumeration, description and appearance, content uniformity and dissolution), use of alternative test methods (such as European Pharmacopoeia (Ph Eur) 2.4.20 for heavy metals) or proposed to remove certain tests, such as tests for related substances and acetic acid.

Outcome

After considering all the submissions the following amendments will be made to the test methods for MDMA:

- The specified test method for concentrations and related substances in Schedule 1 and Schedule 2 has been updated to specify the test method must be liquid chromatography as specified in Ph Eur 2.2.29.
- The specified test method for heavy metals in Schedule 1 has been updated to Ph Eur 2.4.20.
- The specific tests for acetic acid and impurities in Schedule 1 have been removed. Testing for these substances may be covered by testing for residual solvents.
- Schedule 2 will include a test for disintegration as specified in either Ph Eur 2.9.1 or USP Chapter 701.
- Schedule 2 will include a test for uniformity of dosage units as specified in Ph Eur 2.9.40.

We determined that testing for nitrosamines, loss on ignition, description and appearance and dissolution are not required for MDMA hydrochloride and/or MDMA hydrochloride products. Manufacturers can choose to include additional tests in their own testing program at their discretion.

Microbial enumeration testing requirements are already set out in *Therapeutic Goods (Microbiological Standards for Medicines) (TGO 100) Order 2018* and should not be duplicated in other TGOs. A reminder that MDMA products may have to comply with standards other than the new TGO will be included in guidance materials.

Do you agree with the limits applied in the draft standard for MDMA? If not, what changes do you propose and why?

There were 17 respondents that answered the question:

- 9 answered 'Yes" they agreed with the limits included.
- 8 answered 'No' they did not agree with the limits included.

The 8 respondents that answered 'no' proposed either to tighten or relax the proposed limits for chloride, impurities, and average content of MDMA hydrochloride in a finished product. There was also a request for further clarification on the limits for related substances in Schedule 2.

Outcome

After considering all the submissions the following amendments will be made to the limits:

- The limits for related substances in Schedule 1 and Schedule 2 have been updated to comply with the limits specified in Ph Eur 5.10.

- The limits for residual solvents in Schedule 1 and Schedule 2 have been updated to comply with the limits specified in Ph Eur 5.4.
- The limits for heavy metals in Schedule 1 have been removed and replaced with the limits specified in the ICH Q3D guideline document.
- The limits for average content of MDMA hydrochloride in Schedule 2 have been updated from not less than 95 per cent and not more than 105 per cent to not less than 90 per cent and not more than 110 per cent.

The specified limits for chloride in Schedule 1 will not be changed, as altering this limit may affect the dissolution rate.

Do you agree with the requirement for unlicensed compounding pharmacists to use an API that has been tested in an Australian GMP-licensed laboratory? If not, what changes do you propose and why??

There were 17 respondents that answered the question:

- 15 answered 'Yes" they agreed with the requirement.
- 2 answered 'No' they did not agree with the requirement.

There was strong support from the pharmacists and manufacturers to include this requirement "*is utmost public safety requirement that the API is of appropriated quality when it is being utilised for compounding*". Of the two respondents who did not agree, one required additional clarity regarding Australian licensing requirements. The second, a pharmacist, proposed that APIs manufactured overseas under GMP should be exempt from testing in an Australian GMP-licensed laboratory, as this poses additional restrictions for accessing MDMA for Australian patients, particularly those in clinical trials.

Outcome

The requirement for the API to be tested in an Australian GMP-licensed laboratory before its use in extemporaneous compounding will not be changed, as it intended to ensure consistency of products supplied to Australian patients. Consistent quality is essential to support the known safety and efficacy of any medicine.

The TGO will not apply to goods supplied and imported for use under the clinical trial notification (CTN) and clinical trial approval (CTA) schemes.

Do you agree with implementation of the new TGO to commence with its registration on the Federal Register of Legislation in March 2024. If not, what changes do you propose and why?

There were 18 respondents that answered the question:

- 14 answered 'Yes' they agree with the implementation.
- 4 answered 'No' they do not agree with the implementation.

The four respondents who did not agree with implementation commencing with the registration of the TGO proposed including a transition period to allow manufacturers and testing laboratories sufficient time to develop and validate methods for testing the API and finished product.

Outcome

When the TGO is registered on the Federal Register of Legislation, it will have a commencement date of 6 January 2025 to allow industry time to develop and validate methods for testing the APIs and finished products.

