Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Guidelines on the pre-market application and evaluation process for OTC medicines

## Australian regulatory guideline for over-the-counter medicines

Version 1.3, April 2014

TGA Health Safety Regulation

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# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

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# Version history

| Version | Description of change | Author | Effective date |
|---|---|---|---|
| V1.0 | Original publication | OMA - OTCME | 15/04/2013 |
| V1.1 | Improved hyperlinks and information regarding applications for umbrella branded medicines.<br><br>Clarified requirement for analytical validation summary forms and included hyperlink.<br><br>Clarified the requirements for GMP clearance.<br><br>Clarified 'calendar days' through-out and changed from 'working days' to 'calendar days' for ACNM cut-off date.<br><br>Highlighted where requirements are subject to staged implementation. | OMA - OTCME | 15/04/2013 |
| V1.2 | Minor formatting updates<br><br>Added hyperlinks to OTC N2 application requirements and OTC Medicine Monographs. | OMA - OTCME | 06/09/2013 |
| V1.3 | Delete some references to staged implantation.<br><br>Update reference to 'other' change codes.<br><br>Correction and consolidation of information regarding fees.<br><br>Clarified that certification of registration is sent out after receiving the S26B certificate or notification. | OMA - OTCME | 09/04/2014 |

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# Introduction

This interim guideline details the new regulatory processes for the approval of new and changed OTC medicines. The new process is to be implemented in stages. This guideline describes the process that will apply when fully implemented and is to be read in conjunction with the guidance regarding the implementation stages for the new process. The initial stages of implementation allow more flexibility around the process and greater opportunity for the sponsor to remedy incorrectly submitted applications. Where the requirements detailed in this guideline differ during the stages of implementation, this will be highlighted throughout.

This guideline will be updated and revised as needed throughout the staged implementation of the new process.

The new process uses a risk based approach to regulating OTC medicines and aims to:

- deliver more efficient and cost-effective OTC medicines evaluation processes
- provide greater transparency and predictability of the regulatory process
- ensure consumers have timely access to safe and effective OTC medicines
- harmonise the OTC medicines evaluation processes in Australia and New Zealand
- improve the quality of OTC medicine applications
- ensure an appropriate benefit/risk model is applied to approvals of OTC medicines
- deliver appropriate cost recovery of OTC medicines regulation.

# Risk based approach to regulating OTC medicines

The TGA applies risk management principles described in the international risk management standard ISO 31000:2009, to the regulation of therapeutic products. This standard was also used as the basis for the risk categorisation frameworks for OTC medicine applications.

Risks are rated in terms of the likelihood of an event occurring and the consequence if it were to occur. Consequence is the outcome of an event affecting objectives, whereas likelihood is the chance of something happening, whether defined, measured or determined objectively or subjectively, qualitatively or quantitatively, and described using general terms or mathematically (such as a probability or a frequency over a given time period).

## Risk based application levels

For new product applications, there are five risk levels, from Level N1 to Level N5. For application to change an OTC medicine, there are four risk levels, from Level C1 to Level C4.

The application levels have timelines that are defined on the TGA website and submission requirements that are detailed in the *OTC application categorisation framework* and the *OTC dossier documents matrix*. OTC medicines that contain well-understood active

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ingredients and clones of existing OTC medicines fall into the lower risk levels, while more complex applications such as those involving new active ingredients or new indications fall into the higher risk levels. Lower risk application levels require less supporting information and follow a shorter timeline than applications in higher levels.

In summary, the application levels include:

- N1. Clones and flavour/fragrance/colour variants.
- N2. Generic medicines that fully meet a specific OTC monograph and all of the general requirements.
- N3. Generic medicines that do not require data to support the safety or efficacy of the product.
- N4. Includes generic medicines that:
  - require safety and/or efficacy data or a justification for not providing data. (For example, bioequivalence data, safety data to support a new excipient or data to support a new label claim.)
  - have not been previously evaluated as an OTC medicine following down-scheduling.
  - require a higher level assessment due to the umbrella segment of the product name.
- N5. New medicines that are not generics (e.g. new chemical entities, new indications).
- C1. Minor changes (self-assessable requests and safety related requests) that were previously categorised as notifications in the AUSCOM.
- C2. Changes to quality aspects and non-quality aspects where no safety and efficacy data are required.
- C3. Changes to the product name where a higher level of assessment is required due to umbrella branding. Non-quality changes where some safety and efficacy data may be required, other than C4 changes.
- C4. Changes to the indications or directions for use where safety and efficacy data are required.

