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REGULATORY REQUIREMENTS FOR APPROVAL OF OVER THE COUNTER DRUGS AS PER AUSTRAILIAN (TGA) GUIDELINES

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Abstract:

The Therapeutic Goods Administration is a Commonwealth Government agency that regulates medical devices and drugs. Prescription medicines and over-the-counter medicines which meet Australian standards of quality, safety and efficacy are included on the Australian Register of Therapeutic Goods. Non-prescription or OTC medicines are considered to be 'low risk' in comparison with prescription medicines. They are evaluated for quality, safety and efficacy by the TGA and the Medicines Evaluation Committee, in accordance with the Australian Regulatory Guidelines for OTC Medicines, 1 July 2003 before they may be registered on the ARTG. TGA is monitoring the all aspects for drug approvals and monitoring the human health. As per the TGA act all the medicines are classified in to prescription, non-prescription medicines and export only medicines. TGA act states those medicines require registering or listing at TGA. Registration and listing requirements are based on the level of risk. All prescription and some non-prescription medicines are required to register at TGA and some non-prescription medicines and export only medicines are need to list at TGA. TGA has adopted the most of the EDQM guidelines for medicines. Post marketing activities of the TGA include investigating reports of problems, laboratory testing of products on the market, and monitoring to ensure compliance with the legislation.

Keywords: *TGA, ARTG, OTC, Non-prescription.*

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INTRODUCTION:

'Therapeutic goods are defined in the Act. All therapeutic goods (other than those which are exempt) must be registered or listed in the Australian Register of Therapeutic Goods (ARTG) before they can be imported, exported, manufactured or supplied in Australia. Therapeutic goods are divided into 'medicines' and 'medical devices'. Some 'medicines' are limited to prescription-only while others are available without a prescription. Non-prescription medicines may be 'complementary medicines' or 'OTC medicines' and may be 'listed' or 'registered' in the ARTG [1].

Therapeutic Goods Administration (TGA):

The Therapeutic Goods Administration (TGA) is the regulatory agency for medicines, medical devices, blood and tissues in Australia. Australian Register of Therapeutic Goods (ARTG) is a database and contains the information of therapeutic goods. Figure-1 represents the complete organogram of TGA [2-5].

Australian TGA advisory committee:

Australian therapeutic goods administration has different advisory committees for medicines and devices evaluation, approval and monitoring the activities of safety and efficacy. The TGA advisory committees are:

1. Australian Drug Evaluation Committee (ADEC): Prescription medicines
2. Adverse Drug Reactions Advisory Committee (ADRAC)
3. Medicines Evaluation Committee (MEC): OTC medicines
4. Complementary Medicines Evaluation Committee (CMEC): Complementary medcines
5. Therapeutic Devices evaluation Committee (TDEC): Medical devices
6. National Drugs and Poisons Scheduling Committee (NDPSC)
7. Therapeutic Goods Committee (TGC)

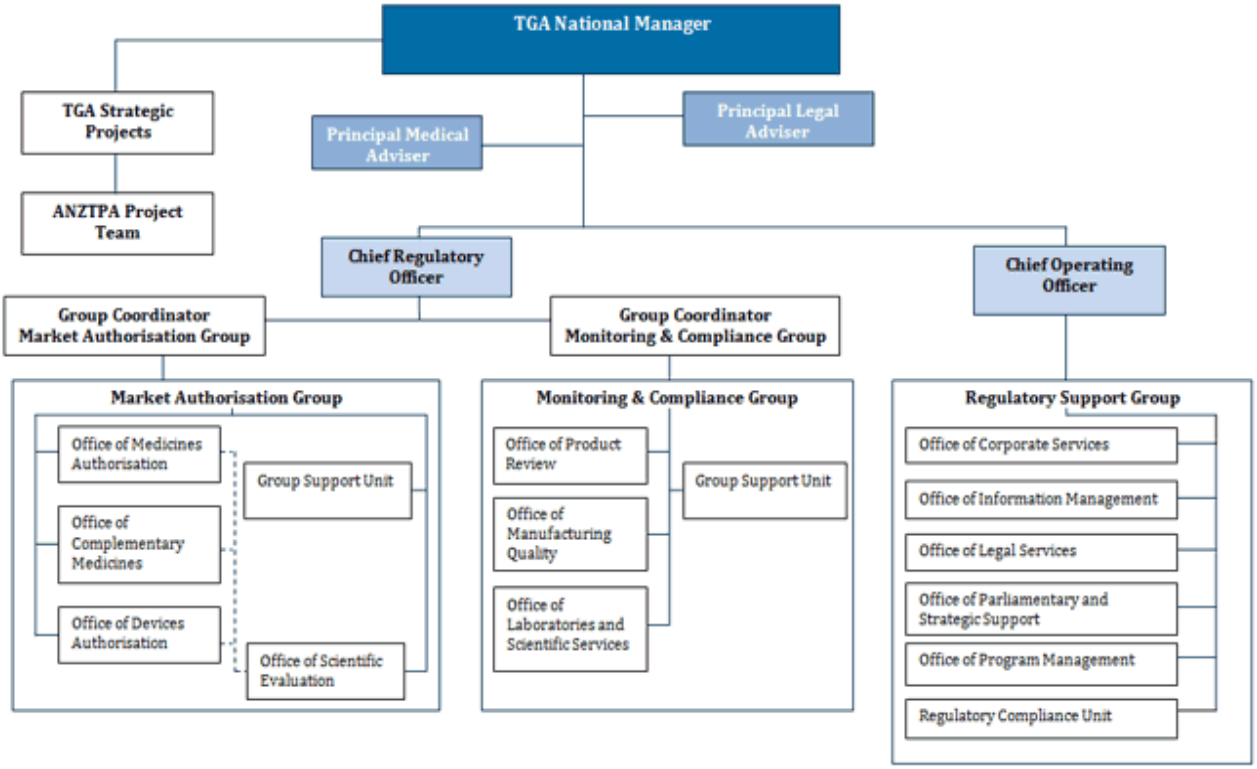

Fig 1: Organogram of Therapeutic Goods Administration

Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) [6-8]:

The SUSMP, is established under Section 52D of the Therapeutic Goods Act 1989, and is a compilation of the decisions made under Section 52D of the same Act. The SUSMP should be read in conjunction with the Scheduling Policy Framework (SPF) of the National Coordinating Committee on Therapeutic Goods. It is a document used in the regulation of drugs and poisons in Australia. It is produced by the National Drugs and Poisons Scheduling Committee (NDPSC), a committee of the TGA. As per the TGA act, The SUSDP has scheduled the all substances, their classifications, labelling and packaging requirements. The classification takes into account a substance's toxicity profile, pattern of use, indications, product formulation and dosage, potential for abuse and need for access. Medicines listed in the SUSDP are considered high-risk.

THERAPEUTIC GOODS:

As per the TGA act regulations all type of goods are divided in to medicines and devices. Medicines are again divided in to:

- Prescription medicines,
- Non-prescription medicines
- Export only medicines.

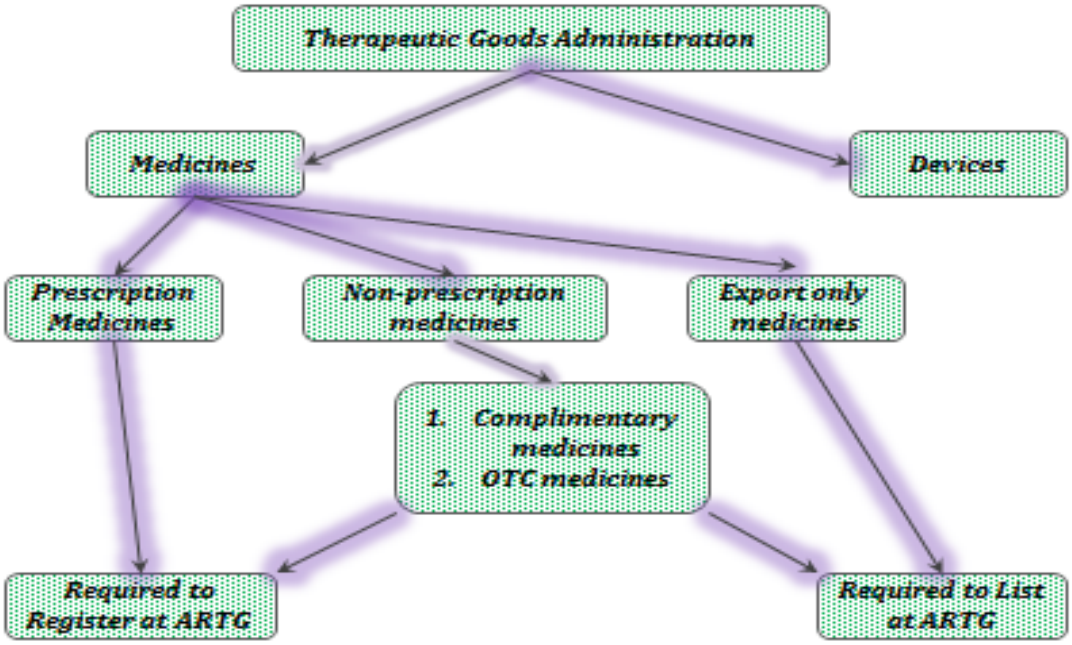

Fig 2: TGA medicines and Devices

Prescription medicines (PM): [9-12]

Prescription medicines are high-risk medicines that contain ingredients described in Schedule 4 and 8 or Schedule 9 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) and are available by prescription only.

- The Drug Safety Evaluation Board (DSEB) evaluates the majority of prescription medicine applications. **Ex:** insulin for diabetics.
- All prescription medicines must be registered in TGA.

Non-prescription medicines (NPM):

NPM are classified in to two categories that are,

A. OTC Medicines

B. Complementary medicines

OTC medicines:

An over the counter (OTC) medicine is a therapeutic good mentioned in Part 3 of Schedule 10 of the Therapeutic Goods Act 1989 that does not meet the criteria for mention in Schedule 4, 8 or 9 of the Poisons Standard. **Ex:** Antiseptics, Sunscreens. The Non-prescription Medicines Branch (NPMB) is responsible for evaluating OTC medicines. The majority of OTC medicines are non-prescription registered medicines and examples include mild analgesics, cough/cold preparations and antifungal creams.

Complementary medicines (CM) [13]:

CM is consisting wholly or principally of one or more designated active ingredients, each of which

has a clearly established identity and for traditional use. Complementary medicines are also known as 'traditional' or 'alternative' medicines. **Ex:** Vitamins, minerals, herbals, and homoeopathic products.

