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OTC DRUG REGULATORY REQUIREMENTS AND APPROVAL PROCESS IN AUSTRALIA

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ABSTRACT

In recent days, a lot of changes were observed in the regulations for OTC drugs. Developing a new non-prescription drug requires an enormous amount of complete research work in Chemistry Manufacturing Control, preclinical and clinical trials or showing similarity in bioavailability and bioequivalence studies. Department of a regulatory agency is responsible to evaluate the research data supporting the quality control examinations and drug safety, the efficacy of the new OTC product to serve public health. Regulatory authority varies from country to country and having their own roles and responsibilities. These authorities are responsible to apply the rules, related regulations and guidelines to be issued for the marketing of any non-prescription products. In Australia, the Australian Register of Therapeutic Goods is responsible for the registrations of non-prescription medicines. Thus, the article focuses on the regulatory requirements and approval process for non-prescription drug products in Australia.

INTRODUCTION

TGA (Therapeutic Goods Administration) being the commonwealth Government agency regulates drugs and medical devices. Prescription and non-prescription medicines meeting the Australian Standards of safety, efficacy and quality included on the ARTG. Those products getting registered are evaluated and labeled with an AUST R number. Nowadays, all the active ingredients in OTC (Over-the-counter) medicines firstly enter the market as prescription medicine ingredients. To assess the ingredient as a non-prescription category, medicines are required to be used as prescription medication in the market for at least 2 years. Not all the active substances are transmitted from prescription to non-prescription medicine. The information Collected regarding the safety and efficacy of the OTC products is less because the registration of the non-prescription medicine can get the accumulated experiences as a prescription product. New OTC products are assessed by the TGA for safety, efficacy and quality [1]. The quality and manufacturing standards and circumstances for such things are as same as prescription medicines. [2, 3] OTC medicines are available widely and can be purchased without any prescription for example internet, health food stores or supermarkets. OTC medicines are very important component for the primary health care like they include cold and cough medicines, anti-fungal treatments and basic analgesics. If these medications used appropriately then it can save

customers money and time by providing them access to the safe and effective medicines and treatment for many occurring conditions. The use of OTC is extremely common. In Australia, it was estimated that over 80% of adults and 40% of children used an OTC in any given month of the year 2013. The economic impact of OTCs use is enormous. The current value of OTCs provided to the health system is high as it is estimated that consumer self-care through OTC use currently saves the Australian AUD10.4 billion. The Australian legislative framework for OTCs is different to many other countries, with legal classification of non-prescription medicines being: unscheduled, Pharmacy Medicines (Schedule 2) or Pharmacist Only Medicines (Schedule 3). It has been suggested that sales and purchasing behavior of OTCs may be influenced by such classifications. [4]

METHODOLOGY: Regulatory guidelines related Australia for OTC products were studied

AUSTRALIA: The guidance for new OTC medicines registration process is projected to support applicants to register over-the-counter (OTC) or non-prescription medicines on ARTG (Australian Register of Therapeutic Goods).
The registration process includes following guidance:

- Categories of the regulatory process
- Direction to the applicant to follow the procedure step-by-step.
- Usage of links to relevant forms and guidance.

The various steps involved in the registration process are as follows

Step 1: Verification of OTC medicine and access to business services.
Step 2: Checking new medicine ingredients.
Step 3: Evaluation of application level.
Step 4: Examination of guidelines and mandatory requirements.
Step 5: Ensuring valid GMP evidences.
Step 6: Compiling data for the application.
Step 7: Completion and submission of the application.
Step 8: Paying the fees.
Step 9: Screening of the application.
Step 10: Evaluating and requesting information.
Step 11: Making OTC registration decision.
Step 12: Finalize OTC registration.[5]

Step 1: Verification of OTC medicine and access to business services.
If the medicine is decided as OTC, it should be registered in ARTG. Applicant should have client ID number with the password to contact TGA Business services, then applicant can directly start from Step 2.

