Australian Government
Department of Health
Therapeutic Goods Administration

Requirements for OTC new medicine N2 applications (using OTC medicine monographs)

Australian regulatory guideline for over-the-counter medicines

Version 1.1, July 2021

TGA Health Safety Regulation

Contents

Introduction

This document outlines the requirements for market authorisation of OTC medicines applied for via the New Medicine N2 application route.

This document should be read in conjunction with the OTC Medicine Monograph that is specific to the proposed medicine.

Applications for medicines that comply with the requirements of a product-specific OTC medicine monograph and with the requirements specified in this document can be submitted as OTC New Medicine N2 applications, with reduced requirements for data assessment.

In lieu of providing full supporting data, sponsors of OTC New Medicine N2 applications will need to provide a list of assurances confirming that the medicine meets the specified requirements.

Sponsors are required to hold a complete data set for their product, in accordance with requirements outlined in the *Australian Regulatory Guidelines for OTC Medicines (ARGOM)*. This is to be made available to the TGA in the required application format within 30 calendar days of a request.

This document and the specific OTC medicine monographs are not intended to describe all regulatory requirements. Medicines applied for under OTC New Medicine N2 application must also comply with all relevant legislation and guidelines, including:

- The *Therapeutic Goods Act 1989* (the Act)
- *Therapeutic Goods Regulations 1990*
- Therapeutic Goods Orders
- Required Advisory Statements for Medicine Labels (RASML)
- The Poisons Standard
- Therapeutic Goods Advertising Code
- Australian Regulatory Guidelines for OTC medicines (ARGOM)
- *Competition and Consumer Act 2010*
- any other state and territory and Commonwealth legislation as relevant.

Monographs apply only to medicines containing the specific ingredient Australian Approved Name (AAN) mentioned in the monograph. All salts and derivatives not specifically mentioned in the monograph are excluded.

If the proposed medicine is not in accordance with all requirements as specified in this document and in the relevant OTC medicine monograph (e.g. the indications, dosage instructions, dosage forms or strengths go beyond, or are different to, those listed as acceptable in the relevant monograph), the application will not be considered as an N2 application and must be submitted as a higher level application.

Labelling

1. Full scale, full colour draft labelling for each proposed pack size must be provided electronically with the application, for assessment of the product's presentation.
2. Medicine labelling must comply with the following:
   - Labelling requirements as specified in the applicable OTC Medicine Monograph (e.g. directions, warnings).
   - Therapeutic Goods Order No. 69
   - Required Advisory Statements for Medicine Labels (RASML)
   - Australian Regulatory Guidelines for OTC medicines (ARGOM)
   - Therapeutic Goods Advertising Code
   - Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)
   - *Competition and Consumer Act 2010*
3. Label indications/claims must be entirely consistent with those permitted in the relevant OTC medicine monograph.
4. A medicine label may include a statement that the medicine does not contain an excipient known to cause adverse effects in some individuals (e.g. gluten free, sugar free, alcohol free, lactose free) provided the statement is correct and in accordance with *ARGOM Appendix 3: Guidelines on presentation aspects of OTC applications, 3.1.1 Absence of excipient*.
5. Internet addresses may be included on labelling provided an assurance is given (included in the document Assurances to accompany an OTC new medicine N2 application) that the information about the medicine included on the website (including any direct links from that website) will be consistent with the information approved by the TGA for the medicine.

Active substances

1. All active substances must be controlled by the finished product manufacturer to the requirements of the relevant and current monograph of the British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), or United States Pharmacopeia-National Formulary (USP-NF), as specified in *ARGOM Appendix 2: Guidelines on quality aspects of OTC applications*.
2. Active premixes[1] are not permitted unless explicitly stated in the specific OTC medicine monograph.
   a. Finished product manufacturer acceptance specifications for active ingredient premixes must be in accordance with those specified in the relevant specific OTC medicine monograph.
   b. The individual components in any active premixes are to be controlled by the supplier to relevant and current BP, Ph. Eur., or USP/NF monographs.
3. Active substance overages are not permitted unless allowed for in the relevant specific OTC medicine monograph.

[1] For more information on proprietary ingredient mixtures that contain an active ingredient see Streamlining proprietary ingredient categories.

Formulation

1. Applications for modified release dose forms will not be accepted as OTC New Medicine N2 applications unless this is expressly permitted by the specific OTC medicine monograph.