- The Office of Complementary Medicines (OCM) is responsible for the evaluation of complementary medicines at the TGA.
- Complementary medicines can be regulated as listed medicines.
- Complementary medicines are generally available for use in self-medication by consumers and can be obtained from retail outlets such as pharmacies, supermarkets and health food stores. While the majority of complementary medicines are indicated for the relief of symptoms of minor, self-limiting conditions, many are indicated for maintaining health and wellbeing, or the promotion or enhancement of health.

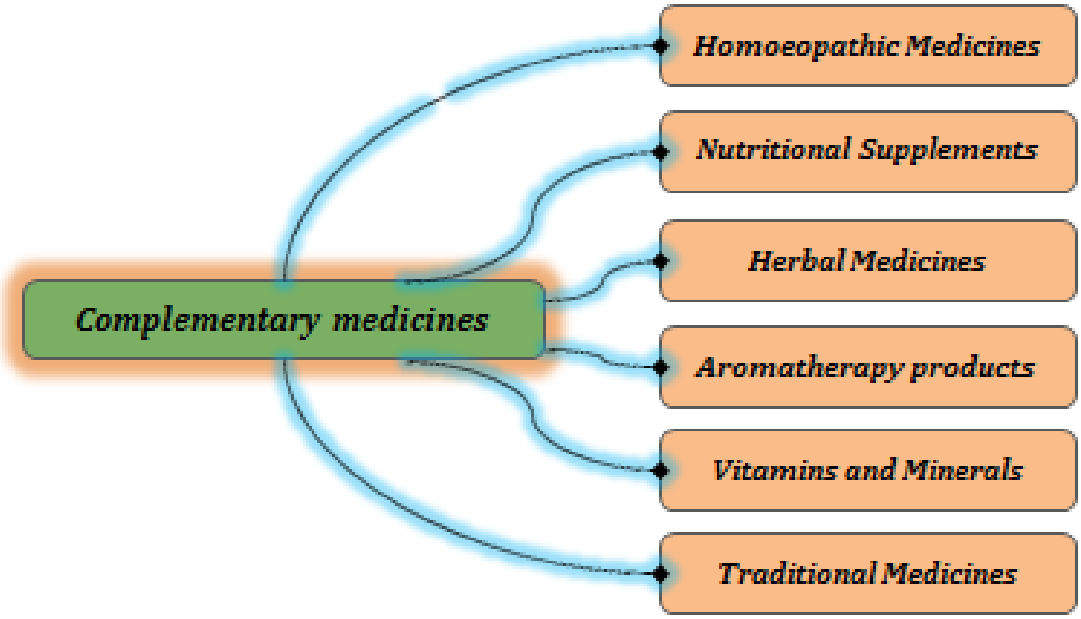

Fig 3: Sub group medicines in Complementary medicines

Export only medicines: Products containing substances, quantities of substances or labels without mandatory warning statements required for listing for supply in Australia which would require registration for domestic supply will be assessed under Section 26 of the Act.

Eg: Commercial export of medicines**,** Export of medicines for donation or humanitarian purposes**,** Export of human body fluids/ tissue**,** Export of medical devices.

Over-the-counter (OTC) medicines [14-16]

Over-the-counter (OTC) medicines are drugs you can buy without a prescription. Some OTC medicines relieve aches, pains and itches. Some prevent or cure diseases, like tooth decay and athlete's foot. Others help manage recurring problems, like migraines.

OTC medicines can treat or prevent other health problems here are some examples:

Allergy Prevention & Treatment, Antacids and Acid Reducers, Antihistamines, Antidiarrheal and Laxatives, Anti-itch Lotions and Creams, Anti-fungal, Asthma, Condoms and other contraceptive devices, Contact Lenses Solutions, Cough Suppressants, Decongestant/ Nasal Decongestant and Cold Remedies, Eye Drops for Allergy/Cold Relief, Internal Analgesic/antipyretic, Liniments, Menstrual Cycle Medications, Migraine, Nicotine Gum or Patches and Smoking Cessation Aids, Toothache and teething pain relievers, Wart removal medications.

Pain and fever are two of the most common reasons people use OTC medicines. There are five active ingredients used to reduce fever and to treat mild aches and pains caused by headaches, muscle aches, backaches, toothaches, menstrual cramps, and the common cold. Acetaminophen, Aspirin, Ibuprofen, Naproxen sodium, Ketoprofen. The last four active ingredients are all members of a drug family called non-steroidal anti-inflammatory drugs, or NSAIDs. Like over-the-counter medicines, dietary supplements can be bought off the shelf without a doctor's order (prescription). They can come as tablets, capsules, soft gels, liquids, or powders, so they may also look a lot like medicine you take by mouth. But dietary

supplements aren't OTC medicines. Dietary supplements are taken by mouth to add to the food you eat. Dietary supplements may contain vitamins, minerals, herbs, and other ingredients.

The Current Over-the-Counter Medicine Label [17-19]:

Reading the product label is the most important part of taking care of yourself or your family when using over-the-counter (OTC) medicines (available without a prescription). This is especially true because many OTC medicines are taken without seeing a doctor. The OTC medicine label has always contained important usage and safety information for consumers, but now that information will be more consistent and even easier to read and to understand. The Therapeutic Goods of Administration(TGA) has issued a regulation to make sure the labels on all OTC medicines (from a tube of fluoride toothpaste to a bottle of cough syrup) have information listed in the same order; are arranged in a simpler eye-catching, consistent style; and may contain easier to understand words. While the new labels on a majority of OTC drug products will be appearing on store shelves soon, some products and companies have additional time to comply with the new labelling regulations. If you read the OTC medicine label and still have questions about the product, talk to your doctor, pharmacist, or other health care professional.

Tamper-Evident Packaging [20]:

The makers of OTC medicines widely use tamper-evident packaging for their products. This is to help protect consumers against possible criminal tampering. Drug products with tamper-evident packaging have a statement on the packaging describing this safety feature. It is always important to inspect the outer packaging before you buy an OTC drug product and to look at the product again before you take it.

METHODOLOGY:

AUSTRALIAN REGULATIONS OF OVER THE COUNTER MEDICINES:

Over-the-counter medicines (OTC) are medicines that are not prescription medicines and are not complementary medicines. OTC medicines can be supplied as: pharmacy medicines (included in Schedule 2 to the Poisons Standard); or pharmacist-only medicines (included in Schedule 3 to the Poisons Standard); or general sales medicines that are not included in any of the Schedules to the Poisons Standard. Medicines are grouped into schedules according to the appropriate level of regulatory control over their availability to consumers.

The TGA regulates over the counter medicines:

The Act requires that all medical products to be imported into, supplied in, or exported from Australia (other than those that are exempt) must be included in the Australian Register of Therapeutic Goods (ARTG).

In order for a medicine to be included in the Australian Register of Therapeutic Goods, a sponsoring company is required to lodge an application to the TGA. The TGA has developed the Australian Regulatory Guidelines for OTC Medicines (ARGOM) to assist sponsors of OTC medicines to meet their legislative obligations.

OTC medicines can be registered or listed on the Australian Register of Therapeutic Goods, depending on the level of risk associated with making the product available and accessible to consumers. Registered OTC medicines are considered to be of lower risk than prescription medicines, but they still require an appropriate level of scrutiny.

Registering an OTC medicine in the ARTG:

An application to register an OTC medicine is submitted on-line through the Services facility. The online application needs to be accompanied by Data that support the safety, quality and efficacy of the product, Copies of all labelling, Copies of Product Information and Consumer Medicine Information documents, Completed forms, The payment of fees. The ARGOM contains detailed information to assist sponsors to prepare applications and describes the information to be supplied with applications for registration of new OTC medicines for human use in Australia, or to vary existing medicine registrations.

The decision to register an OTC medicine:

When making the decision to register an OTC medicine, the decision maker takes into account all of the advice given by the TGA scientific and medical experts and the advice given to it by the Advisory Committee on Non-prescription Medicines, along with the information provided by the sponsor.

Appeal process:

If the sponsor does not agree with the decision made by the TGA, the Act provides a comprehensive system for review of administrative decisions. The appeal mechanisms are described in more detail in the ARGOM. Briefly, the formal appeal process usually involves:An appeal under Section 60 of the Act. This can be followed by: An appeal to the Administrative Appeals tribunal (AAT).

Applications to change conditions of registration:
As per the TGA regulations high risk medicines should be registered and low risk medicine need to list at ARTG for marketing the drug products in Australian region. Registered and listed medicines categories are mentioned. After approving the medicine, it can get the assigned number either an AUST R number (registered) or AUST L number (listed medicines). They include all prescription only medicines and many over-the-counter products such as those for pain relief, coughs and colds and antiseptic creams. It will assess for safety, quality and effectiveness. Prescription only medicines do not display their purpose on the label as the decision for using those lies with a doctor; however, over -the-counter medicines must have a purpose displayed. Once a product has been registered, the sponsor can make further applications to change the conditions of registration. Some examples of changes that might be sought include Label changes, Shelf life changes, Formulation changes, Quality control changes, Changes to indications, Changes to directions for use. A 'Change Table' is included in the ARGOM that provides details of changes that can be made and the information required to support a particular type of change.

Registered medicines:
Registered medicines are assessed by the TGA for quality, safety and efficacy, All prescription medicines are registered, Most over-the-counter medicines are registered, Some complementary medicines are registered.

Listing an OTC medicine in the ARTG:
The process involved in listing an OTC medicine is different to that associated with registering a medicine. Further information on requirements relating to listing of OTC medicines on the ARTG can be found in the Australian Regulatory Guidelines for Complementary Medicines.

Listed medicines:
Listed medicines are assessed by the TGA for quality and safety but not efficacy, some over-the-counter medicines are listed, Most complementary medicines are listed.

AUST L medicines:
They are used for minor health problems and are reviewed for safety and quality. They include sunscreens over SPF4 and many vitamins, mineral, herbal and homoeopathic products.

Complementary Medicines Listing:
Complementary medicines are listed through Electronic Listing Facility (ELF) by creating the E-business account. Office of Complementary medicines will evaluate the complementary medicines. After creating the E-business account, then applicant need to give the complete information of the product like, reference product details, product name, type, formulation details including dosage form, route of administration, container type, container volume, container closure, maximum single dose, maximum daily dose, minimum weight of each dosage, components and their quantities, manufacturer's details including whether the manufacturer is Australian or an overseas manufacturer. If applicant is overseas manufacturer then need to submit the clearance ID or GMP Reference number. When you submit your application, it becomes available for view on the ARTG listing. A random selection of submissions is subject to review by the OCM. They may request to see information relating to the presentation, advertising materials, or information about product manufacture. Listing procedures are clearly represented in fig 5.

