

# **Guideline on the Regulation of Therapeutic Products in New Zealand**

## **Part 2:**

### **Obtaining approval for new and changed medicines and related products**

**Edition 1.0**

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## Section 1: Introduction

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### 1.1 The New Zealand Medicines Act 1981

The following sections of the Medicines Act 1981 (the Act) are most relevant to the approval of new and changed medicines and related products.

*Medicines Act 1981:*

- ☞ [Section 3](#): Meaning of medicine, new medicine, prescription medicine and restricted medicine
- ☞ [Section 20](#): Restrictions on sale or supply of new medicines
- ☞ [Section 21](#): Applications for Minister's consent
- ☞ [Section 22](#): Procedure in respect of applications for Minister's consent
- ☞ [Section 23](#): Minister may give provisional consent
- ☞ [Section 24](#): Distribution of changed medicines restricted
- ☞ [Part 7](#): Related products

### 1.2 Other information relevant to this guideline

- ☞ [Application forms](#) including guides to completing an application
- ☞ [Fees](#) payable for applications
- ☞ [Regulatory timelines](#)
- ☞ [Application search](#)
- ☞ [Application status](#)
- ☞ [Medsafe's position statement on biosimilars](#)
- ☞ [Guideline for the Regulation of Therapeutic Products in New Zealand Parts 1, 4, 5, 6, and 10](#)

### 1.3 Overview of the approval of new and changed medicines

Medsafe interprets New Zealand's medicine legislation to mean that in most circumstances medicine distributors need to obtain Ministerial consent before commencing distribution.

Applications for consent are submitted to Medsafe along with evidence to demonstrate that the medicine meets the claimed safety, efficacy and quality standards. Medsafe's role is to assess the evidence provided against the standards expected of medicines. Medsafe provides advice to the Minister's delegate regarding the safety, efficacy and quality of the medicine and whether it has an acceptable risk : benefit profile.

The standard expected of medicines is briefly outlined in the Medicines Act and associated regulations. However the legislation does not specify what factors constitute an acceptable risk : benefit profile. Therefore Medsafe refers to international guidance to ensure medicines supplied meet the expectations of the New Zealand public.

In general Medsafe expects that medicines supplied in New Zealand meet all applicable national and international standards unless adequately justified by the product owner. Justifications are assessed and accepted on the basis that the overall risk profile of the medicine is not compromised by use of an alternative standard.

The risk profile of a medicine is proportional to the amount of data required to be assessed to ensure that the risks inherent in any medicine have been adequately mitigated. To facilitate processing of applications with varying risk profiles, Medsafe uses application categorisation tools to stream application types.

Fees are payable for applications as outlined in [regulation 61](#) of the Medicines Regulations 1984. Medsafe uses standard fee waivers to develop a schedule of fees for the application types.

## Section 2: Who can submit an application

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The [Medicines Act 1981](#) requires that a **New Medicine Application (NMA)**, **New Related Product Application (NRPA)**, **Changed Medicine Application (CMN)** or **Changed Related Product Notification (CRPN)** is lodged by or in the name of a manufacturer, importer or proprietor resident in New Zealand.

The New Zealand resident manufacturer, importer or proprietor may be an individual or a company and is designated the “sponsor” (or “licence holder”) for the product concerned. The sponsor is legally responsible for all aspects of the product in New Zealand, including any regulatory action relating to it. The sponsor is responsible for ensuring the accuracy of any information submitted to Medsafe in support of any NMA, NRPA, CMN or CRPN.

An overseas pharmaceutical company wishing to market a medicine or related product in New Zealand therefore needs to have a New Zealand-based subsidiary, or appoint a local individual or company as a New Zealand agent to act for them in New Zealand as sponsor for the product concerned. The New Zealand subsidiary or agent is the sponsor responsible for the product, including any supply of the product under [section 2](#) of the Medicines Act and any recall of the product from the market.