# OTC pre-market evaluation process

## Overview

The OTC medicine evaluation process is made up of five phases shown in Figure 1. Each phase of the process includes defined requirements for progressing to the next phase. The general process and phases are followed for all application levels, although there are differences in the requirements within each phase.


**Figure 1: OTC medicine application process – overview**

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The following principles apply to the process:

- Applications are to be submitted electronically in CTD format for both new medicine applications and applications to change a medicine. The application format is subject to staged implementation in the new process.
- Applications are screened by the TGA upon receipt.
- Incomplete applications, including applications incorrectly assessed as being a lower application level, are not accepted for evaluation and the application fees are forfeited. This is subject to staged implementation in the new process.
- There are a limited number of occasions for requests from the TGA for the applicant to provide clarification or address issues that have been identified.
- Sponsors will be given a specified time period in which to respond to requests from the TGA to provide clarification or address issues that have been identified.
- There will be no opportunity to submit new data or make changes to the application after submission, unless specifically requested by the TGA or if it is safety data.
- The evaluation is aimed to be completed within a specified target time. Information regarding target times for each phase can be located on the TGA website.
- The delegate will make a decision following the evaluation phase. The decision is aimed to be completed within the specified target time.

## How long will the OTC evaluation process take?

The TGA aims to complete the OTC evaluation process within a specified target time. The target times differ for different application levels. Lower application levels have shorter target times than higher level applications. These target times are TGA times and do not include 'sponsor time'. 'Sponsor time' is the time taken by the sponsor to respond to a request by the TGA for information or action by the sponsor. For example, the time taken for a sponsor to rectify minor errors identified during screening is considered to be 'sponsor time'. Information regarding the target times is located on the TGA website. The target times will be subject to review, based on process performance data as it becomes progressively available.

## Determining the application level

Before submitting an application, use the following tools and guidelines in order to determine the correct application level and data requirements:

- Guidance and tools for determining the correct application level for OTC medicines.
- Guidance on the *OTC application route for umbrella branded medicines*. Applications for umbrella brand extensions are identified as requiring an increased level of assessment when the risks to consumers are considered to be higher. These applications are restricted to Level N4 and above for new medicines and Level C3 and above for applications to change the medicine name.
- *ARGOM Guidelines for changes to OTC medicines*
- *Requirements for OTC new medicine N2 applications using OTC monographs*
- Specific OTC monographs
- *OTC dossier documents matrix*

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- Relevant ARGOM guidelines:
  - *Appendix 1. Guidelines on efficacy and safety aspects of OTC application*. This describes the types of evidence that should be submitted and is particularly relevant for application levels N4, N5, C3 and C4.
  - *Appendix 2. Guidelines on quality aspects of OTC applications*. This provides guidance on the quality requirements for all OTC medicines and the data requirements for applications that require CTD Module 3.
  - *Appendix 3. Guidelines on presentation aspects of OTC applications*. This provides guidelines on various aspects of presentation of OTC medicines, including umbrella branding, and is relevant to all application types.
  - *Appendix 4. Guidelines on OTC applications for new substances*. This provides guidance that is relevant to applications involving new active ingredients (level N5) and excipients (level N4), including new routes of administration.
  - *Appendix 5. Guidelines on OTC applications for specific substances*. This provides product specific guidance for a wide range of medicines.

The application level must be correctly identified and the required data submitted. The dossier is to be in CTD format and needs to be submitted in soft copy (e.g. with the application or on DVD). Consult the document *ARGOM Guidance on electronic OTC dossiers* for the requirements applying to electronic submissions.

The format of the application and requirement to correctly identify the application level is subject to staged implementation in the new process.

## Preparing applications for new products

### N1 applications—clones

The N1 application level includes applications for clones. The term 'clone' is used in relation to OTC medicines that are identical in all respects to an existing fully evaluated medicine, apart from the aspects detailed below. Where a product is accepted as a clone, no supporting data are required apart from the proposed labelling, PI and CMI and finished product specifications; however, certain assurances are required.