OTC Medicines Listing:
OTC medicines are listed by using e-business account with OTC Products Application Lodgment (OPAL) system. In order to create a listing of OTC medicines need to submit the following information, Applicant reference details and Product name and any relevant export names, Product type, Dosage form, route of administration, container type and closure and Pack size, Payment exemption number (if you received one from the TGA), Label name and export names (if applicable), Proposed therapeutic indications, Ingredients including whether the ingredient is active, an excipient, active homeopathic or a proprietary ingredient Components and their quantities, Manufacturer's details including whether the manufacturer is Australian or an overseas manufacturer. If an overseas manufacturer is selected then clearance ID or GMP reference number must be provided, Indication of supporting data that has been sent to the TGA including chemical, stability, toxicological, clinical or other data, Printed labeling and packaging materials, When you submit your application, it becomes available for view on the ARTG listing.

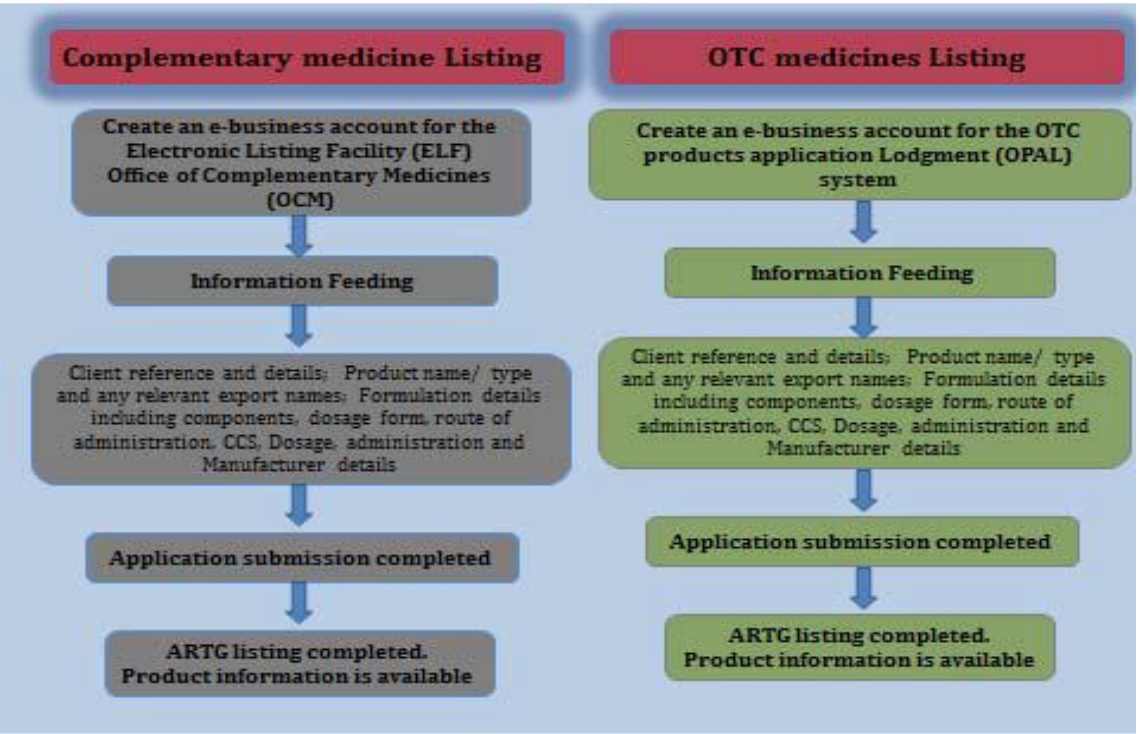

Fig 4: Listing procedure of Complementary and OTC medicines at ARTG

Complementary Medicines Registration:

Complementary medicines can be registered at ARTG, for registration of complementary medicines the application needs to submit at chemicals and non-prescription medicines branch (CNMB). After paying the application fee TGA will issue the TGA ID number for application. Office of Complementary medicines (OCM) will evaluate the application and prepare the evaluation report. OCM will submit the evaluation report to Complementary Medicines Evaluation Committee (CMEC) for additional evaluation and finally the report sent to TGA. If the report is positive, then TGA will give the approval for the product. If the report is negative, then applicant can appealed/ reapply to the TGA. Fig 6 represents the flow of complementary medicines approval procedure.

OTC Medicines Registration:

OTC medicines registration procedure also same with the complementary medicines like application submission, TGA ID number issue and evaluation report. OTC application will be evaluated by Medicines Evaluation Committee (MEC). Figure 7 represents the OTC drug approval at TGA.

Monitoring the safety of OTC products:

The TGA has a multi-faceted program for monitoring therapeutic products that are on the market. The TGA has a problem reporting system for reporting: Medicine deficiency or defect, Adverse reaction to a medicine, Random and targeted sampling of approved products is undertaken by the TGA Laboratories, Random and targeted desk-based audits of listed products, Audits of GMP, Controls for the advertising of therapeutic goods. Once a problem has been identified possible regulatory actions vary from continued monitoring to withdrawing the product from the market. Actions the TGA can take include: Informing health care professionals and consumers about the risks of using the product, Re-assessing the benefit-risk profile, requiring product labelling changes, Requiring design or manufacturing change, Recalling products, Removal of the product from the ARTG.

Guidelines on regulatory presentation aspects of OTC applications:

The presentation of OTC medicines is critical for their safe use. It is defined in the Therapeutic Goods Act 1989 (Section 3) as "the way in which the goods are presented for supply, including matters relating to the name of the goods, the labelling and packaging of the goods and any advertising or other informational material associated with the goods". Presentation is one of the factors that must be taken into account by the TGA delegate in making decisions on the registration of medicines (Section 25). The Act states that the presentation of a medicine is unacceptable: If it is capable of being misleading or confusing as to the content or proper use of the goods, If it states or

suggests that the goods have ingredients, components or characteristics that they do not have, If a name applied to the goods is the same as the name applied to other therapeutic goods that are supplied in Australia where those other goods contain additional or different therapeutically active ingredients; or If the label of the goods does not declare the presence of a therapeutically active ingredient; or If a form of presentation of the goods may lead to unsafe use of the goods or suggests a purpose that is not in accordance with conditions applicable to the supply of the goods in Australia. This Chapter describes various aspects of presentation and gives guidance on what constitutes acceptable presentation for OTC medicines. It is divided into five sections as follows: Product name, Labelling, Product Information, Consumer Medicine Information, Changes to scheduling.

Product Information (PI):

Product Information (PI) is a term used to describe the technical information approved by the TGA and intended for distribution to health professionals. It is often distributed via publications such as MIMS and the APP Guide. The PI should present a scientific, objective account of the product's usefulness and limitations, consistent with the data supporting the application, for the benefit of health professionals recommending or prescribing the product. It must not include promotional material (refer to the ASMI's Code of Practice1 for further information regarding promotional material). All applications to register 'Pharmacist Only Medicines' (Schedule 3) must be accompanied by a draft PI document which will be evaluated as part of the application. The draft PI should be annotated to give references for all technical information (eg. doses, contraindications, precautions, adverse reactions). For those products that have moved from 'Prescription Only Medicine' (Schedule 4) status, where no changes have been made to the TGA-approved PI, a copy of the PI should be included in the application, together with an assurance that no changes have been made. A draft PI should be submitted for approval by 31 December 2003 for those 'Pharmacist Only Medicine' (Schedule 3) products which were approved for registration before 4 July 1995.

Product description:

This section should include a description of the dosage form a list of the active ingredients expressed quantitatively; and a list of the excipients expressed qualitatively; and, for a new chemical entity a description of the relevant physical and chemical characteristics of the active ingredient(s) and the formulation.

Pharmacology:

A description of the pharmacology, including pharmacokinetics and pharmacological actions. Pharmacokinetic information should be relevant to the route of administration of the product (eg. oral, topical). For products containing new chemical entities or new combinations of active ingredients or with new indications approved on the basis of clinical trials, a subsection on clinical trials should be included.

Indications:

The therapeutic indications of the product. These must be consistent with the indications to be included in the ARTG.

Contraindications:

Conditions for which, or under which, the product should not be used. This section would generally include a reference to hypersensitivity to any of the ingredients or to active ingredients of the same pharmacological/chemical class (where relevant).

Precautions:

Precautions or actions that must be taken to avoid or minimise anticipated hazards. This section should include information under the subheadings Use in pregnancy, Use in lactation and Interactions with other drugs. Other subsections, such as Use in children, Use in the elderly, Use in renal/hepatic impairment and Carcinogenic and mutagenic potential, should be included where this information could be relevant. Under the subheading Use in pregnancy, the proposed or approved Australian Pregnancy Categorisation, any relevant standard text and other information consistent with this categorisation should be included. For multi-component products, only the highest pregnancy category for the active ingredients should be given.

Consumer Medicine Information (CMI):

The Therapeutic Goods Regulations 1990 require that sponsors supply Consumer Medicine Information (CMI) with all 'Pharmacist Only Medicine' (Schedule 3) products approved for registration after 4 July 1995. All 'Pharmacist Only Medicine' (Schedule 3) products will require a CMI from 1 January 2004. The CMI must be Written in English, Clearly legible, Written in language that can easily be understood by patients, and Consistent with the PI. The CMI must comply with the requirements specified in Schedule 13 to the Regulations, although the information does not have to be set out as listed there. CMIs must not include promotional material (refer to the ASMI Code of Practice1 for further information regarding promotional material). The sponsor is responsible for writing, updating, and

distributing CMI to the point of supply of a medicine to the patient. The CMI may be provided in the primary pack (eg. as a leaflet in the carton) or 'in another manner' (eg. in electronic form via pharmacy computers).

Changes to scheduling:

When the classification of a product is changed following a decision of the National Drugs and Poisons Schedule Committee (NDPSC), changes will be required to labels and possibly package inserts, PI and CMI. The regulatory responsibility for dealing with changes to a product that is currently 'Prescription Only Medicine' (Schedule 4) rests with the TGA's Drug Safety and Evaluation Branch. However, the Non-prescription Medicines Branch (NPMB) will consider applications for changes to these products when the NDPSC has made an initial decision to move the medicine to a non-prescription category. If the decision is not confirmed by the NDPSC, the application must be withdrawn.. The sponsor is responsible for ensuring that labelling and any other changes arising out of a rescheduling decision are either notified to or approved by the NPMB.