An NMA or NRPA or CMN or CRPN is submitted to Medsafe in the name of the sponsor. An overseas branch of the company or a local or overseas regulatory affairs consultant may act on the sponsor’s behalf and prepare the paperwork for an application and submit it to Medsafe. For administrative purposes, the identity of the “applicant” depends upon the circumstances:

- Many applications and notifications are prepared, signed and forwarded to Medsafe by an employee of the sponsor (e.g., a regulatory affairs manager or associate). In this case the applicant is the sponsor.
- Some applications and notifications are prepared and submitted on the sponsor’s behalf by an independent regulatory affairs consultant who signs the documentation as if he or she was an employee of the sponsor. In this case the applicant is the sponsor.
- Some applications and notifications are prepared and submitted on the sponsor’s behalf by a local or overseas consultant who signs the documentation, not as an employee, but in his or her own right as a contracted agent of the sponsor. In this case the consultant (not the sponsor) is the applicant.
- Some applications and notifications are prepared and submitted on the sponsor’s behalf by an overseas branch of the company. An employee of the overseas company signs the documentation and forwards it to Medsafe. In this case the overseas branch of the company is the applicant while the New Zealand branch is the sponsor.

Where a local or overseas regulatory affairs consultant or an overseas branch of a company acts on behalf of the sponsor in submitting an NMA, NRPA, CMN or CRPN, a letter (or copy of a previous letter) from the sponsor confirming the consultant’s or overseas company’s authority to act on the sponsor’s behalf should be forwarded to Medsafe, either with the application/notification or separately.

All Medsafe correspondence relating to the application or notification will be sent to the applicant, irrespective of whether the applicant is also the sponsor, unless the applicant specifically requests otherwise.

Joint applications in which all or part of the data are shared, may be made by two or more sponsors. It should be clearly indicated in the application that each sponsor supports the

shared use of the data. This may be indicated by the covering letter(s) being signed by all sponsors. The letter(s) must identify the person to whom questions and other correspondence relating to the application should be addressed.

Such joint applications commonly relate to one product to be distributed under two or more brand names. For administrative purposes, each brand name is treated as a separate product. However, the application fee is calculated as for one principal product attracting a full fee with each additional brand name attracting a smaller additional fee as if it was for an “additional name” of the principal product.

Each sponsor is required to hold a complete copy of the regulatory file.

## 2.1. Sponsor obligations

Once a medicine or related product is approved the sponsor then assumes additional responsibilities.

The responsibilities and expectations of sponsors are summarised below:

Responsibility	Legislation reference
Comply with the requirements of the Medicines Act 1981 and the Medicines Regulations 1984	
To be a manufacturer, importer, proprietor in New Zealand or their duly appointed agent	s21(1)(b)
Maintain a physical address within New Zealand	s21(2)(a)
Hold a licence to sell by wholesale	s17
Produce on demand and understand the significance of current specifications, certificates of analysis and batch documentation for each batch of the medicine distributed in New Zealand	s42
Comply with any conditions associated with consent	s23
Provide technical data and advice as required	
Accept responsibility for the distribution of unapproved medicines	s29
Undertake the reporting of adverse reactions for medicines	s41
Undertake recalls and withdrawals	reg50
Accept responsibility for the advertising and promotion of the medicine	s57

Medsafe’s task is to ensure that the sponsors of medicines are able to meet their responsibilities under the medicines legislation themselves or have contracted out these responsibilities to agents who have the skills to be able to handle such tasks.

The minimum requirements for sponsors are listed below.

- ☞ Sponsors of medicines must have a legal presence in New Zealand and be licensed as wholesalers as they are offering to sell (refer ‘sell’ - [section 2](#) of the Act).
- ☞ A sponsor must be able to define how they meet the responsibilities listed above.
- ☞ Should a sponsor contract out some of those responsibilities the contracted company must have the skills to fulfil their responsibilities and hold any applicable activity licences.



To ensure the supply of safe and effective medicines and ensure timely responses to stakeholders, Medsafe also expects sponsors to have:

- ☞ procedures to manage complaints and recalls
- ☞ procedures for effective batch release and tracking of distributed stock
- ☞ contracts with overseas principals/suppliers that clearly describe the roles and responsibilities of each party (bearing in mind that the ultimate responsibility for the product on the New Zealand market cannot be delegated)
- ☞ protocols for responding to consumers, healthcare professionals and other interested parties (e.g., the media)
- ☞ procedures for supplier audits
- ☞ procedures to advise Medsafe of emerging issues such as recalls, withdrawals, suspension of market authorisation in other jurisdictions
- ☞ procedures to advise Medsafe of significant issues raised during site audits
- ☞ adequately qualified and trained staff to ensure they can correctly obtain and interpret technical information provided by a third party and assess its impact on the New Zealand market.