➢ **Verifying an OTC medicine**

A guidance Pathway to evaluate applicant medicinedirects to verify OTC medicine registered in ARTG.
The Pathway to evaluate applicant medicinedetermines the type of medicine that is:

- Prescription medicine - Evaluated by Prescription Medicines Authorization Branch
- OTC and complementary medicine - Evaluated by Complementary and Over-the-counter medicines branch

➢ **Client identification and access to Business services**

Applications are completed and submitted through business services. The applicant needs both to access to business services.

- Client ID number
- Password

If client does not have client ID and password:
Go to Business services: Getting started with TGA
Complete and submit online organization details form
Organization details form: It includes details to be filled by the sponsor, manufacturer and the agent. The details of organization are as follows.

- Concerned with the manufacture or supply of Therapeutic Goods in Australia.
- Clinical trial conducted in Australia.
- Concerned with the supplying of Proprietary Ingredients.
- Or the person providing regulatory services on behalf of above mentioned organization (Agents).

Step 2: Checking for new medicine ingredients

The applicant should ensure the assessments details of OTC medicine ingredients, before stepping into the preparation of application for OTC medicine to register.

Checking ingredients in The TGA table:

Checking for the ingredients in the tables under Public TGA information if it is included.

- ✓ Ingredients Table
- ✓ Proprietary Ingredients Table

New proprietary ingredients

An application Notification of a Proprietary Ingredient form has to be filled completely to obtain Proprietary ingredient ID number for the registration of the OTC medicine.

For new substances (active ingredient and excipients)

Two pathways should be followed to apply for the approval of a new substance (active ingredient or excipient). Applicant can either follow:

1. **Applying as a part of OTC application.** If this process is followed then use following steps to determine the application level (Step 3)
    - Covering letter must include necessary information.
    - Must issue the data described in the Guidelines on OTC applications for new substances
2. **Applying before submitting the application for OTC medicine:** This option is usually used for active ingredients or new excipients in sunscreen. If this process is followed then use the given login access in the business services which was given to access application form.
    - Completing application form for a new substance.
    - Must issue the data mentioned in the Guidelines on OTC applications for new substances

Recommending a name for new substances

It is needed to suggest a name for the new substance. In order to do this:

- ➢ Must select a specified application form for suggesting names.

Various types of application forms are available as follows:

- Australian Approved Name (AAN)
- A herbal substance Name (AHS)
- Australian Cell and Tissue Name (ACN)
- A botanical name for a herb (AHN)
- Australian Botanical Name (ABN)

- ➢ Submission of concerned form through e-mail to TGA Names.
- ➢ Make sure to submit and state the new substance application or OTC medicine application form through covering letter.

Ingredients that need assessment

Ingredients present in Ingredient table might not have got approval for applicant proposed concentration or proposed use.

Ingredient table contains less information on the restriction of use. For example, for ocular use only.

It does not mean applicant have got approval for the proposed concentration or proposed use if Ingredient table is not containing restrictions.

If safety and efficacy assessment is required for OTC medicine ingredient make sure to:

- Include ingredient into account for the determination of the application level (Step 3).
- Mention ingredient in the OTC medicine application along with covering letter.
- Must issue the data described in the Guidelines on OTC applications for new substances

Step 3: Evaluation of application level

Based on various fee structure, target evaluation times and risk, application levels are categorized into 5 levels.

Determination of correct application level

Scrutinizing the correct application level is important. If data is not meeting the application levels then evaluation will not proceed under Therapeutic Goods Act 1989.

For OTC medicines there are five application levels

N1: OTC new medicine N1 application requirements are met by N1 Generic medicines (color variants/flavour/fragrance or clones of a presently registered medicine).

N2: General requirements for OTC new medicine N2 application and specific

OTC monograph requirements are met by N2 Generic medicines.

N3: Application requires CTD modules 1 and 3. N3 Generic medicine is not a part of N1, N2 or N4 level of application.

N4: Requires supporting data for safety and efficacy. Generic medicine it can be one or more of the following:

- Previously medicine was not registered under OTC medicine.
- Requires increased level assessment because of the product name under umbrella segment.