Guidelines on efficacy and safety aspects of OTC applications:

The Therapeutic Goods Act 1989 requires that applications for registration be evaluated "having regard to whether the quality **safety** and **efficacy** of the goods for the purposes for which they are to be used have been satisfactorily established". This Chapter sets out the information that should be submitted to support the efficacy and safety of a registrable OTC medicine. Deviations from these guidelines may be accepted provided sound justification is given. For full dossiers, sponsors are encouraged to submit according to the CTD (Common Technical Document) format or in the 'old' European Union (EU) format. Details of these guidelines can be found on the TGA.

Well documented active ingredients:

Where adequate information on the use of each active ingredient in the formulation is contained in standard reference texts and/or these guidelines, further information on the safety and efficacy of the product is not required (eg. paracetamol administered orally at a dose of 500 mg to 1g every 4 to 6 hours for pain relief in adults). The majority of OTC medicines will fall into this category. The following are examples of reference texts which are usually acceptable as sources of information on the safety, efficacy and dosage regimen of ingredients in an OTC medicine: Martindale: The complete drug reference, Sweetman SC (Ed.), Pharmaceutical Press, UK, Handbook of nonprescription drugs, American Pharmaceutical Association, USA, Remington's Pharmaceutical sciences, Gennaro AR (Ed.), Mack Publishing Company, USA, Handbook of pharmaceutical excipients, Kibbe AH (Ed.), American Pharmaceutical Association, USA and Pharmaceutical Press, UK, AHFS Drug information, McEvoy GK (Ed.), American Society of Health System Pharmacists, USA.

Products containing active ingredients that are not well documented:

• Where the use of any ingredient is not well documented in standard reference texts, further evidence of safety and efficacy will be required. Unpublished clinical studies with significant supporting data (not summary information) are acceptable as well as reports published in 'peer reviewed' journals. Sponsors should make sure that any studies that are provided are of a sound scientific standard. Information on the process for approval of a 'new' active or excipient substance (ie. one which is not included in any products currently entered in the register for supply in Australia) is included in Chapter 6B, new substances. If there is inadequate evidence of efficacy and/or safety in the published scientific literature for the active ingredients or the product or for the proposed indication or dosage, it will be necessary to provide reports of clinical trials that the sponsor has conducted to establish the efficacy and safety of the product proposed for registration. These trials should be performed and reported according to established ethical, scientific and clinical practice.

The submission:

Whether the submission is bibliographic or in the form of specific trials conducted on the product proposed for registration, it should include: An index of contents, an overview referenced to the submission by page number, An expert report referenced to the submission by page number, Full copies (not abstracts) of all relevant reports and clinical trials.

Bibliographic submissions:

A bibliographic submission may be appropriate where adequate evidence of safety and efficacy is available in the published scientific literature. A bibliographic submission should represent a comprehensive and unbiased review of the available literature in relation to the application using a medical/scientific database such as Medline. For older drugs or where relevant reports are few, the search may need to include all records in Medline and/or other databases such as Embase. Details of the search strategy should be included (preferably on disk as well as hard copy) to enable critical analysis by TGA librarians or duplication of the search if necessary. Published reports of clinical trials should

only be included in the submission where: The trials are conducted using the same active ingredient(s) with a similar dosage regimen, dose form and route of administration to the product proposed for registration, The trials are reported in sufficient detail to allow an independent assessment of the results (including methods and a statistical analysis of the results) in relation to the efficacy and safety of the product proposed for registration, Trials should be excluded if they are conducted on different actives, for different indications or different routes of administration or are poorly conducted or reported or not of sufficient power to produce statistically significant results, Well-conducted, published reviews may be of assistance as supporting material and should be included where relevant, A list or table of reports which have been excluded from consideration should be presented together with reasons for the exclusion. All relevant, well-conducted and reported trials should be included regardless of whether their findings are adverse to the product proposed for registration.

The overview:

The overview should include a table with summary details of all reports which are present in the submission including: Abbreviated publication details (author(s) and journal reference) where relevant, The type of report (eg. double blind, randomised, multi-centre, cross-over trial), The number of subjects included in the trial, The duration of the trial, A brief statement of conclusions in terms of efficacy and safety; and Details of the dose form, formulation and dosage schedule of the product used in the trial. The sponsor should indicate those studies that are considered pivotal to the submission, and their reasons for doing so. Data from randomised, double blind, controlled studies would be expected to be given greater weight than data from non-randomised, uncontrolled or open studies. With regard to safety data, there should also be tabulation and appreciation of all adverse events (including abnormal laboratory values, drug interactions etc) for all documented clinical studies and any adverse events which have been reported to the sponsor. All submitted data/papers etc should be cross-referenced to the submission to allow the papers to be located easily. For bibliographic submissions, the overview should also include a list or table of reports, which have been excluded from consideration together with reasons for the exclusion.

'Generic' products:

Medicines those are essentially similar to an 'innovator product' may be designated as 'generics' or 'branded generics'. An 'innovator' product (also known as the 'originator' product) is a medicinal product authorised and marketed on the basis of a full dossier which may include chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. A medicinal product is essentially similar to an 'innovator' product, which has been approved in Australia on the basis of a full dossier, where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active substances, having the same pharmaceutical form, and being bioequivalent (unless it is apparent in the light of scientific knowledge that it differs from the 'innovator' product as regards to safety and efficacy). Where the clinical data provided with the originator product are not 'protected' (Section 25A of the Therapeutic Goods Act 1989 refers), the TGA will accept applications to register 'generic' products without clinical data on the basis of data that demonstrate that the 'generic' and 'innovator' products are bioequivalent, or a justification that bioequivalence data are not required. The requirements for bioequivalence data and justification for not providing bioequivalence data are set out in the EU guidelines.

Products with a 'new' dosage form:

Products with different dosage forms are not 'generics' as defined in 'Generic' products above. However, by extension, the concept of essential similarity also applies to different immediate release oral dosage forms (eg. tablets and capsules) that contain the same active ingredients. Where a product is proposed in a 'new' immediate release oral dosage form (eg. an effervescent tablet where only capsules are currently included in the ARTG), and the clinical data provided with the 'innovator' product are not 'protected' (Section 25A of the Therapeutic Goods Act 1989 refers), the TGA will accept applications to register the 'new' product without clinical data on the basis of data that demonstrate that the 'new' and 'innovator' products are bioequivalent, or a justification that bioequivalence data are not required (as stated in the EU guideline, Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)1).

Post-marketing experience:

Where the active ingredient is included in products currently marketed in Australia it is usually not necessary to provide post-marketing data. However, if the product is not marketed in Australia it may be relevant to include details of adverse drug reaction reports from the relevant authorities and Periodic Safety Update Reports (PSURs) where available.

Topical products:

Where the efficacy of the product is likely to be formulation dependent (eg. Head lice preparations, surgical scrubs, skin disinfectants, topical minoxidil), the efficacy of the particular formulation proposed

for registration will need to be established. Registered OTC medicines are evaluated in terms of quality, safety and efficacy. Some topical OTC medicines have a long history of use in many different formulations and their efficacy is well accepted. Examples include salicylic acid for treatment of warts and benzoyl peroxide for treatment of acne. Efficacy data are generally not required to support the registration of such products. The Medicines Evaluation Committee (MEC) has identified other groups of topical products where the efficacy and/or safety of the product is influenced by the formulation. In these cases, a change in non-active ingredients may affect the extent of penetration of the active substance and therefore efficacy data is usually required before the product is recommended for approval. Because OTC medicines are so diverse, the committee has advised a flexible approach in which the need for data should be determined on a case-by-case basis.

The following categories of OTCs have been identified by the MEC as being formulation-dependent in terms of efficacy and/or safety: Head lice preparations, Aciclovir for treatment of cold sores, Minoxidil, NSAIDs, Antibacterial hand washes, surgical scrubs and antiseptics (other than for the 'first aid' treatment of minor wounds), Antidandruff shampoos containing imidazole antifungals as active ingredients, Dithranol preparations, Products containing glyceryl trinitrate, Terbinafine, This list will be updated by the TGA as new categories are identified by the MEC as being formulation dependent.

Review of decisions:

The Medicines Evaluation Committee – 'opportunity to be heard':

Where an application is under evaluation by the MEC and it appears that rejection is to be recommended, the committee has established a procedure whereby the sponsor is invited to appear at a committee meeting and present a submission in support of the application. This is not a formal appeal mechanism but is simply a means of ensuring that you have an opportunity to personally present a case to the committee. It has no bearing on any subsequent right of appeal to the Minister or Administrative Appeals Tribunal if the application is rejected.

Guidelines on post market surveillance

Products which are already being marketed are subject to a number of levels of surveillance by the TGA.

The sampling program:

The TGA Laboratories undertake a continuous sampling program in all states of Australia. Products are purchased in the marketplace, or obtained from manufacturers or sponsors, and subjected to analysis and regulatory scrutiny. Products not meeting the required standards may be subject to corrective action, recall or removal from the register.

Good Manufacturing Practice (GMP) audits:

Manufacturers of therapeutic goods in Australia are subject to regular inspections by the TGA's Manufacturer Assessment Section. Details of requirements for manufacture are specified in the Australian Code of Good Manufacturing Practice for medicinal products1.The evaluation committees may request that particular problems encountered during the evaluation process be followed up with the manufacturer during subsequent GMP audits.

'Grandfathered' products:

Those products entered in the ARTG under the 'grandfather' provisions of the Act may be subject to future evaluation to determine whether they should remain on the Register. If you are the sponsor of such a product, you should ensure that you hold evidence to substantiate the quality, safety and efficacy of the product. You should also ensure that an ongoing stability testing program is in place for each product under your control.

The Surveillance Unit:

The Surveillance Unit investigates breaches of the legislation and coordinates prosecutions.

Problem reporting and recall:

Recalls of therapeutic goods are coordinated by the TGA's Recalls Section. Information can be obtained from the TGA.

MEC Guidelines:

This Chapter represents a summary of the views of the TGA and the Medicines Evaluation Committee (MEC) with respect to OTC medicines (including new substances) at the time of publication and is intended to assist sponsors in submitting acceptable applications for registration of OTC medicines. Products are assessed according to the best clinical and scientific information at the time of evaluation. If you believe that a particular application warrants a departure from the Guidelines, a justification should be submitted with the application. The guidelines are not mandatory for existing products. However sponsors of existing products are encouraged to update labels to comply with the relevant guidelines when submitting label variation applications Suggested statements (for labelling purposes) are written in this chapter of the guideline as dot points and in italics. Comments relating to these suggested statements are in normal font and are not intended for inclusion on the labels.