Medsafe interprets the Act to mean that as the sponsor is responsible for the New Zealand market, parallel importing is prohibited unless expressly authorised by the New Zealand sponsor. Medsafe considers that the prohibition extends to supply of unapproved variants of consented medicines under [section 29](#) of the Act due to the risk of confusion regarding responsibility.

## Section 3: New medicine application types

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### 3.1. When is a medicine a “new medicine”?

The term “new medicine” is defined in [section 3](#) of the Act. In practical terms, a new medicine is defined as one of the following:

- ☞ a medicine for which Ministerial consent for distribution in New Zealand has not previously been granted
- ☞ an approved medicine that has undergone a material change that has resulted in its referral to the Minister under [section 24\(5\)](#) of the Act
- ☞ a medicine that has previously been approved but has not been generally available in New Zealand during the five years immediately preceding the date on which it is proposed to become available.

A medicine is considered to have been “generally available” if, during the relevant five year period one of the following has been met:

- ☞ the product has been sold or offered for sale in or export from New Zealand on one or more occasions, or the product has been advertised in New Zealand as available for sale
- ☞ the regulatory file for the approved medicine has been updated through a Changed Medicine Notification (CMN) (note that a SACN for a change in sponsor is not sufficient evidence that the medicine has been generally available)
- ☞ the product has been the subject of a submission made to PHARMAC for a tender.

#### 3.1.1. Evidence that a medicine has been generally available

An applicant wishing to show that a product is not a new medicine because it has been “generally available” must support that claim by providing one of the following:

- ☞ evidence of one or more sales during the relevant period (e.g., invoice)
- ☞ evidence of importation (e.g., customs clearance form)
- ☞ evidence of listing in a sales catalogue or price list from the relevant period
- ☞ a statement identifying regulatory activity for the product, such as a CMN.

The claim must be supported by a declaration from a person in New Zealand that the evidence is genuine, and that any documents provided are true copies of the original documents. The original documents must be made available on request.

#### 3.1.2. Previously approved medicine that has not been generally available

When a sponsor wishes to commence or re-commence distribution of a previously approved product that has not been generally available in New Zealand in the last five years a NMA must be submitted, otherwise, the medicine may only be supplied as an unapproved medicine under [section 29](#) of the Act.

Applications must be accompanied by data to attest to the claimed safety, efficacy and quality. It may be acceptable to refer to data already held on file if the data meets expected standards.

Where the product details are identical to those submitted in the original application for consent, or in any subsequent CMN, it is sufficient to submit a declaration to that effect.

Where the details differ, the difference should be detailed and supporting data provided in the same way as is required for a CMN. If the change(s) is such that the safety profile of the product may have been altered, the data package should include a report of post-marketing surveillance from other countries in which the product has been marketed.

### **3.1.3. Combination packs of currently approved medicines**

A new combination pack containing two or more currently approved medicines packaged together constitutes a new medicine and the Minister's consent for its distribution must be obtained before it may be distributed. [Section 2](#) of the Act provides a definition of package.

## **3.2. New Medicine Applications**

An NMA is an application under [section 20](#) or [section 23](#) of the Act seeking the Minister's consent to distribute a new medicine.

In practice, the power to approve medicines is delegated to a senior Ministry of Health officer, referred to as the Minister's delegate.

To facilitate administrative processing of applications, NMAs are divided into three types as detailed in the following subsections.

Each unique product is the subject of a separate product approval and has its own separate entry in Medsafe's Therapeutic Products Database (SMARTI). A unique product is defined by its name, dose form, active ingredient(s), strength, flavour (if applicable) and classification.

When an application is made for consent to distribute a new unique product, an NMA must be submitted. Reduced data requirements and evaluation fees apply to NMAs for products that are closely related to an existing approved product.

## **Application selection tools**

Further assistance on selecting the correct NMA category may be made by reference to the application placement flow and the application placement question and answer tool in Appendices to this Guideline.