If the application is approved, the clone will be registered in its own right in the ARTG. From the time of registration onwards, the clone will bear no legal relationship to the parent product. The sponsor of the clone will be fully responsible for that product.

Clone applications must comply with the following requirements:

- The clone must be identical to the parent in all respects other than:
  - The product name. However, the product name cannot include any claim or indication that is not part of the parent product name.
  - Sponsor identifying details and logo on the labels.
  - The design of the labels including background colours.
    - However, the relative prominence of the text and graphics should be the same as the parent and no new graphical representations are allowed on the label. For example, if the parent product includes a photo of a child that is awake, the

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clone could include a similar graphic or photo of a child of the same age but could not include a graphic or photo of an infant or of a child that is asleep. Similarly, if the parent product has a graphic of a head with a target on the nose, the clone could include a similar graphic of a head with the nose highlighted but could not include a graphic of a head with the nose and forehead targeted.

  - Pack size only for solid dose products and where the change in pack size does not create a higher schedule product than the parent.

- The parent product must have been fully evaluated (i.e. not a grandfathered product) and comply with all current standards, including the RASML, the SUSMP, relevant therapeutic goods orders and default pharmacopoeial standards. If the parent product does not comply with all current standards it cannot be used to support a clone application.
- The sponsor of the parent must authorise the TGA to access the parent information and files. If the clone and parent belong to the same sponsor, the sponsor should grant the TGA access to the parent product files.
- The product name cannot include an umbrella segment that requires a higher level assessment. The umbrella branding flowchart should be used to determine what level of assessment will be required.
  - If the clone product name contains an umbrella segment where there is no restriction on application level, the sponsor must make their own assessment of the labelling including the unique segment of the medicine name to ensure consumers can easily differentiate the medicine from other medicines in the range.

The clone application needs to include the following documentation:

- A letter from the sponsor of the parent product authorising the TGA to access information on the parent to support the clone application.
- A cover letter for the application that gives assurances from the sponsor for the clone application that:
  - all quality aspects of the proposed clone product are identical to the parent product, and that the sponsor will ensure that the clone product will comply with all applicable regulatory requirements and
  - the clone will comply with any specific conditions imposed by the TGA on the parent product.
  - the clone and parent products, including the labels, PI, CMI (where applicable) and finished product specifications comply with current standards, including the RASML, the SUSMP, relevant therapeutic goods orders and default pharmacopoeial standards.
- Marked up and clean copies of all clone labels, PI and CMI (where applicable).
- Copies of the most recently approved labels, PI and CMI for the parent product.
- If the clone product name contains an umbrella segment where there is no restriction on application level, labels for other medicines in the umbrella range may be requested to demonstrate that differentiation is adequate.
- A copy of the finished product specifications, which need to comply with current standards, including Therapeutic Goods Orders and default pharmacopoeial standards.
- If a different pack size is proposed provide the following assurances:
  - The container type (as defined in *TGA approved terminology for medicines*) is unchanged and container material is unchanged.

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– The new pack size does not introduce a higher schedule product than the parent.

The sponsor needs to check the *OTC dossier documents matrix* to determine where in Module 1 the required information should be located.

### N1 applications—flavour/fragrance/colour variants

The N1 application level includes extension applications for flavour/fragrance/colour variants, where the medicine meets all of the requirements applying to a clone except for the addition and/or removal of a flavour/fragrance/colour.

A flavour/fragrance/colour extension application can only be submitted as an N1 application if it complies with the following:

- All of the requirements applying to clones, with the exception of the addition or removal of a flavour/fragrance/colour.
- The total flavour/fragrance/colour agents in each of the parent and the new variant must be not more than 2% w/w or w/v.
- If the new flavour/fragrance/colour agent is a proprietary ingredient, the formulation details need to have been disclosed to the TGA and the TGA reference number of the ingredient obtained.

A flavour/fragrance/colour extension application must include all of the information and assurances required for a clone application, together with the following:

- The cover letter for the application should include an assurance that all quality aspects, other than those directly related to the flavour/fragrance/colour, of the proposed clone product are identical to the parent product, and that the sponsor will ensure that the clone product complies with all applicable regulatory requirements.
- A copy of the raw material specifications for the parent flavour/fragrance/colour and the new flavour/fragrance/colour. The ARGOM Appendix 2 *Guidelines on quality aspects of OTC applications* gives guidance on the requirements for raw material specifications.