OTC medicine monographs:

OTC 'N2' applications will be accepted for evaluation by the TGA from 1 October 2013, as part of a 12

month trial of the new application route.The N2 application route is available for proposed medicines that comply fully with a specific OTC medicine monograph and with associated general requirements. N2 applications involve reduced requirements for data assessment by the TGA and consequently shorter evaluation timelines. In lieu of providing full supporting data with the application, sponsors need to complete a list of assurances confirming that the product meets the specified requirements. Post-market monitoring of products approved via the N2 route will be conducted by the TGA to gain assurance regarding sponsor compliance with requirements.

OTC medicine monograph: Pholcodine:

This OTC Medicine Monograph outlines the requirements for Australian market authorisation of oral liquid preparations containing pholcodine as a single active ingredient when applied for as an OTC new medicine N2 application.

OTC medicine monograph: Topical nasal decongestants

This OTC Medicine Monograph outlines the requirements for Australian market authorisation of topical nasal decongestant medicines containing oxymetazoline hydrochloride or xylometazoline hydrochloride as a single active ingredient when applied for as an OTC New Medicine N2 application.

OTC medicine monograph: Aspirin tablets for oral use

This OTC Medicine Monograph outlines the requirements for Australian market authorisation of tablets containing aspirin as a single active ingredient when applied for as an OTC New Medicine N2 application.

OTC medicine monograph: Paracetamol for oral use

This OTC Medicine Monograph outlines the requirements for Australian market authorisation of oral medicines containing paracetamol as a single active ingredient when applied for as an OTC New Medicine N2 application.

RESULTS AND DISCUSSION:

The submission:

In general, a submission for registration of an OTC medicine should include the following components: Specifications and stability data as specified in Quality, Copies of all labelling including package inserts, A copy of the Product Information (PI) and Consumer Medicine Information, (CMI) documents where relevant Presentation Efficacy and safety information where relevant Efficacy and safety and New substances.

The evaluation process:

Instructions for lodging applications are given on the application form. On receipt at the TGA, applications are screened to ensure that they comply with the following criteria: Correct fees paid, Form filled correctly, All necessary data present (including stability and validation data Quality – Stability testing), All necessary attachments present (eg. labels, PI and CMI documents, where relevant), Information on the GMP status of manufacturer(s) provided (usually in the form of a clearance letter from the TGA's Manufacturer Assessment Section), If any of these factors are absent, the application may be returned to the sponsor on the basis that "An application is not effective unless: the applicant has delivered such information as will allow the determination of the application" (Section 23 of the Act). In such cases the application fee is not eligible for refund but the evaluation fee may be refunded on the basis that evaluation had not commenced.The sponsor may also be contacted at this stage (before evaluation commences) if, in the opinion of a senior evaluator, the application is unlikely to be approved. In such cases the sponsor will be given the option of withdrawing the application (with loss of the application fee but not the evaluation fee) or requesting that the application proceed regardless. Where a product is required to be sterile (eg. eye drops), the sterility and preservative efficacy aspects of the product will be evaluated concurrently by the TGA's Microbiology Section. The microbiology evaluator may contact the sponsor directly if there are any issues relating to this part of the evaluation. Where a product contains ingredients of animal origin the sponsor must comply with the requirements specified under Ingredients of human or animal origin. Applications for new products may be referred to the Medicines Evaluation Committee (MEC) for assessment and recommendation. However, the delegate may choose to make a decision on the basis of information already to hand without advice from the committee. For example: Where the new product is a 'clone' (i.e. identical in all respects except for the name) of an existing evaluated product (with the consent of the sponsor of the 'parent' product), Where the new product is similar to products which have been evaluated in the past (eg. a new brand of paracetamol tablets) and bioequivalence data are not required, Where all issues have been dealt with by the MEC in the past and the Delegate does not require further advice from the committee, Applications which are presidential or which contain issues that have not been fully addressed in the past will usually be referred to the MEC, The MEC comprises members with expertise

and experience in medicine, Pediatric medicine, clinical pharmacology, pharmacy, toxicology, microbiology, regulatory affairs, pharmaceutical chemistry, manufacturing and forensic pharmacy.
Its secretariat is provided by the OTC Medicines Section and meetings are held on a two-monthly basis. Further details of the composition and terms of reference of the MEC can be found on the TGA website1. An evaluation report is prepared by a TGA evaluator for submission to the MEC.The purpose of the evaluation report is to provide an objective regulatory and scientific assessment and summary of the application to assist the committee in reaching a conclusion about the suitability of the product for registration. Applications for variation of existing products are generally not referred to the MEC unless the advice of the committee is specifically required. Circumstances where this may occur include: • new indications, directions for use or claims for an existing product, a chemistry, quality control or labelling issue which is presidential; or where the delegate requires technical or policy advice from the committee. Where the product is to be referred to the MEC, the sponsor will be sent a copy of the TGA's evaluation report at least ten days before the cut-off date for the meeting at which the application is to be considered. Comments from the sponsor will be given to the MEC. In general, comments must be limited to three pages and should only address substantial issues raised in the evaluation report. Minor and administrative issues can be dealt with separately by the evaluator. Additional data will not be accepted at this stage. Where an application is recommended by the MEC for rejection, the committee will usually offer the sponsor the opportunity to appear before a future meeting in support of the application. If the sponsor chooses to accept this invitation, the following considerations will apply.

- The sponsor should contact the OTC Medicines Section as soon as possible to arrange a suitable meeting;
- The sponsor is allocated half an hour (usually towards the end of the meeting) to present their case.
- New data that require evaluation are not usually accepted at this stage;
- Presentation aids (eg. PowerPoint, overhead projector) will be available on request;
- The committee may ask questions at the end of the presentation.

This procedure has been accepted as a long-standing custom of the MEC. It is not a formal appeal and does not affect the sponsor's appeal rights under Section 60 of the Therapeutic Goods Act 1989.

Guidelines on quality aspects of OTC applications:
This chapter describes the information regarding the quality of the product to be supplied with applications for registration of OTC medicines. It is divided into six sections as follows: Manufacture, Formulation, Starting material specification, Finished product specifications, Stability testing, Microbiological testing. In addition to the requirements as detailed in the specific sections, the quality section of the submission should include an overview of the pharmaceutical aspects of the application. This overview should include a development pharmaceutics section as detailed below and critical summaries of the starting material specifications, the finished product specifications and the stability studies.The TGA will accept European format Pharmaceutical Expert Reports as an alternative to critical summaries as described in this chapter.

Development pharmaceutics:
This section should include a table of the ingredients in the product and their purpose in the formulation (eg. disintegrant, antimicrobial preservative). Where the use of an overage of an ingredient or a range in the quantity used in batch manufacture is proposed, the reasons for the proposed overage or range should be discussed. Where a product has modified or unusual drug release characteristics (eg. sustained release or enteric coated) or an unusual method of manufacture, the 'Development pharmaceutics' section should include a detailed discussion of product development, and the relationship with the finished product specifications where relevant (eg. the reasons for choosing a particular dissolution test method and limit or the pH dependence of drug release in dissolution testing). Where a sponsor wishes to obtain approval for a range in the quantity of an ingredient (active or excipient), the 'Development pharmaceutics' section should include details of the reasons for the proposed range(s). The commentary should also refer to supporting validation data where appropriate.

Manufacture:
This section provides guidance as to the requirements of the Non-prescription Medicines Branch for the manufacture of OTC medicines and starting materials. Status of manufacturer finished product. Where Australian manufacturers are nominated in an application, each manufacturer must be licensed to perform manufacturing of the type proposed. The manufacturer's license carries details of the types of manufacture permitted under the license. Where a

product is imported, each nominated overseas manufacturer is expected to comply with the equivalent standard of good manufacturing practice (GMP) as would be required of an Australian manufacturer. Pre-clearance of overseas manufacturers is strongly recommended. Details of the information required to establish the standard of an overseas manufacturer are contained in the Standard of Overseas Manufacturers1. Details of requirements for manufacture are specified in the Australian Code of Good Manufacturing Practice for medicinal products2 and the EU Guide to GMP for Medicinal Products Annex 1 – Manufacture of Sterile Medicinal Products (available from the TGA Publications Office).

Status of manufacturer – starting materials:

For OTC medicines, evidence of licensing or approval of the manufacturer of starting materials is not required.Where manufacture of a proprietary ingredient is considered a significant step in the manufacture of the finished product (eg. a tablet granulation or excipient premix, or a vehicle for a topical product), evidence of licensing or approval of the manufacturer will be required. GMP evidence is not required where manufacture of a proprietary ingredient is not considered a significant step in finished product manufacture (eg. most colours, printing inks, flavours and fragrances, and proprietary ingredients whose sole purpose is as a source of the preservative system for the finished product). It is the responsibility of the manufacturer of the product to ensure that the quality of all starting materials is acceptable (Clauses 1.2 and 5.25 to 5.34 of the Australian Code of Good Manufacturing Practice for medicinal products3 apply).

Manufacturing information:

Details of the steps of manufacture should be provided for each manufacturing site. Typically these steps may include manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for sale. A brief outline of the method of manufacture of the finished product must be included with the application.

Batch to batch variations in quantities of certain excipients:

It is recognized that it may be necessary to vary the quantities of certain excipients from batch to batch in order to achieve acceptable results during the manufacturing process . Changes to the nominal amounts of certain excipients may be made as set out below. pH adjusting ingredients qs, Volume adjusting fluids qs, Quantity of ingredients whose function is to contribute to viscosity ±10%, Colour in tablet coating (but not in body of tablet) qs, Solvent in granulating fluid qs, Granulating fluid (fixed composition) ±10%, Disintegrant (even if the excipient serves more than one role in the formulation) to +25%, Coating solution qs, Talc and water soluble lubricants and glidants -25% to +100%, Water insoluble lubricants and glidants except talc (eg. magnesium stearate, stearic acid) ±25%, Filler (bulking agent) in hard gelatin capsules ±10%.

Formulation:

This section provides guidance on the formulation of OTC medicines. Colouring ingredients Amended 25 June 2004. All colours contained in medicines for oral use should be included in the list of 'Colours permitted in medicines for oral use' on the TGA website1 (Colours permitted in medicines for oral use). This restriction does not apply to dermal products or medicated lipsticks.

Proprietary ingredients:

The term 'proprietary ingredient' means a formulated ingredient obtained from another manufacturer for which the formulation details are not necessarily known to the sponsor (flavouring and colouring ingredients, for instance, are often sourced as proprietary ingredients). Formulation details have already been disclosed to the TGA (in which case you should state the ingredient's ARTG number in the application form); or you have requested the manufacturer of the proprietary ingredient to provide the TGA with details of the formulation on a Notification of a Proprietary Ingredient form, available from the TGA. If your label contains a negative disclosure (eg. 'Sugar free' or 'alcohol free'), you should also check that the substance is not contained in any proprietary ingredient included in the formulation.