N5: This is not for generic medicine. It is for one or more new chemical entity (active ingredient)

- Indication
- Dosage form
- Combination of API
- Strength
- Patient population
- Direction for use

Step 4: Checking mandatory requirements and guidelines

When OTC medicine filing is performed, it is necessary to understand guidelines and applicable mandatory requirements.

Mandatory requirements

The mandatory requirements will help the application to pass screening more effective and makes it easy to accept for evaluation:

- Mandatory requirements for an effective OTC medicine application
- Module 1 CTD:For those application that needs higher-level assessment because of umbrella segment of the product name. The requirements for umbrella brand assessment should be submitted in CTD Module 1.5.8
- General requirements for dossier
- Covering Letter.
- CTD format

Relevant guidelines

Relevant guidelines to be checked for any advice or specific requirements that are required for the application:

➢ OTC - Specific guidelines

➢ European Union and ICH guidelines adopted in Australia – ICH guideline and European Committee for Medicinal Products for Human Use (CHMP) should be adopted by TGA.

Step 5: Ensuring valid GMP evidences.

For the manufacturing of registered OTC medicine, manufacturers require a valid evidence for each step in the manufacturing process.

Application will not be validated (Step 7), if valid GMP evidence is not submitted by each of the manufacturer.

Accepted evidence

Reviewer accepts the application:

- TGA issued GMP license: Australian manufacturers
- TGA issued GMP clearance: Overseas manufacturers

In both of the above-mentioned cases GMP evidence is valid for each steps in the manufacturing and dosage forms designated on the clearance or license.

Duration for overseas manufacturers GMP clearance

Application cannot be finalized for each overseas manufacturer without a valid and current GMP (TGA issued) clearance. Also ensure that during the evaluation time frame GMP clearance should not expire.

When application is submitted in Step 7, ensure that minimum timeframe should not expire for GMP clearance:

N1 application - 3months

N2 application – 4 months

N3, N4 and N5 application – 6 months

Due to expire – GMP clearance

If the expiry dates for GMP clearance is within the minimum timeframe or being expired before the final application:

➢ GMP clearance has to be applied for renewal.

➢ Seeking an extension for GMP clearance expiry.

Both renewal and seeking an extension for OTC medicine must be done through a covering letter

Step 6: Compilation of data for application

OTC dossier must be prepared containing technical and administration documentation should be submitted for evaluation.

General requirement for dossier

General requirements for dossier should be followed while compiling dossier that includes:

- For registration of medicine (OTC, complementary or prescription) on the ARTG.
- Evaluation of information is required to include a biological on the ARTG.
- Assessed medicines are listed (evaluation is performed on the given information).
- Conformity assessment certification for medical device (including IVD).
- Evaluating listed medicines for new ingredients.
- Supporting information is required to vary ARTG record.
- If advise was given to provide information for audit to include medical device (including IVD).

Guidance not applied to the application:

- To list an OTC or complementary medicine (for evaluation no information is required).
- To include medical device on the ARTG (other than those medical device already selected for audit).
- If no supporting system is required to vary the ARTG record.
- For GMP (Good Manufacturing Practice) certification or overseas GMP clearance manufacturers.

Organisation and structure of the dossier

According to CTD electronic dossier is compiled.

CTD modules for application is identified by checking:

➢ CTD Module 1: OTC medicines

➢ Mandatory requirements for an effective OTC medicine application.

Mandatory requirements

Ensure that the application dossier includes all of the technical and administration data necessary for the application level.

It is necessary to check and ensure the dossier:

✓ Is fully completed

✓ According to the required format

Electronic dossier application must be submitted.

✓ Contains information required for an effective application detailed in:

- OTC medicine: CTD module 1
- Mandatory requirements for an effective OTC medicine application
- Guidance to prepare covering letter

Application is checked for effectiveness and should meet the requirements, if not it will not be accepted for evaluation (Step 9).

Step 7: Finishing and submission of application

OTC medicine application form has to complete and submitted.