### N2 applications—OTC Monograph

The introduction and trial of N2 OTC Monograph applications is subject to staged implementation.

Applications within the N2 level are for medicines that comply fully with a specific OTC Medicine Monograph and all of the associated general requirements. N2 applications are classified as lower risk and consequently the data requirements and level of assessment are reduced. In lieu of providing data, sponsors submitting an application through the N2 route will need to provide a complete list of assurances.

If the application requires higher level assessment for other aspects, such as evaluation of a higher risk umbrella brand name or assessment of safety and efficacy data (e.g. to support a label claim, or request for a brand equivalence statement), then it cannot be submitted as an N2 application.

If the product name contains an umbrella segment where there is no restriction on application level, the sponsor must make their own assessment of the labelling, including the unique segment of the medicine name, to ensure consumers can easily differentiate

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the medicine from other medicines in the range. Labels for other medicines in the umbrella range may be requested in order to demonstrate that differentiation is adequate.

N2 applications should be submitted through TGA eBusiness Services (eBS) as a 'New medicine application and identified as an N2 application in the application covering letter. Standard new product evaluation fees apply, but target times for evaluation are shorter. Data requirements are shown in the *OTC dossier documents matrix*.

### Level N3-N5 applications

Applications for new products within the N3–N5 levels are more complex than lower level applications and have different data requirements depending on the nature of the particular application. The *OTC dossier documents matrix* provides an overview of the requirements for these applications and the ARGOM Appendices 1–5 provide more detailed guidance. The following general requirements apply to Level N3–N5 applications.

- CTD Module 3 is required to support the quality of the product. The ARGOM Appendix 2 *Guidelines on quality aspects of OTC applications* gives detailed guidance on the requirements for quality aspects of the OTC medicines and preparation of Module 3. Applications that require Module 3 analytical validation data also need to include completed OTC analytical validation summary forms.

  Where the quality aspects of the product are identical to a parent product that has been previously fully evaluated, the sponsor may provide an abbreviated module 3 dossier (including finished product specifications) together with the following:

  – a letter from the sponsor of the parent product authorising the TGA to access information on the parent files to support the application, and

  – an assurance in the cover letter for the application that all quality aspects are identical to the parent product.

- CTD Module 4 and Module 5 may be required for Level N4 and N5 applications to support the safety and efficacy of the product. The ARGOM Appendix 1 and Appendix 4 provide guidance on aspects relating to the safety and efficacy of OTC medicines and new substances, respectively.

- Applications that have been restricted to Level N4 or C3 and above due to the requirement for higher level umbrella branding assessment are to include the labels for other medicines in the umbrella range. Assessment of umbrella brand names should be in accordance with the relevant guidelines in the ARGOM Appendix 3 *Guidelines on presentation aspects of OTC applications*.

- If the product name contains an umbrella segment where there is no restriction on application level, the sponsor must make their own assessment of the labelling, including the unique segment of the medicine name, to ensure consumers can easily differentiate the medicine from other medicines in the range. Labels for other medicines in the umbrella range may be requested in order to demonstrate that differentiation is adequate. Assessment of umbrella brand names should be in accordance with the relevant guidelines in the ARGOM Appendix 3 *Guidelines on presentation aspects of OTC applications*.

## Preparing an application to change an OTC medicine

Where a sponsor of a registered OTC medicine wishes to make a change to the medicine, it is a condition of registration that, with limited exceptions, the change(s) require prior TGA approval.

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The *ARGOM Guidelines on changes to OTC medicines* and the 'Changes table' detail the types of applications required when a sponsor wishes to change the details of their registered OTC medicine. With the exception of changes requiring a 'new' application, the selection of a 'change code' will be linked to an application level (C1, C2, C3, or C4). This will determine the level of the application.

Where more than one change type is being proposed within a single application, the application level is determined by the highest application level (with C1 being the lowest level and C4 the highest).

The application should include a table describing each of the changes in detail and the reason for the change, as well as any relevant supporting data.

**What if the proposed change is not in the Changes Table?**

If the proposed change is not described in the Changes Table, contact the staff of the OTC Medicines Evaluation Section. The absence of the proposed change from the Changes Table does not imply that the change may proceed without requesting prior approval from the TGA.