Ingredients of human or animal origin:

Any materials of human or animal origin used as ingredients, excipients or during manufacture (eg. fermentation medium) need to be assessed for viral and prion safety. The TGA Approach to minimising the risk of exposure to Transmissible Spongiform Encephalopathies (TSEs) through medicines and medical devices can be found on the TGA website1. The TGA has adopted the European Agency for the Evaluation of Medicinal Products (EMEA) Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products2, EMEA 410/01 and its subsequent revisions. In this guideline, ruminant materials (bovine, ovine, caprine or cervid) are classified into the following risk categories according to infectivity studies.

Modified release products:

Modified release oral dosage forms may be appropriate where: The active ingredient has rapid

absorption and elimination (eg. half-life of less than 6 to 8 hours) associated with a correspondingly rapid loss of clinical effect, The site of absorption is not confined to a limited region of the gastrointestinal tract, The product is intended for use in conditions of sufficient duration to warrant the use of a sustained release formulation, The product is able to provide therapeutically effective doses of the active ingredient throughout the dosage interval, Applications for registration of modified release formulations must be accompanied by evidence to demonstrate that 'dose-dumping' cannot occur and that the product meets controlled release claims. The evidence should include clinical data to demonstrate the product's bioavailability and pharmacokinetics. Generally, the following bioavailability studies would be appropriate, depending on the product type: Studies comparing a single dose of the modified release product with a registered conventional release product, Studies comparing the steady state profile of the modified release product under the proposed dosage regime with that of a registered conventional release product under the approved dosage regime. Studies comparing a single dose of the modified release product taken in a fasted state with the same product taken with food (preferably a high fat meal). In some circumstances, bioavailability studies comparing the proposed formulation with an already registered modified release product may be appropriate, either in addition to the comparison with a conventional release product, or instead of these studies. If you believe a particular application warrants a departure from this guideline, submit a full justification for the departure with the application.. Information concerning different types of modified release tablets and capsules is given in TGO 56 (General standard for tablets, pills and capsules)1 – see Clause 2 (Interpretation) and the Supplementary notes.

Multicomponent products:

A product may contain two or more active ingredients provided that: Each active ingredient makes a contribution to the claimed indications. The effect of combining the active ingredients in one product does not decrease the safety or efficacy of the product. The product provides rational concurrent therapy for a significant proportion of the target population. Multi-component products that have the same actives as an existing evaluated product will usually not require efficacy or safety data. Where new combinations are proposed (in respect of the actives present and/or strengths), the safety and efficacy of the combination will need to be justified. Clinical and/or pharmacokinetic data comparing the proposed product with the active ingredients used separately will usually be required to support the efficacy and safety of the proposed combination. Expert reports and summaries will not be counted in the clinical data pages and may be attached to the cover letter or included with the relevant data.

Overages:

If overages are used during manufacture (ie. where the amount of an ingredient added during manufacture is greater than that nominated in the product's formulation), include details of the overage used. The 'Development Pharmaceutics' section of the application should include a justification for the proposed overage. Any assay limits which are unusually wide as a consequence of the proposed overage should also be discussed. Details of some commonly applied assay limits are included in Chapter 4D, Finished product specifications (under further considerations). Note that overages are not to be stated in the formulation details section of the application form.

Starting material specifications:

General principles:

Applications to register OTC medicines should include information concerning specifications for all ingredients. The term 'starting materials' (also called ingredients or raw materials) includes active substances, excipients, proprietary ingredients and solvents lost by evaporation during manufacture. In all cases, the specifications must characterise the substance and ensure that all batches are of suitable and consistent quality for use in finished product manufacture.

Critical summary of starting material specifications:

A critical summary should be provided of the specifications applied to each ingredient (active substances, excipients and proprietary ingredients). Where all of the tests, limits and test methods are of either a BP/Ph. Eur. or USP/NF monograph (and none of the compendial tests has been deleted) this should be stated. Where non-pharmacopoeial specifications are applied, a brief list of the tests, test methods and limits should be provided (eg. assay (non-aqueous titrimetry): 99.0-101.0%). The specifications applied should be justified in respect of their ability to assure the quality and consistency of the ingredients used. Similarly, where a pharmacopoeial monograph is used as the specification, the deletion or modification of pharmacopoeial tests, test methods or limits should be justified.

Pharmacopoeial monographs Vs Company Specifications for starting materials:

Generally, it is acceptable to adopt the tests, limits and test methods of a relevant British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) or US

Pharmacopeia/National Formulary (USP/NF) monograph as the specification for a substance. Where a sponsor wishes to do this, it would be sufficient to state that this is the case. However, it is generally not acceptable to: Adopt only some of the tests from a pharmacopoeial monograph, Selectively combine some tests and/or limits from the relevant BP monograph with some tests and/or limits from the USP monograph (without having ensured full compliance with either one or the other monograph), Where a sponsor applies pharmacopoeial limits but wishes to use different test methods this should be stated and full details of the test methods should be provided (especially in respect of related substances tests). This will permit the Quality – Starting material specifications TGA to assess whether the in−house and compendial methods are equivalent and/or whether the modified specifications ensure the overall quality of the substance, Where there is no pharmacopoeial monograph or sponsors, for whatever reason, wish to use their own in-house specifications, full details of the limits and test methods should be provided for evaluation. In proposing tests and limits, sponsors should note the requirements given in pharmacopoeial monographs for similar substances.

Single-component non-pharmacopoeial starting materials:

Specifications for starting materials which essentially consist of one component would typically include tests and limits for: Appearance/description, Identification, Content/assay, Impurities (eg. water, residual solvents, loss on drying, sulfated ash, heavy metals, synthetic impurities and degradants). Tests for the presence or the proportion of isomers, optical rotation, microbial contamination, particle size distribution, and the clarity, colour and pH of solutions may also be relevant.

Intrinsic mixtures:

Substances which are intrinsically mixtures (for example, synthetic polymers or fatty acid esters of glycerol, where mono, di, and triacyl glycerol species are present and where a range of different fatty acid residues is also present eg. surfactants) may require additional tests which control the composition of the mixture such as: Acid value, Iodine value, Saponification value, Viscosity, Density, Refractive index.

Proprietary ingredients:

The specifications applied to proprietary ingredients should be appropriate for the nature of the ingredient, its function in the finished product and its proportion in the finished product. For example, for a perfume which is a minor component in a liquid or semi-solid product, it may be appropriate to have tests for: Description (odour, colour and general appearance), Refractive index or density, Prominent peaks in a GC or HPLC trace, or major spots in a thin layer chromatogram., For an ingredient blend which contains the active substance (for a tablet or capsule, for example) it may be appropriate to include tests for Identification of the active, Content of the active, Impurity tests.

Starting materials – additional considerations:

The specifications for active ingredients, for which there is no BP/Ph. Eur. Or USP/NF monograph should include tests and limits for related substances Quality – Starting material specifications (Synthetic impurities and degradants). The related substance limits should be proposed after consideration of the: Toxicology of the impurity and the active ingredient itself., Route of administration, Daily dose, Target population (eg. children or the elderly), Duration of therapy and the proposed indications.

In general, the following limits on impurities will not need to be supported by a detailed justification: Individual identified impurities not more than 0.5 %, Individual unidentified impurities not more than 0.1 %, Total impurities not more than 1.0 %

Colours permitted in medicines for oral use: (Guideline amended 25 June 2004)

A list of colours permitted in medicines for oral use, together with applicable raw material specifications, is included on the TGA website1. Indicative data requirements for the evaluation of new colours for inclusion in medicines for oral use are also provided.

Finished product specifications:

This section provides guidance on specifications that apply to the finished product at batch release and at expiry.

General principles:

The finished product specifications are a set of tests and limits which are applied to the product in order to ensure that every batch is of satisfactory and consistent quality throughout its shelf life. The specifications should monitor all parameters (generally by physicochemical testing) where variation would be likely to affect the safety or efficacy of the product. Batch release testing, which is the responsibility of the sponsor, is usually performed on every batch whereas shelf life testing may be performed by the TGA Laboratories throughout the batch shelf life (as part of a routine sampling program or in response to complaints).

Critical summary of the finished product specifications:

The suitability of the tests, limits and test methods proposed for the finished product should be discussed with reference to the results of the method validation

studies and the ability of the specifications to guarantee the quality and consistency of the finished product. A detailed commentary or justification for any unusual features in the finished product specifications should be included. A brief list of the tests, test methods and limits should be provided (eg. assay (capillary GC): 95.0-105.0%). For dissolution tests, brief details of the apparatus, medium and limit should be provided (eg. dissolution (paddle at 50 rpm, 900 mL of water, Q=80% at 30 minutes)). The summary list should give details of both the batch release and expiry specifications. Where the expiry specifications differ from the batch release specifications, this should be noted.The specification code number and date should be stated. The limits applied at batch release should be discussed in terms of their ability to ensure that the product will remain within the expiry specification throughout the product shelf life. Any changes or unusual variability in the results obtained in the stability studies require comment in this respect.

Further considerations:

Your application should include a copy of the batch release and expiry specifications. Where the tests and limits applied at batch release and at expiry differ this must be clearly indicated. Where analytical test methods in the finished product specifications differ from those used for stability testing, validation data should also be provided for those test methods (where applicable).

Quality – Finished product specifications:

Usually, tighter limits are applied at batch release to critical parameters to allow for analytical error during batch release testing and to allow for possible changes to the product during storage (eg. decomposition of the active). The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product's shelf life. The expiry specifications should include all of the tests which are included in the batch release specifications. (It is not sufficient to provide the stability specifications alone as they generally do not include a complete set of tests.) The specifications must include the requirements listed in any relevant Therapeutic Goods Order (eg. TGO 56). Where your product is subject to a monograph in the British Pharmacopoeia (BP), the expiry specifications must include all of the tests and limits in that monograph. However, if you consider that the test method used by the BP is unsatisfactory for your product, you should substitute another method which has been validated. If there is no BP monograph for your product, the specifications must include all of the requirements in the BP General Monographs (for dosage forms). You should also check the BP and the United States Pharmacopeia/National Formulary (USP/NF) for monographs for similar products to determine appropriate tests and limits to include in the specifications. Any expiry limits which are less stringent than those commonly applied to the relevant dosage form should be justified in detail. (Note: TGO 56 allows wider limits for content of some active ingredients.) Some commonly applied expiry limits are:

Content of active ingredient(s)

• In tablets and capsules 92.5 - 107.5% of stated content

• In creams and ointments 90.0 - 110.0% of stated content

• In oral liquids 90.0 - 110.0% of stated Content of preservative(s) present as excipients

• Antimicrobial upper limit 120% of stated content lower limit – sufficient to be effective

• Antioxidant upper limit 120% of stated content lower limit – sufficient to be effective

• The specifications for finished products which may reasonably be expected to contain significant quantities of ethylene oxide or ethylene chlorohydrin should include the following limits:

Microbiological requirements

Sterile products:

The official requirements for sterility tests in Australia are those specified in the current gazetted edition of the British Pharmacopoeia. This is the minimum standard with which manufacturers must comply. The sterility tests published in editions of the BP and Ph. Eur. prior to 1998 are not acceptable. The TGA guidelines for sterility testing of therapeutic goods2 provide guidance for sterility **Quality – Finished product specifications** .testing of sterile therapeutic goods supplied in Australia for human use. These guidelines, however, are not mandatory for industry.