Steps to complete application form are as follows

1. Log in to Business services page.
2. Click the option ′Applications′
3. Select the appropriate OTC application, for example, select ′Non-Prescription Composite Pack ′for composite packs and select ′Non-Prescription Medicine ′ for single component.
4. Ensure that appropriate OTC application form and complete it.
5. Application dossier is attached to the OTC application. One can also choose DVD/CD/USB for the submission of dossier.
6. Tick agree the declaration and other relevant assurances. Click the option ′Submit′

ID number submission: ID Submission number is automatically issued as soon as OTC application submitted, which helps in identification of application. Any further communication can be done through this ID number.

Monitoring the status of application: Status of workflow is monitored through Business services.

After processing of fees, the status shows ‘Under Review’, states that the application is in screening stage.

Application withdrawal: Until the final decision is ends at any time applicant can choose to withdraw the application. Intension to withdraw the application is informed in writing. If the applicant is withdrawing due to safety issues then agency asks the applicant to provide adverse safety data if any.

Table 1. Schedule of fees and charges.

Listed medicine charge	Amount
Application fee	$840
Processing fee	$430
Annual charges	$1,140
Application for consent by the Secretary under sections 14 and 14A of the Act to the import, export or supply of therapeutic goods that do not comply with an applicable standard	$480

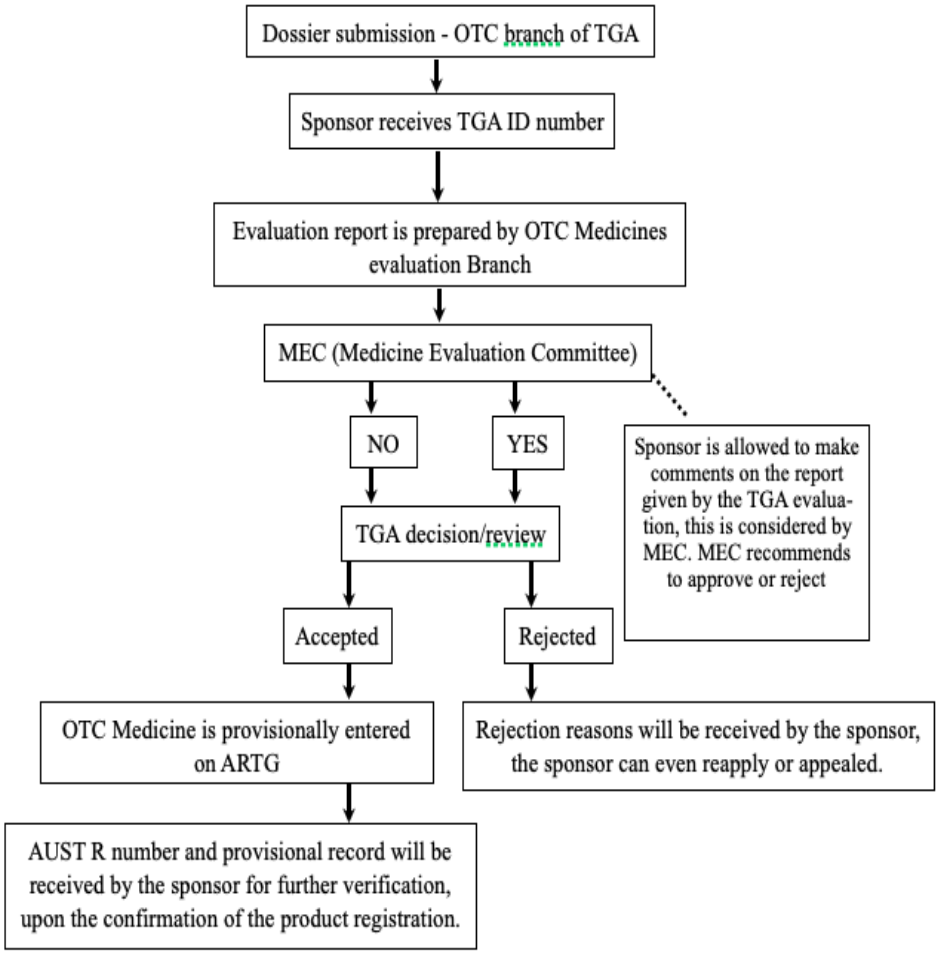

Fig 1: Flow chart of OTC Drug Approval Processs

Table 2. Standard time Schedule for evaluation

Application level	Total Evaluation Time (days)	Number of RFI (Request for Information)	Standard time permitted for sponsors to reply to RFI (days)
N1	45	1	5
N2	55	1	15
N3	150	2	1st – 43 2nd – 21
N4	170	2	1st – 43 2nd – 21
N5	210	2	1st – 43 2nd – 21

Refund after withdrawal of application: If the evaluation process is not started, evaluation fee is refunded. Application fee is not refunded once the review process starts.