If it is determined, in consultation with the OTC Medicines Evaluation section, that none of the specific change codes are relevant to the proposed change, then one of the 'other' change codes (OT1, OT2, OT3, OT4) will be used. The OTC Medicines Evaluation section will provide written confirmation to the sponsor, typically in the form of an email, endorsing the use of the 'other' change code and advising the application level (C1-C4) appropriate for the particular change. The application 'level' will be determined in accordance with the *OTC application categorisation framework* for changes to approved medicines.

This written confirmation from the TGA must be included with the application as an attachment to the cover letter and should be explicitly referred to in the cover letter.

**Making the same changes for multiple products**

A sponsor can submit an application to make identical change(s) to multiple OTC products. This type of application applies only when the change does not require separate assessment for individual products, or when there is no change unique to one particular product within the group that requires separate assessment.

An example of an acceptable application of this type is where a sponsor requests a change to the same principal licensed manufacturer for a range of registered products. However, if the sponsor wants to make an additional change to one out of the group of products (e.g. the addition of an Australian manufacturing site), then that product should not be included with the multiple change application. The changes for that product should be submitted as a standalone application.

Sponsors of applications involving more than one product should submit separate, individual product-specific copies of the relevant supporting documents for each Australian Registration number (AUST R) that the change applies to, for record-keeping purposes.

Applications involving 'Groupable' changes cannot be submitted as part of an application involving more than one product; 'Groupable' changes require a separate application for each product.

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# Application lodgement

The OTC medicine pre-market evaluation process commences when a sponsor lodges an application seeking marketing authorisation for a new or changed OTC medicine. The application must be submitted through TGA eBusiness Services (eBS). The application must contain current and correct details for the entire submission in order to pass validation in eBS.

For an application that is making the same change to multiple products, each ARTG entry included in the application must contain current and complete details for the entire submission to pass validation in eBS.

The application must:

- Have the correct application level identified.
- Include a cover letter clearly stating the nature and scope of the application, the reason for selecting the application level and any relevant background information. For applications to change an OTC medicine, the change(s) must be described in the sponsor's own words and the reason for the change given. It is not sufficient to restate the change codes that are applicable. Where multiple changes are being made, this information needs to be presented in a table. For example, for an application making multiple changes to the text and layout of a label, each change to the label should be listed in a table together with a justification or reason for the change.
- Include all of the required data, information and/or assurances.
- Have a submission dossier that is
  - in CTD format, and
  - in electronic format (e.g. DVD, CD)

  The *ARGOM Guidelines on electronic OTC dossiers* provides detailed information on the required format for electronic submission dossiers.
- Have current and valid evidence of GMP for all steps of manufacture. This must be in the form of valid TGA certification or clearance. The sponsor needs to ensure that the TGA certification or clearance has sufficient duration before expiry to allow for completion of the application process, as an application cannot be finalised without current and valid TGA certification or clearance. If necessary, an extension to the TGA clearance should be obtained from the Office of Manufacturing Quality before application lodgement. Where a request for an extension to a TGA clearance has been made to the Office of Manufacturing Quality this needs to be stated in the application cover letter.

The requirements for correct identification of application level and the format of the submission dossier are subject to staged implementation.

**Confidentiality**

Details of an application will only be discussed with the sponsor or the sponsor's appointed agent.

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### Acknowledgement of application

Lodgement of an application will result in the automatic provision of a Submission Number which uniquely identifies the application. This number should be quoted in any correspondence or enquires concerning the application.

### Monitoring the application progress

Sponsors are able to monitor the workflow status of applications through online access in the TGA eBusiness Services sponsor portal and the menu option 'View lodged submissions', under the column 'Workflow Status'.

The new OTC online application system will result in an enhanced ability for the applicant to monitor the progress of the application through the pre-market evaluation process.

## Fees

This section describes the process for determination and invoicing of fees from the time that the upgrade to the OTC online application system comes into operation on 9 April 2014 until a revised fee structure that reflects the application categories contained in this guideline, has been approved for implementation. Advance notice will be given to industry when the commencement date for the revised fee structure is known.

Full details of the current application and evaluation fees are contained in Schedule 9 to the Regulations. A summary of fees and charges is available on the TGA website. The TGA provides a range of payment options.