Consultation questions on Psilocybin

Do you agree with the tests included in the draft standard for psilocybin? If not, what changes do you propose and why?

There were 21 respondents that answered the question:

- 14 answered 'Yes' they agree with the tests.
- 7 answered 'No' they do not agree with the tests.

The 7 respondents who did not agree with the tests proposed to specify particular chromatographic techniques, include additional testing (such as tests for pesticides, loss on ignition, microbial enumeration, description and appearance, and dissolution) or proposed to remove certain tests (such as tests for identification of the psilocybin mushroom by microscopic examination and chromatographic procedures and the specified tests for the concentration of psilocin) and proposed alternative test methods, such as Ph Eur 2.4.20 for heavy metals for synthetic psilocybin.

Outcome

After considering all the submissions the following amendments will be made to the limits:

- The specified test method for specified contents, concentrations, related substances and impurities in Schedule 1, Schedule 2, Schedule 3 and Schedule 4 have been updated to specify the test method must be liquid chromatography as specified in Ph Eur 2.2.29.
- The specified tests for the concentration of psilocin in Schedule 1 Part 2 (psilocybin isolate) and Schedule 3 (synthetic psilocybin) have been removed. Psilocin has been categorised as an impurity for synthetic drug substance and will be covered by the specified tests for impurities.
- The specified test method for heavy metals in Schedule 3 has been updated to Ph Eur 2.4.20.
- The test for uniformity of weight (mass) in Schedule 2 (Part 1 and Part 2) and Schedule has been replaced with test for uniformity of dosage units as specified in Ph Eur 2.9.40.

We determined that testing for pesticides, loss on ignition, description and appearance and dissolution are not required for plant derived psilocybin, plant derived psilocybin products, synthetic psilocybin or synthetic psilocybin products. Manufacturers can choose to include additional tests in their own testing program at their discretion.

Identification of the psilocybin mushroom by microscopic examination and chromatographic procedures aligns with other Australian quality standards for similar therapeutic goods and will remain.

Microbial enumeration testing requirements are already set out in *Therapeutic Goods (Microbiological Standards for Medicines) (TGO 100) Order 2018* and should not be duplicated in other TGOs. A reminder that psilocybin products may have to comply with standards other than the new TGO will be included in guidance materials.

Do you agree with the limits applied in the draft standard for psilocybin? If not, what changes do you propose and why?

There were 21 respondents that answered the question:

- 14 answered 'Yes' they agree with the implementation.
- 7 answered 'No' they do not agree with the implementation.

The 7 respondents that answered 'no' proposed to specify limits for heavy metals and include limits for arsenic in plant derived psilocybin, tighten the proposed limits for impurities for synthetic

psilocybin and remove limits for specific solvents in synthetic psilocybin and synthetic psilocybin products.

Outcome

After considering all the submissions the following amendments will be made to the limits:

- The limits for heavy metals in Schedule 1 (Part 1 and Part 2) and Schedule 3 have been removed and replaced with the limits specified in the ICH Q3D guideline document.
- The limits for related substances in Schedule 2 (Part 1 and Part 2) and Schedule 4 have been updated to comply with the limits specified in Ph Eur 5.10.
- The limits for impurities in Schedule 3 have been tightened from not more than 8.0 per cent total impurities to not more than 2.0 per cent total impurities.
- The limits for specific residual solvents in Schedule 3 and Schedule 4 have been removed and replaced with the limits as specified in Ph Eur 5.4.
- The limits for disintegration in Schedule 2 (Part 1 and Part 2) and Schedule 4 have been changed from 'not more than the limits specified in Ph Eur 2.9.1 or USP Chapter 701' to 'complete disintegration of the capsule is to occur in period of not more than 30 minutes'.
- The requirements specified in column 4 of Schedule 2 (Part 1 and Part 2) and Schedule 4 have been removed and replaced with 'not more than 30 minutes.'

Do you agree with the requirement for unlicensed compounding pharmacists to use an API that has been tested in an Australian GMP-licensed laboratory? If not, what changes do you propose and why?

There were 20 respondents that answered the question:

- 17 answered 'Yes" they agreed with the requirement.
- 3 answered 'No' they did not agree with the requirement.