Step 8: Paying fees

When OTC medicine is applied for registration, application fee and evaluation fee invoice is sent to the corresponding applicant.

Concurrent fees listed in schedule of fees and charges.

Reduce or waive evaluation fees: When the applications are not appropriate for paying concurrent fees, some cases can be possible to reduce or waive the evaluation fees under the regulation of TGR (Therapeutic Goods Regulations). Therapeutic Goods Regulations checked for the eligibility.

If your application is eligible then it is stated in the covering letter with justification and request. Decision is made prior to accept the application for assessment.

Paying fees: To pay the fees, 2 options are available:

- Payment option
- Fees and payment

Payment through cheque

- Covering letter should state that the payment is paid to TGA Finance through cheque.
- Pay the payment, with a copy of relevant invoice, in a separate post:

TGA Finance
PO Box 100
WODEN ACT 2606
Australia

NOTE: Do not include credit card or cheque details with the submission.

Paying extra evaluation fees: If the applicant gets invoice for paying additional fees it should be paid by the applicant within 60 days from the date of invoice received or the subsequent will occur:

Lost the application fees. Application lapse and may not proceed for evaluation. [6]

Step 9: Screening of application

Screening of application is performed to verify the level of application and meeting the requirements.

Requirements to shape an effective application

1. Paying prescribed application fee.
2. All information required in an application included to allow reviewer to make a final decision.
3. Samples are delivered only on request by the TGA.
4. Restricted medicine application included in product information in the form approved.

   Information about the medicine is filled:

   - OTC Medicine name
   - Quantitative and qualitative composition
   - Pharmaceutical form
   - Clinical details
   - Pharmacological properties
   - Pharmaceutical parameters
   - Medicine schedule
   - Sponsor name and address

- Date of first Approval
- Revision date

Information in the covering letter is the basis to know the corresponding data requirements and application level.

Chances for minor modifications: During the time of screening process, chances are given to make specified slight corrections, if the error has chance to rectify promptly.

For example, a document is not attached but it is mentioned in the covering letter, so the agency gives an opportunity to the applicant to attach the document mentioned in the covering letter.

Effective Applications: If the application is found effective, the agency will:

- Accept it
- Can send both:
  - Email as a notification, informing that the application is accepted for evaluation.
  - If applicable an invoice is sent to the applicant for the payment of remaining evaluation fees.
- Undertaking for evaluation

Ineffective Applications: If application was found to be ineffective:

- Application is not accepted for evaluation
- Application is removed from Business services
- Reason should be mentioned for an ineffective application
- Evaluation fee refunded
- Applicant loses application fee

If the applicant is planning to reapply, ensure that the application fulfils the criteria to obtain effective application. If ARTG registration is not done, the supply, export or import of the medicinal product is lawfully not allowed.

Step 10: Evaluating and requesting information

Any additional information requested during evaluation step is provided by the applicant.

OTC medicine application evaluation

In evaluation process:

- Assess the information and data
- Response to the queries or requests information.
- Findings document.

Time frame for evaluation

OTC medicine application should be evaluated within specified time schedule.

These target time depends upon:

- It varies from every application level.
- Applying to TGA process time.
- Not responded within estimated time.

The clock is stopped after requesting for information and clock restarts after the applicant responds.

Additional Information Request

Additional information is requested by the agency to clarify. Maximum numbers of queries are:

- N1 and N2 application – 1 request
- N3, N4 an N5 application – 2 requests

Under section 31 Act, agency requests for additional data and the applicant has to submit the response within scheduled period. Standard response time frames provided according to that the process proceeds.