### Invoicing the fees

An invoice for the application and evaluation fee is automatically issued when the TGA receives the electronic application (automated when you submit the application).

The screening of the application will not commence until the fees are paid. Hence it is important to pay the fees at the time you submit the application to prevent delays with commencing the screening process.

The evaluation fee may need to be adjusted from that invoiced at the time of submission if:

- The application contains clinical or toxicological data for evaluation and a higher evaluation fee based on page count applies.
- A waiver or reduction in the evaluation fee is granted.

The evaluation fee will be assessed during screening and if necessary:

- An invoice will be issued for any additional fees that apply.
- A refund will be issued if a waiver or reduction of the evaluation fee has been granted.

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### Waiver or reduction of evaluation fees

In some circumstances, a waiver or reduction of the evaluation fee (but not the application fee) may be possible under the provisions of Regulation 45 of the Therapeutic Goods Regulations. If you are eligible:

- Include a request and justification for a waiver or reduction of the evaluation fees in the covering letter of the application.
- The decision to grant a waiver or reduction of the evaluation fee will be made prior to accepting the application for evaluation.

### Making payments by cheque

If you are paying the fees by cheque:

- Indicate in the covering letter that payment has been forwarded directly to TGA Finance section.
- Do not include cheque/credit card details with the submission.
- Forward payment together with a copy of the relevant invoice by separate postage to the address below

Office of Corporate Services
PO Box 100
WODEN ACT 2606
Australia

## Application screening

All applications are screened by the TGA to check that they have been submitted correctly and include all of the required information. The screening process involves checking that:

- the application is for an OTC medicine
- the sponsor has correctly identified the application level
- all required data and information have been provided and the application is complete
- the application has been submitted in the required application format
- current and valid evidence of GMP has been provided for all steps of manufacture in the form of valid TGA certification or clearance.

During screening, the TGA may identify deficiencies or errors in the application. Where there are minor errors or omissions that can be readily addressed, the sponsor will be given the opportunity to remedy these. However, absence of data or obvious deficiencies is indicative of an incomplete application.

### Accepted applications

When it has been determined that an application is complete, the screening phase will conclude and the application will be accepted for evaluation. In this case, the sponsor will be advised that the application has been accepted. The application will enter the evaluation phase and the online status will move to the next phase from screening to awaiting evaluation.

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### Unaccepted applications

If during the screening phase it is determined that the application is not complete or is not submitted at the appropriate level, the application will not be accepted for evaluation. Under these circumstances, the sponsor will be notified that the application will not be accepted for evaluation[1]. The application will be removed from the application lodgement system in TGA eBusiness Services and the application fee forfeited. The sponsor will be refunded the evaluation fee. The sponsor will also be provided with a list of deficiencies that should be addressed in a future resubmission of the application.

Common reasons for why an application cannot be accepted for evaluation include:

- Application submitted at the incorrect application level.
- Incorrect format.
- Deficient in any of the required data and information.

The forfeiting of applications fees for applications that are submitted at the incorrect level or in the incorrect format is subject to staged implementation.

### Additional evaluation fees

If you have been invoiced for additional evaluation fees during screening, these should be paid immediately.

- For new product applications, application will lapse if the evaluation fee is not paid within 2 months of the date of the invoice[2].
- For change applications, evaluation will not commence until the full evaluation fee has been paid.

## Evaluation

Evaluation of an application to register or change an OTC medicine involves:

- Evaluation of the data and information provided by the sponsor in accordance with the applicable application level.
- If required, evaluation of the information provided in response to requests for information (RFIs) to clarify specific aspects of the application.
- Documentation of findings.

Each stage of evaluation is aimed to be completed within a specified target time. Information on the target times is available on the TGA website.

### Requests for Information (RFI)

The request for information (RFI) stage allows the TGA to seek clarification from the sponsor about matters that will assist the delegate in making a decision, including the

[1] For new product applications, the application is considered 'not effective' under Section 23(2)(b) of the *Therapeutic Goods Act 1989*.
[2] Section 24 (2)(a) of the *Therapeutic Goods Act 1989*.



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quality, safety, efficacy and presentation of the product. During evaluation, the evaluator will identify any matters that require clarification or information, and where necessary a consolidated set of questions (the 'RFI') will be prepared by the TGA delegate and sent to the sponsor (Section 31 of the *Therapeutic Goods Act 1989*).