2. Excipient ingredients must be established pharmaceutical excipients that are common for the proposed dosage form. They must already be present in other products on the ARTG with the same route of administration, at doses that do not exceed those for existing products. If applicants are unsure, they should contact the TGA.[2]

3. Excipient-only premixes are restricted to colourings, flavours, fragrances, printing inks, film coatings and capsule shells.

4. Proprietary ingredients must have been notified to the TGA and identification numbers must already have been allocated.

5. Any colourings, flavours, or fragrances must not exceed 2% w/w or w/v of the finished product.

6. Only those colourings that are included in the list of colourings permitted in medicines for oral use in Australia are permitted, regardless of the route of administration of the medicine containing the colouring.

Manufacturing

1. All sites involved in the manufacture, packaging, labelling, testing and release for supply of the finished product must have a current and valid TGA GMP Certificate or TGA Licence to Manufacture. TGA certification (for overseas manufacturers) or licensing (for Australian manufacturers) is the only acceptable form of evidence of valid GMP. Current and valid evidence of GMP is also required for any manufacturers of active ingredient premixes.[3]

2. The product must be manufactured using standard processes (as defined in *CPMP/QWP/2054/03: Annex II to note for guidance on process validation CHMP/QWP/848/96 and EMEA/CVMP/598/99 non standard processes*).

3. The manufacturing process must have either been validated on a minimum of two commercial scale batches of product in accordance with the Australian Code of Good Manufacturing Practice (as defined in the Therapeutic Goods (Manufacturing Principles) Determination No. 1 2009), or an assurance provided that such validation will be completed prior to distribution in Australia.

   In either case, the manufacturer's validation report and related information must be available for review, on request by the TGA, within 3 months of release for supply of the first production batch.

4. Certificates of analysis for two pilot or production scale batches of the finished product must be provided with the application. 'Pilot' batches are as defined in CPMP/ICH/2736/99*: Stability Testing Guidelines: Stability Testing of New Drug Substances and Products (Revision 2)*.

[2] If any excipient ingredients are found not to be in accordance with this requirement, the application will need to be resubmitted as a higher level application and data provided accordingly.

[3] For more information on proprietary ingredient mixtures that contain an active ingredient see Streamlining proprietary ingredient categories.

Control of excipients

1. All excipient ingredients, with the exception of premixed flavours, fragrances, printing inks, film coatings, capsule shells and colourings (see 2-4 below), must be the subject of a current BP, Ph. Eur., or USP/NF monograph and must be controlled by the finished product manufacturer to the requirements of the relevant pharmacopoeial monograph. Where the USP/NF is applicable, and there are both USP and NF monographs for the same substance, the USP monograph must be applied.

2. The individual components of any active ingredient premixes,[4] capsule shells or proprietary film coating mixtures must be controlled by the supplier to a relevant and current BP, Ph. Eur., or USP/NF monograph (except that any colourings within these must be controlled as described below).

3. Only those colourings that are included in the list of colourings permitted in medicines for oral use in Australia are permitted, regardless of route of administration. Colourings (including those in film coatings or printing inks) must comply with BP specifications where there is a current BP monograph. Where there is no BP monograph, colourings must comply with either the specifications in the Food and Agriculture Organization (FAO) / World Health Organization (WHO) Compendium of Food Additive Specifications (as published by the Joint FAO / WHO Expert Committee on Food Additives (JECFA) on its website) or those defined in the European Commission Directive 2008/128/EC (specific purity criteria concerning colours for use in foodstuffs).

4. The finished product manufacturer's acceptance specifications for any flavours, fragrances, and film coatings must include the following tests:

    a. Flavours and fragrances:

        - appearance/description
        - identification (using a specific spectroscopic or chromatographic method such as IR and/or GC)
        - other appropriate tests such as flavour and/or odour, specific gravity, refractive index (if liquid).

    b. Film coatings (when sourced by the manufacturer as a premix):

        - appearance/description
        - identification (using a specific spectroscopic or chromatographic method such as IR and/or TLC)
        - other tests such as film forming, total ash/sulphated ash, identity tests for components of the film coating, as appropriate.

Note: For film coatings, individual components must be tested by the supplier to a current pharmacopoeial monograph as described above, or for included colourings, tested as described above for colourings.