Responding to RFI: Accurate and complete information provided by the applicant as a response to RFI in a given time frame.

If the response is not complete or accurate, then the medicine will not get registered.

Preparing response: If RFI is related to modules in the dossier submitted:

- Response in electronic copy in CTD format provided.
- No extra additional data should be provided if not specifically requested.

Last date for the response to RFI: Applicant should not wait until the last date to response. Extension of due date is not given unless until a valid reason is stated. If the response was not submitted on time or partial response was submitted, the agency will continue to evaluate with the available documents.

Unsolicited Information: Spontaneously submitted information is not evaluated, unless:

- It is a new safety data negatively influencing benefit-risk review of the medicine. It is informed as soon as the information is available.

- TGA manufacturing clearance or license updates for the sites provided in application.

Advice from Expert Advisory Committee: Advice obtained from ACNM related to the issues relevant to the application.

Incorrect level application submission: If application passes screening at incorrect level and did not contain adequate information relevant to the data requirement and application level because covering letter did not state necessary information, agency will:

- Inform the applicant about the restricting the application to the level, in which it was accepted after screening.
- Evaluating the data which is necessary only for that application level.
- Advising to make changes so that criteria are met for that particular application level.[7]

Step 11: Making OTC registration decision: Before making final decision, it is better to cross-verify the details mentioned in the application and modifications made during the evaluation period.

Things to consider before decision are made:

The decision maker should:

➢ Review all the documents linked with the application submitted, including:

- The dossier and applications submitted
- Evaluated reports
- Responses to RFI
- Advice received from expert advisory committees
- Other relevant information or advice.

➢ Consider the details described about the safety, efficacy and quality of the medicine.

Step 12: Finalizing OTC registration: If the final decision is registering of medicine, a decision letter is sent to the applicant. This letter will consist of advice given by the Secretary to implement some specific conditions and standards on registration of the medicinal product, under the section 28 of the TGA. It is very important to follow those given instruction and complying with those given conditions.

If not complied then registration on ARTG is cancelled.

Australien Patent certification : It should provide patent certification under subsection 26B (1) of the TGA 1989.

After the completion of review and notification, patent certification form is signed stating that

- Medicine is registered in ARTG.
- Patent certificate downloaded from Business services. Guidance is provided to follow printing your ARTG certificate.

If registration is rejected:

- Reason is stated for the rejection of the application.
- Information on your rights to seek a review of the decision
- Australien Patent certification

The future thus promises the use of OTC medications for a wider variety of indications. It is the responsibility of the regulatory authority to 'move with the times' and amend its regulations accordingly albeit without compromising patient safety.

DISCUSSION

Based on the risk there are 5 levels of application to register an OTC medicine in Australia.

- Lower risk level: Application consisting of a OTC medicine which is identical to the existing OTC medicine or a well known and understood active ingredient.
- Higher risk level: Complex application such as OTC medicine for new indication or new active ingredients.

The application levels will have definite submission requirements and timelines. Short target times and less supporting information apply to lower risk level applications.[8, 9] Application dossier is submitted electronically in CTD (Common Technical Document) format. Once the application is received, it is determined thoroughly to check if it meets the requirements for an effective application. If application fulfils the requirements it is accepted for evaluation. At the time of

evaluation, agency may request for more information from the applicant to address those issues found in the application. Following the evaluation, the decision maker decides whether to register the OTC medicine on the ARTG. [10, 11, 12]

CONCLUSION

This study evaluated the drug registration process and requirements for registration of OTC medicines in Australia. The OTC drug approval processes in Australia and other countries differ in various aspects. Adopting a CTD format for regulatory submission and enabling electronic submission would facilitate regulatory review process by speedy review, easy communication with the applicant, reducing regulatory burden and also improving industry compliance. Applicant firstly files an application to carry out clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. The information regarding the quality, safety and efficacy of drug is submitted to regulatory authorities of Australia. The future thus promises the use of OTC medications for a wider variety of indications. It is the responsibility of the regulatory authority to 'move with the times' and amend its regulations accordingly albeit without compromising patient safety.

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