Non-sterile products:

The Guidelines for assessing the results of microbiological tests on non-sterile OTC medicines (Chapter 4F) set out microbial limits which apply to non-sterile dosage forms. All non-sterile dosage forms should include limits for microbial content in the finished product batch release and expiry specifications. Microbial specifications for solid oral or dry powder products may not be necessary if it can be justified in the application by establishing during product development that the product is at a very low risk of contamination and microbial growth is not supported. It is not a requirement that every batch of a product be tested at batch release. Once it has been demonstrated that the manufacturing processes do not permit contamination by excessive numbers of

microorganisms, by testing a number of routine production batches to establish a product history, testing could be reduced to once every 6 to 12 months or on a selected basis (eg. every tenth batch). Products with a significant water content (eg. creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications. In addition, for products containing an antimicrobial preservative(s), both the batch release and expiry specifications should include physicochemical tests and limits for content of preservatives. Given that the effectiveness of many preservatives is pH dependent, the specifications for such products should usually include requirements for pH which will ensure preservative efficacy.

Stability testing:

(Reference to prescription medicine guidelines corrected 28 June 2006)

Full details of stability testing conducted on the product together with associated validation must be included in the submission. This section provides guidance as to the design, conduct and reporting of stability studies for OTC medicines. The guidelines are based on the principles and requirements set out in Guidelines on the stability testing of pharmaceuticals, included as Appendix 14 to the Australian regulatory guidelines for prescription medicines (ARGPM) 1. Departure from the principles set out in this document will only be considered when adequately justified.

General principles:

The objective of a stability study is to determine the time during which a pharmaceutical product meets appropriate standards when stored under defined conditions. The product must be shown to remain, or is likely to remain, within its expiry specifications throughout the proposed shelf life when stored under the proposed storage conditions. Thus the difference between release and expiry specifications must take into account the results of stability testing.

Critical summary of the stability studies:

In addition to providing full details of the stability studies undertaken in support of registration of a product, a separate critical analysis of each study should be provided. Each of the points listed below should be addressed separately for each stability study. A table giving batch numbers, batch types (pilot or production), batch size or scale, storage conditions (temperature, humidity, lighting conditions, and storage upright or inverted for liquids), and storage durations. If the storage conditions were not controlled, this should be stated. A statement whether all (or some) of the batches tested were identical with the product intended for marketing in terms of formulation and container (if not, the differences should be justified, and full details provided). A statement whether the method of manufacture and manufacturing equipment for the batches tested were identical with the product intended for marketing (If not, the differences should be justified, and full details provided). Brief details of the results observed for each of the test parameters included in the studies, as follows. Separate comments should be provided for each test parameter.

Active raw material:

Stability data should be provided for an active raw material which is a new chemical entity. While not mandatory for existing OTC active substances, inclusion of such information with an application may provide a useful guide to the problems which may be encountered during stability studies on finished products.

Finished product:

At the time of submission, the data package should include sufficient stability data to justify a shelf life of at least 12 months. This requires studies in which satisfactory results have been obtained under the following duration and conditions of storage: 12-month duration with storage at the proposed maximum storage temperature; or 6 month duration with storage at both the proposed maximum storage temperature and at least 10 degrees higher; and at least 3 months duration at elevated humidity if the container is potentially moisture permeable. If the stability studies would not support a shelf life of 12 months, the application may be considered premature and returned to the sponsor for resubmission when complete. The TGA will accept for evaluation stability data generated using storage conditions as outlined in the EU document Note for guidance on stability testing of existing active substances and related finished product (CPMP/QWP/556/96)1. However, the shelf life which is assigned to the product on the basis of such data will be determined according to the general principles outlined in this chapter.The formulation of the finished product must be the same as that proposed for registration in Australia. It may be acceptable to provide stability data from similar formulation(s) as supporting data, subject to full stability testing being commenced on at least the first two production batches of the new product (refer to Post registration requirements in this Chapter). However, it may be useful to contact the OTC Medicines Evaluation Section for advice in this regard.

Note that:

A requested shelf life will not normally be approved for the purposes of registration if there are no data on the actual formulation registered. The maximum permitted shelf life is five years. Stability testing

should be carried out in the container/closure system in which the product will be marketed in Australia. It may, however, be acceptable to provide stability data on the same formulation packaged in different materials, depending on the nature of the materials involved. It may be useful to contact the OTC Medicines Evaluation Section for advice in this regard. Stability data in different container/closure systems are particularly relevant when studies of the two types of pack are provided which clearly show the equivalence or superiority of the container/closure system intended for registration over the system used in the stability studies. Stability information should be generated on a minimum of two batches. All manufacturing processes should have been carried out on these batches (eg. filtration, packaging, and sterilization). However, production batches may not be available at the product development stage. Where this is the case, a requested shelf life may be approved provided data are supplied on at least two pilot batches, subject to full stability testing being commenced on at least the first two production batches. As far as practicable, pilot batches must reflect the manufacture of full production batches using the same type of manufacturing equipment and the same manufacturing method. Pilot batches must be of sufficient size, appropriate to the dosage form and formulation, to be able to adequately reflect the physical conditions encountered in the manufacture of production batches. The use of laboratory scale batches is generally inappropriate. Where the product is registered in several strengths, stability data should be generated on two batches of each strength. If the different strengths are a direct scale, at least one batch of each of the highest and lowest strengths should be tested. Conditions of storage likely to be encountered in Australia should be a consideration in designing the stability study. Storage conditions should be clearly defined, preferably in terms of the categories specified in the Therapeutic Goods Order No 691 (or as revised from time to time):

• Store below –18°C (Deep freeze)
• Store below –5°C (Freeze)
• Store below 8°C (Refrigerate)
• Store at 2°C to 8°C (Refrigerate. Do not freeze)
• Store below 25°C
• Store below 30°C

The use of uncontrolled temperature conditions in stability studies is undesirable Terms such as 'room temperature' and 'normal warehouse conditions' are discouraged, as these allow the product to be exposed to a wide range of conditions and make shelf life assessment difficult. If storage in a refrigerator is proposed without the caution 'Do not freeze', then stability, particularly physical stability (eg. no formation of a precipitate, no denaturation of a protein) at about –5°C, must be demonstrated. Stability studies at elevated temperatures are useful in predicting longer term shelf life periods from short term data. These predictions should be verified by studies on production batches to shelf life (refer to Prediction of shelf life from accelerated stability data and Post registration requirements, in this Chapter). The precision of a procedure is generally determined by performing repeat assays of the product (with all steps including sample weighing and extraction being repeated). Data obtained on different days by different analysts and different equipment may be useful.

Demonstrating specificity in respect of excipients and extraction solvents Specificity in respect of excipients is generally demonstrated by performing the assay procedure on an excipient (placebo) blend. Similarly, it is sometimes useful to demonstrate that extraction solvents do not interfere with the analysis by performing the assay procedure in the absence of a sample (or placebo sample). Where a chromatographic procedure is used, copies of relevant chromatograms should be provided. Demonstrating specificity in respect of degradation products Sponsors should demonstrate that the test method is sensitive to degradation of the active ingredient. When the identity of all usual degradants is well known, specificity may be demonstrated by analysing the known degradants and demonstrating that they do not interfere with the analysis. It may be appropriate to analyze known degradants as pure substances and also when admixed with a sample extract or reference solution.

When the identity of the degradants is not clear or when the sponsor does not have access to authentic specimens of the degradants, forced degradation studies should be undertaken. Commonly used forcing degradation conditions include treatment with, An aqueous solution of a mineral acid, An aqueous solution of sodium hydroxide, An aqueous solution of a strong oxidising solution such as hydrogen peroxide.

Microbial content testing:

All non-sterile dosage forms should include limits for microbial content in the expiry specifications unless departure from this requirement is justified (see Microbiological requirements – Non-sterile products in Chapter 4D). Where this exemption does not apply, microbial content testing should be carried out at the end (and preferably at the beginning) of shelf life during stability studies to demonstrate that the product remains within product specifications until expiry. Preservative efficacy: Products that are intended for multi-dose use should be adequately

preserved for the duration of the claimed shelf life. This applies to both non-sterile products (eg. aqueous creams, lotions, and oral liquids) and sterile products (eg. Eye preparations). It is necessary to prevent microbial proliferation in, or microbial contamination of, such products during their normal conditions of storage and use.

During product development, preservative efficacy testing should be performed at the beginning and end of the claimed shelf life to demonstrate that the antimicrobial activity of the product as such or, if necessary, with the addition of a preservative(s), has not been impaired by storage. Data must be specific to the formulation and the container. If the requested shelf life is based on data generated under accelerated conditions, preservative efficacy tests should be performed on samples that have been stored at the higher temperature.

For all multi-dose products, tests in accordance with the BP/Ph. Eur. Efficacy of antimicrobial preservatives in pharmaceutical products are mandatory (consistent with Therapeutic Goods Committee resolutions 15/9, 16/10 and 16/11). Chemical assays of the level of preservative are not accepted as substitutes for biological tests. For sterile products (eg. eye preparations), that are intended for multiple use, the preservative efficacy of the product over the open shelf-life period (eg. 4 weeks for eye preparations) must also be demonstrated. Such testing should involve repeated microbial challenges over the open shelf-life period as this most closely mimics the in-use situation. Alternatively, microbial content testing may be carried out on partially used containers that have been used by patients for the full open shelf life. Modifications of a pharmacopoeial preservative efficacy test (preferably the Ph. Eur./BP test) that include a rechallenge with reduced numbers of organisms could be used. Guidance may also be obtained from the normative part of the international standard ISO 14730 Ophthalmic optics – Contact lens care products – Antimicrobial preservative efficacy testing and guidance on determining discard dating which describes a test procedure and performance criteria for preservative efficacy over an open shelf life period of 28 days.