[4] For more information on proprietary ingredient mixtures that contain an active ingredient see Streamlining proprietary ingredient categories.

Control of finished product

1. A copy of the finished product specifications (at release and expiry) must be provided with the application.
2. Product-specific specification requirements are detailed in the relevant OTC medicine monographs. In addition to those specified, the following are required:
    a. Any other necessary tests and limits, in accordance with the ICH Q6A guideline, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*.
    b. Any required tests and limits for residual solvents, in accordance with the ICH Q3C guideline *Impurities: Residual solvents*.
3. The tests for identification, assay, impurities and dissolution must use either a relevant pharmacopoeial method validated for specificity and accuracy or an alternative equivalent or superior method (e.g. HPLC instead of titration or TLC) validated fully as described in the ICH guideline, CPMP/ICH/381/95 *Note for Guidance on Validation of Analytical Procedures: Text and Methodology*.
4. Tests for preservative content must also be validated as described in the ICH guideline.
5. An OTC analytical validation summary form must be completed for each critical identification or assay test method. Inclusion of the form in the submission is not required, but it should be retained by the sponsor and provided to the TGA within 30 calendar days if requested.
6. Where the directions for use permit the subdivision of tablets (e.g. ½ tablet doses), the efficacy of the break-mark(s) must be assessed during the development of the product, to ensure that the intended dose can be administered (see *ARGOM Appendix 2: Guidelines on quality aspects of OTC applications, 7.5.2 Subdivision of tablets*).

Container/measuring device

1. Packaging must be limited to conventional containers and materials for the dosage form (e.g. oral liquids in bottles, tablets in bottles or blister packs).
2. The packaging materials, containers, seals and closures must be suitable for the intended pharmaceutical use and adequately controlled, as described in ARGOM; Appendix 2.
3. The container must comply with Therapeutic Goods Order No. 80 - Child-Resistant Packaging Requirements for Medicines, as relevant.
4. For any measuring device to be supplied with the medicine:
    a. The measuring device must meet requirements as specified in ARGOM Appendix 2: Finished product container.
    b. Specific assurance must be provided that the measuring device complies with the test and requirement for Uniformity of Weight (Mass) of Delivered Doses from Multidose Containers (Ph. Eur. monograph 2.9.27) specified in BP/Ph. Eur. Appendix XII C. Consistency of Formulated Preparations. This assurance is included in the document Assurances to accompany an OTC new medicine N2 application.
    c. Details of the calibrations on the measuring device must be provided with the submission (a sample may also be requested).

Stability

1. A maximum shelf life of 3 years can be proposed for products submitted as N2 applications, unless otherwise specified in the monograph. If a longer shelf life is required, product approval must be applied for under a higher level application.
2. Stability data to support the nominated shelf life must have been generated in accordance with ARGOM Appendix 2: Guidelines on quality aspects of OTC applications:

   The nominated shelf life must also have been determined in accordance with ARGOM Appendix 2: Guidelines on quality aspects of OTC applications.
3. Test methods used in stability studies must be validated as described above under 'Control of finished product'.
4. Stability batches used in the stability studies must be identical with respect to formulation and container type/material to the product to be marketed and must have been manufactured at pilot or production scale, using a process that simulates the final process intended for manufacture of the product to be marketed.
5. Where a shelf life is nominated on the basis of anything less than full-term data on two production batches, a stability testing program must be initiated on the first production batches of the goods (to a total of two), and any adverse results must be immediately reported to the TGA (an assurance in this regard is to be provided in the document Assurances to accompany an OTC new medicine N2 application).
6. An ongoing stability testing program must be carried out in accordance with GMP requirements (refer to details contained in the questions & answers on the code of good manufacturing practice for medicinal products, Quality control (Chapter 6), or for additional advice contact the TGA).

Application checklist

The following need to be included for OTC N2 applications:

- Completed application form via TGA eBusiness Services (eBS)
- Completed assurances document
- Colour label(s) (as described under labelling)
- Finished product specifications at release and expiry
- Certificates of analysis (C of A) for two batches of the finished product
- Details of calibrations used on any supplied measuring device (if relevant).

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	OTC Medicines Evaluation/OMA	06/09/2013
V1.1	Addition of footnotes to information about active premixes	COMB	July 2021

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Reference/Publication #