One request for information will be permitted for application levels N1, N2, C1 and C2, with all other application levels allowed a maximum of two requests for information, after which the application will proceed to the decision phase.

The RFI will include sufficient information to allow the sponsor to understand the issues and concerns. It will also specify the maximum number of days allowed for the sponsor to provide a formal response. The default time period and number of RFIs allowed are:

- N1 and C1 applications: 1 RFI allowed with a default response time of 7 calendar days.
- N2 and C2 applications: 1 RFI allowed with a default response time of 21 calendar days.
- N3, N4, N5, C3 and C4 applications: Up to 2 RFIs allowed with a default response time of 60 calendar days for the first RFI and 30 calendar days for the second RFI.

If the sponsor believes that the time allowed by the delegate is insufficient, these concerns must be raised straight away with the delegate. Generally, no extension is given unless the sponsor can demonstrate that the time allowed is not reasonable. The sooner the sponsor's response can be received the sooner the TGA can proceed to complete the evaluation.

The sponsor's RFI response will need to address all issues raised. The sponsor should pay close attention to the questions raised in the RFI, as there are limited opportunities to provide this information. If the RFI response relates directly to the content of a module of the submission dossier, the response needs to be provided in CTD format. An electronic copy of the response must be submitted. If a response is not received within the specified time or only a partial response is received, then the evaluation and decision making process may proceed on the basis of the information available.

Additional data cannot be included in an RFI response, unless it has been specifically requested by the TGA or is safety related. The RFI process is not intended to provide sponsors with an opportunity to supply information that should have been included in the original application.

### Final evaluation

The final evaluation phase involves the evaluation of the sponsor's application and where RFIs have been made, the sponsor's response in relation to the outstanding issues. Where the sponsor's response to the final RFI is inadequate there will be no additional RFI sent. These issues may be significant enough to warrant a recommendation to reject the application or they may be minor and able to be remedied informally.

### Clock stops

During the screening and evaluation process, the TGA may put the application on hold and 'stop the clock'. The TGA will 'stop the clock' if the sponsor has been requested to address minor omissions in the application during screening or provide requested information and clarification (the RFI). The TGA will restart the clock when the sponsor has responded to the RFI or remedied the deficiency. The time period during which the clock is stopped is 'sponsor time' and will not be included in the time taken for the TGA to evaluate the application.

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### The Advisory Committee on Non-prescription Medicines

The TGA has a number of statutory advisory committees from which it can obtain independent expert advice on specific scientific and technical matters to aid the TGA's regulatory decision making and other regulatory processes. The Advisory Committee on Non-prescription Medicines (ACNM) provides advice relating to the inclusion, variation, removal or continued retention of OTC medicines in the Australian Register of Therapeutic Goods. The ACNM may also provide advice to the TGA on other matters concerning OTC medicines, and any other matters referred to it by the TGA. It is composed of independent experts who have expertise relevant to non-prescription medicines. Details regarding the ACNM, including the meeting dates, can be found on the TGA website.

When necessary, the delegate may request advice from the ACNM on specific issues relating to an application. Historically, referral of OTC applications to the ACNM occurs for 3% to 4% of applications. Level N1, N2, N3, C1 and C2 applications are unlikely to be referred to the ACNM for advice. Level N4, N5, C3 and C4 applications are more likely to be referred to the ACNM for advice, particularly where the application is the first of that type to be evaluated by the TGA. For example, an application involving an indication that has not been previously approved by the TGA for similar products is likely to be referred to the ACNM for advice.

During screening an application may be identified as likely to go to the ACNM. In these circumstances the sponsor will be notified during screening of the anticipated ACNM meeting date. If the delegate chooses not to refer the application for advice, the sponsor will be informed of this at the earliest opportunity. The delegate may also choose to seek advice from the ACNM regarding any application at any stage of the evaluation process, regardless of whether this was anticipated during screening. If an application is referred to the ACNM for advice, this will typically extend the evaluation phase and total time to completion by three to six months.