There was strong support from the pharmacists and manufacturers to include this requirement "*is utmost public safety requirement that the API is of appropriated quality when it is being utilised for compounding*". The 3 respondents who did not agree required clarification on countries psilocybin may be manufactured in, as well as GMP and Australian licensing requirements. One of the respondents, a pharmacist, proposed that APIs manufactured overseas under GMP should be exempt from testing in an Australian GMP-licensed laboratory, as this poses additional restrictions for accessing psilocybin for Australian patients, particularly those in clinical trials.

Outcome

The requirement for the API to be tested in an Australian GMP-licensed laboratory before its use in extemporaneous compounding will not be changed as it is intended to ensure consistency of products supplied to Australian patients. Consistent quality is essential to support the known safety and efficacy of any medicine.

The TGO will not apply to goods supplied and imported for use under the clinical trial notification (CTN) and clinical trial approval (CTA) schemes.

Do you agree with implementation of the new TGO to commence with its registration on the Federal Register of Legislation in March 2024. If not, what changes do you propose and why?

There were 22 respondents that answered the question:

- 17 answered 'Yes' they agree with the implementation.
- 5 answered 'No' they do not agree with the implementation.

The five respondents who did not agree with implementation commencing with the registration of the TGO proposed including a transition period to allow manufacturers and testing laboratories sufficient time to develop and validate methods for testing the API and finished product.

Outcome

When the TGO is registered on the Federal Register of Legislation, it will have a commencement date of 6 January 2025 to allow industry time to develop and validate methods for testing the APIs and finished products.

Other issues raised

Some respondents made comments on additional issues that were not covered in the consultation questions. The table below summarises the comments and the outcome.

Table 3: Additional comments raised.

Comment	Outcome
The spelling of psilocybin is not consistent with the Poison Standards or the International Non-Proprietary Name (INN).	The spelling in the TGO will be changed to 'psilocybine'.
The standards do not exclude clinical trial materials.	The TGOs for MDMA and psilocybin will not apply to: a) Goods supplied and imported for use under the clinical trial notification (CTN) and clinical trial approval (CTA) schemes. b) goods imported by certain groups of people subject to conditions. The groups of people include those: i. mentioned in item 1 of Schedule 5 to the Regulations; or ii. mentioned in items 4, 8, 10, 11 or 12 of Schedule 5A to the Regulations, subject to compliance with the conditions specified in those items.
Clarification was sought on 'stated content' for assay limits for active pharmaceutical ingredients (API) for both MDMA and psilocybin.	The wording in the TGOs will be changed from 'stated content' to 'purity' for the API. For example: • *the purity of MDMA hydrochloride must be not less than 98.0 per cent and not more than 102.0 per cent MDMA hydrochloride, calculated on an anhydrous basis* • *the purity of psilocin present in psilocybin extract must not be less than 80.0 per cent and not more than 120.0 of psilocin, calculated on a dried basis*.
Propose to include the following mushroom species: • *Psilocybe tampanensis,* • *Psilocybe Mexicana*, and • *Psilocybe galindoi*	The TGO will not be changed. The standard for psilocybin will initially restrict the medicine to a single species of mushroom – *Psilocybe cubensis.* From our preliminary consultations we identified this was the only species used in Australian clinical trials.
Propose to include psilocybin produced via bio-synthetic means.	The TGO will not be changed. The current definitions in the TGO cover plant derived and synthetic psilocybin API and finished product. A psilocybin produced by bio-synthetic production would be covered under 'synthetic psilocybin'.

Comment	Outcome
Additional clarification was sought on the definition of 'nominated tryptamines' and when these should be listed. Additionally, it was proposed to remove the specified test for nominated tryptamines and cover it under the test for impurities.	Guidance material will be developed to provide clarity on the definition and when to list nominated tryptamines. The specific test for nominated tryptamines will not be changed.
The standards should employ USP or ICH guidelines as an alternative to European pharmacopoeial methods and limits.	The requirements for heavy metal limits have adopted ICH Q3D guidelines. Guidance material will specify that manufacturers do not need to use the methods specified in the standards. They may use: • equivalent methods in established pharmacopoeia, including the United States Pharmacopeia-National Formulary • suitably validated in-house or literature (non-pharmacopoeial) tests that are suitable for the intended purpose. However, in the event of a dispute, the methods of analysis specified in the TGO are the official methods and limits that will be used when a sample is tested by us.

Next steps

We will finalise the TGOs for MDMA and psilocybin and register them on the Federal Register of Legislation in mid-2024 with a commencement date of 6 January 2025.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Manufacturing Quality Branch | Medical Devices and Product Quality Division | Health Products Regulation Group	July 2024

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