Dissolution rate:

The behaviour of the dissolution rate over time should be examined as per the requirement in the relevant Therapeutic Goods Order or BP monograph. Dissolution profiles, generated by sampling at more than one time, may provide useful additional information about possible changes to the dissolution characteristics of the formulation during storage. Testing using a USP monograph method or in-house test method could be considered in the absence of a dissolution test in a relevant Therapeutic Goods Order or BP monograph.

High humidity studies:

Data should be generated to establish the effect of high humidity on solid dosage forms packaged in container/closure systems which are likely to be moisture permeable. This includes containers made from polyvinyl chloride (PVC), with or without a PVDC coating, or low-density polyethylene (LDPE); but does not include bottles made from glass or high-density polyethylene (HDPE). Satisfactory stability results when the product is stored at 25°C and 80% RH or 30°C and 75% RH for 3 months are normally sufficient to establish the adequacy of the packaging to protect the product from moisture for a period of up to 2 years.

Data which show stability for a period of 6 months are normally sufficient to support a shelf life in excess of 2 years. Stability data generated using samples stored at 40°C and 75% RH may also be useful (particularly in the absence of data generated at 25°C/80% RH or 30°C/75% RH). However, sponsors should note that, where rapid change in key stability parameters is observed for this storage condition, interpretation of the results may be difficult. In such cases (and also where the results do not comply with the expiry specifications), stability data generated with storage at 25°C/80% RH or 30°C/75% RH would be required.

RESULTS:

Results obtained at the commencement and at nominated time intervals throughout the study should be provided. This will allow any trends to be detected and will enhance the predictive value of the study.

1 Note: This reference is not being supplied as a standard that must be applied to a product. It is supplied solely to demonstrate the elements of the type of tests that would be required to support an open shelf life period.

Data which do not include initial results (ie. at the start of the study) are of limited value. Where possible, quantitative results should be quoted rather than a statement that the product complies with a particular specification. Assay results obtained during the study should be recorded either as absolute values (such as number of mg of active substance per capsule) or as a percentage of the nominal (labelled) content. If more than one assay result is available, expression of results as a percentage of the values at time zero is useful, but such figures are not sufficient by themselves. For tablets and capsules, an average

content should be obtained by conducting the assay on pooled samples, or by averaging individual dose unit results. This will minimise the effect of individual dose unit variations.The results obtained should be discussed and explanations given where necessary, eg. Anomalous or unusual results, change in assay method, change in appearance.

Prediction of shelf life from accelerated stability data:

The stability of a medicinal substance is directly related to the kinetics of the various degradation reactions. However, the relevant physicochemical equations are strictly applicable only when a single reaction occurs by a single mechanism. Because pharmaceutical products are usually mixtures of substances and may be in the solid state (for example, powders and tablets), these theoretical models do not necessarily hold and cannot be relied upon as predictive tools. The issue of physical stability (for example, dissolution rate and particle formation) adds a further complication. There is, therefore, no substitute for the shelf life being determined empirically, ultimately over the shelf life. However, it is acknowledged that the accumulation of stability data is a lengthy procedure and it is sometimes necessary to predict an interim shelf life for a product stored at a defined temperature from stability data obtained at an elevated temperature. This 'accelerated' stability testing is useful in providing information from which to assess the stability of a new product but it should be ultimately confirmed with long term stability studies at the recommended storage temperature for the duration of the nominated shelf life.

In most circumstances, the following general rule-of-thumb is used:

If no trends are noted after storage for a period of (x) months at an elevated temperature (at least 10°C above the maximum storage temperature proposed for the product) then an interim shelf life of a maximum of 2(x) months may be permitted, where 2(x) does not exceed 3 years. For some products alternative interpretations may be considered, if justified.

Shelf lives of longer than 3 years should be supported by data on production batches stored at the maximum recommended temperature for the duration of the proposed shelf life. Stability studies involving at least two production batches, stored at the maximum recommended temperature, should be continued for the full period to validate the predicted shelf life (refer to Post registration requirements below).

Post registration requirements:

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program on each product (refer to clauses 1.2 and 6.2 of the Australian Code of Good Manufacturing Practice for medicinal products1. For more specific detail, contact the Manufacturer Assessment Section of the TGA). Where a shelf life has been allocated on the basis of Accelerated testing; or Data generated on a related formulation; or Data generated on the same formulation in a different container; or Data generated on batches other than production batches. it is a requirement to provide an assurance that full stability testing will commence on at least the first two production batches and continue for the full period of the product's shelf life (at the recommended storage condition) and that any adverse trends will be reported to the TGA. Data may be requested for review at any time or followed up by the TGA's auditors during GMP audits of the manufacturer. If it is found that the required testing has not been carried out or that adverse trends have not been reported to the TGA, appropriate action may be taken which may include cancellation of the product's registration.

Requirements for a proposed stability testing protocol for self-assessable shelf life extension:

A product's shelf life may be extended on the basis of stability testing conducted according to a protocol which was specifically approved for this purpose. For a stability protocol to be considered for the purpose of self-assessable shelf life extensions, it is normally necessary for at least 12 months data, generated at the maximum recommended storage temperature, to be available on at least two production batches of the proposed formulation, in the container proposed for marketing, or one which is less protective. To provide a suitable margin of safety, the limits for results of critical test parameters should normally be a little tighter than the expiry limits. Where some results are outside these limits, the sponsor may submit the data for evaluation by the TGA.

The protocol should be a standalone document which includes:

A statement of the intended purpose (eg. "This protocol is intended for notification of shelf life increases of up to x years following self-assessment of stability data"), A statement of the criteria for notifying a shelf life increase (eg. "full term stability data will be generated using two production batches stored at y°C,all analytical results obtained will comply with the protocol acceptance criteria"), The precise formulation of the product (if overages are

included, this should be stated and a justification provided), The immediate container specifications, The storage conditions to be included on the label, The finished product expiry specifications and the protocol acceptance criteria (including acceptable limits for results of each test), A statement of the proposed tests and validated test methods (validation data should be included) (refer to Appropriate tests and Prediction of shelf life from accelerated stability data in this chapter); and A matrix indicating the time stations at which each of the tests will be conducted as well as the storage conditions to be used in the study.

Shelf life extensions according to an approved protocol:

Provided that a protocol for self-assessable shelf life extensions has been approved by the TGA for a particular product, the shelf life extension for that product may be implemented following notification to TGA. All results up to the end of the notified shelf life fall within the acceptance criteria as specified in the approved stability protocol, No other changes to the information about this product previously provided to TGA (other than specified in the notification) have been made, or are currently proposed to be made, A stability testing protocol has been approved for the product and a copy of the approval letter is attached to the notification, At least two full production batches of the Australian formulation product packed in the approved container have been used in the studies; and The shelf life is no longer than the time for which stability data meeting the approved protocol are available, and in any case, is not longer than 5 years.

Prospective extensions of shelf life for individual batches:

Under certain circumstances, the TGA may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data. The prerequisites are as follows: The existing shelf life should be at least 2 years, Stability data are available to the TGA which validate the existing shelf life, A recent (less than 2 months old), dated certificate of analysis should be supplied for the batch, showing compliance with specifications, together with the results obtained at batch release; and The sponsor should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life, unless it is purely intended as a one off required ensuring continued supply. Prospective extensions of more than 6 months, or to a shelf life of more than 5 years, are not normally acceptable.

Australian markets are one of the emerging markets as the markets have a huge scope for development especially in context with Pharmaceutical industry. The growth drivers are emerging markets and rural markets. The consumer healthcare sector in Pharmaceutical industry is growing at a higher pace especially in terms of OTC markets. As the OTC markets are growing with a huge potential, even pharmaceutical companies are coming up with more innovative strategies to capture the untapped markets. As the OTC markets are growing, it means customers are indulged in self-medication but the self-medication which is increasing day by day in the informed consumers can lead to serious consequences due to severe side effects. Even the same has been reported for anti-obesity drugs which had been put as OTC medicines. As the list of OTC medicines is increasing day by day, code of ethics should be introduced by the government so that the marketing practices for such markets should be controlled.

In developed countries there is a widespread and growing concern that the current regulatory burden is a significant impediment to innovation, industrial development and international competitiveness. However, the Australia country is starting to review current, established, non-prescription medicines legislation with a view to reducing the regulatory burden on industry and on themselves. The opportunity for self-regulation by industry, with appropriate checks and balances by government, is receiving renewed support. Such ideas for better regulation can also be useful to emerging and developing countries.

Stringent rules and regulations have to be passed to control OTC drug usage in a developed country like Australia. Media is one of the major communicating medium and hence it would be ideal to make the general population aware of the consequences of the OTC drug usage through advertisements in television, radio, and news-paper. Doctors and pharmacists also play a major role in preventing the OTC drugs usage. Balance should be checked regularly between safety and freedom in using OTC drugs. Thus, regular monitoring of the OTC drug usage would further minimize the irrational use of drugs.

The Australia is catching up with the concept of OTC more as reasons are the advent of technology, improving literacy levels, increasing health awareness and high work stress levels. In fact, Australian consumers are confident about sharing healthcare responsibility, especially in case of common ailments. Considering the changing mindset and likely changes in regulatory framework, such as, OTC guidelines and

open distribution, it is expected that within the next ten years, Australia will become a major contributor to the world of OTC market. Currently, aches/pains, cough, colds, hyperacidity, minor topical infections, and indigestion are major OTC categories. Emerging categories include cuts, wounds and burns, muscle pains and sprains, diarrhoea and constipation. An analytical interpretation of various data placed the focus on vitamins, cough & cold, antacids, antipyretics and NSAIDs as opportunity areas for switch in India. From the industry view point, the OTC market is one of the emerging markets with a good growth rate which could be tapped in various ways.

Current Progress in Australia:

The OTC committee of the Organization of Pharmaceutical Procedures of Australia (OPPA) is currently working towards the promotion of responsible self-medication in order to promote the OTC market. It is also aiming on promoting the importance of responsible self-medication through awareness programs and community education. The committee not only promotes OTC use but also emphasizes on safety. Besides promoting OTC's, establishing a balance between wider access of drugs and their safety should also be focused.

Conclusion:

There are proper drug regulations legislated in Australia but are rarely accomplished in practice. The regulatory authority (TGA) should immensely implement such regulations so that the OTC market is thrived and procurement of prescription drugs over the counter is proscribed eventually knocking off the prescription drug abuse which is the prevailing challenge in Australia.

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