Where an application is referred to the advisory committee for advice, the TGA will prepare an evaluation report for the ACNM to consider. The sponsor will be sent a copy of the TGA evaluation report at least fourteen calendar days before the cut-off date for the meeting at which the application is to be considered. The sponsor is given the opportunity to provide comments and clarification for the ACNM to consider at the meeting. The comments are limited to three pages and should only address specific issues raised in the evaluation report that will be considered by the ACNM. Minor administrative issues can be addressed with the TGA outside of the ACNM meeting. Additional data will not be accepted. Following consideration of the application by the ACNM, the sponsor will be sent a copy of the ACNM minutes detailing the advice of the ACNM in regards to their application. A copy of the ACNM minutes will be sent within six weeks of the meeting.

After considering the advice of the ACNM and sending the sponsor a copy of the ACNM minutes, the delegate may:

- directly proceed to make a decision regarding the application.
- give the sponsor the opportunity to respond to any issues that the ACNM have raised and other matters identified by the TGA. If the sponsor is given the opportunity to respond to these issues, the delegate will send a post-ACNM RFI. The conditions applying to a standard RFI will also apply to the post-ACNM RFI and the TGA will 'stop the clock', giving the sponsor a final opportunity to address the issues that have been raised. A copy of the ACNM minutes will be attached as background information to the post-ACNM RFI.

The advice provided by the ACNM is an important element in the undertaking by the TGA of its regulatory functions. However, it forms only part of the information that is available to a TGA delegate making a regulatory decision under the Therapeutic Goods Act. While

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appropriate consideration will be given to such advice, it is important to note that neither the TGA nor a TGA delegate is obliged to follow it.

# The Delegate's decision

The *Therapeutic Goods Act 1989* ('the Act') is written in terms of two parties—'the sponsor' and 'the Secretary'. In practice, where the Act specifies that decisions are to be made by 'the Secretary', those decisions are usually made by an officer of the TGA to whom the Secretary's authority has been formally delegated. Delegations of this nature are generally restricted to senior officers.

When an evaluation has been completed, the delegate makes a decision on whether the product is suitable for either a change to an entry under Section 9D of the Act, or registration in the Australian Register of Therapeutic Goods (ARTG) under Section 25 of the Act. In making the decision to approve or reject an application, the delegate must consider the required matters detailed in the Act, including whether the quality, safety, efficacy and presentation have been satisfactory established or, for a change, that there is no reduction in the quality, safety and efficacy of the product. The delegate considers all documentation in reaching a decision regarding an application, including:

- the application and accompanying data
- the evaluation report
- the sponsor's responses to any RFIs
- advice from the ACNM
- information from other relevant sources.

The sponsor will be required to verify the accuracy of all details in the application, including any changes that may have been agreed to during evaluation, before the delegate approves an application.

The sponsor will be notified of the delegate's decision and in the case of a decision not to register the goods or vary the entry in the register, the sponsor will also be notified of the reasons for the decision. If the decision is to approve the application, the letter will include *standard and specific conditions of registration* made under Section 28 of the Act.

### Rights of appeal

If the Sponsor is dissatisfied with the delegate's decision, directions on how to proceed with an appeal can be found on the TGA website.

# Finalisation

### Australian Register of Therapeutic Goods (ARTG) entry

New OTC medicines require *S26B Certification relating to Patents* to be provided before registration can occur. The certificate or a notification that the certificate is not required can be downloaded from the TGA website. The S26B Certification can be sent in at the time the application is submitted and doing so will help minimise delays during the finalisation phase.

The sponsor will be issued a Certificate of Registration after the S26B notification or certificate is received. The Certificate of Registration will include a number of conditions of



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registration, which should be read carefully. Failure to comply with the conditions of registration may result in the cancellation of the product from the ARTG. The registration of the goods will commence on the day specified for the purpose in the certificate of registration. The goods may not be supplied before this date.

### Section 14 exemptions

If the product cannot comply with the applicable standards then an application for a section 14 exemption may be submitted. Exemption from compliance with a standard may be granted if there is a strong justification and no consequent reduction in the quality, safety and efficacy of the medicine.

## Withdrawal of applications

The sponsor may withdraw an application at any time after lodgement of the application until the delegate's decision is made. The sponsor must inform the TGA in writing of their intention to withdraw the application. Where an application is withdrawn due to safety concerns, the sponsor may be asked to provide any adverse safety data in its possession to the TGA.

There will be no refund of the application fee for applications that are withdrawn. The evaluation fee will be refunded only for applications that have not reached the evaluation phase prior to the time of withdrawal.

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