### **3.2.1. New Higher-risk Medicine Applications**

A New Higher-risk Medicine Application (NMA-H) is an application for Ministerial consent to distribute a:

- new medicine containing a new active substance (i.e., a new chemical, biological or biotechnological entity described as an innovative medicine application according to [section 23A](#) of the Act)
- new medicine with provisional consent under [section 23](#) of the Act (the data requirements are different for these applications)

- ☞ medicine (for full Ministerial consent under [section 20](#)) for which provisional consent for distribution under [section 23](#) has previously been granted
- ☞ new fixed combination product containing a prescription medicine
- ☞ new medicine with a new route of administration or novel pharmaceutical form
- ☞ prescription medicine with a new indication
- ☞ new vaccine
- ☞ new blood product
- ☞ new multi-source biological or biotechnological medicine (including biosimilars).

### 3.2.2. New Active Substance

A chemical or biological active substance (also known as an active pharmaceutical ingredient, API) is a **New Active Substance**, in line with the European Union definition, when it is:

- ☞ a chemical, biological or biotechnological substance for which Ministerial consent for distribution as a medicine in New Zealand has not previously been granted, or
- ☞ an isomer, mixture of isomers, an ester, a complex or other derivative, or a salt, of a chemical substance with Ministerial consent for distribution as a medicine in New Zealand but differing in properties with regard to safety and efficacy, or
- ☞ a biological or biotechnological substance for which Ministerial consent for distribution as a medicine in New Zealand has been granted, but differing in molecular structure, nature of the source material or manufacturing process.

New active substances are also known as new chemical entities (NCEs) or new biological entities (NBEs). New active substances need to be classified by the [Medicines Classification Committee](#) before the new medicine can be granted consent. Applicants are encouraged to submit a classification request prior to lodging applications to avoid delays.

### 3.2.3. New Intermediate-risk Medicine Applications

A **New Intermediate-risk Medicine Application** (NMA-I) is an application for consent to distribute a new medicine that is not a new higher risk medicine and is a:

- ☞ multi-source prescription medicine [Note that a multi-source biological or biotechnological medicine is a higher-risk medicine. The term “multi-source medicine” is now used in place of the term “generic medicine”.]
- ☞ Controlled Drug for which a prescription is required
- ☞ medicine with a new (but not novel) pharmaceutical form or a new strength or additional flavour of an approved prescription medicine
- ☞ prescription medicine with a new combination of excipients where it is intended that the new formulation will be marketed in addition to the existing formulation<sup>1</sup>
- ☞ prescription medicine with an extended indication
- ☞ injectable medicine

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<sup>1</sup> It is expected that changed medicines will be marketed concurrently until stock in market is replaced. It is expected that change in the market will be facilitated in a timely manner. A new medicine application is only required when it is intended that the new formulation represents an extension of the product range.

- irrigation solution
- dialysis solution
- medical gas.

### 3.2.4. New prescription medicines based on a parent product

A 'parent product' is a previously approved prescription medicine where the safety, efficacy and quality of the product have been acceptably demonstrated, and that complies with current standards. These application types are often referred to as line extensions.

Additional strength - Grade 1	<ul style="list-style-type: none"> <li>• new and parent products have the same dose form</li> <li>• new product is a direct scale of parent product, or uses same excipient matrix</li> <li>• all other details identical to parent product except for labelling and specifications</li> </ul>
Additional strength - Grade 2	<ul style="list-style-type: none"> <li>• new and parent products have the same dose form</li> <li>• new product is not a direct scale of parent product</li> <li>• bioequivalence study not required</li> <li>• all other details identical to parent product except for labelling and specifications</li> </ul>
Additional strength - Grade 3	<ul style="list-style-type: none"> <li>• new and parent products have the same dose form</li> <li>• new product is not a direct scale of parent product</li> <li>• bioequivalence study not required</li> <li>• other details different from parent product</li> </ul>
Additional strength - Grade 4	<ul style="list-style-type: none"> <li>• new and parent products have the same dose form</li> <li>• new product is not a direct scale of parent product</li> <li>• bioequivalence study included</li> <li>• method and site of drug substance and drug product manufacture, specification parameters, test methods and packaging unchanged</li> </ul>
Additional strength - Grade 5	<ul style="list-style-type: none"> <li>• new and parent products have the same dose form</li> <li>• new product is not a direct scale of parent product</li> <li>• bioequivalence study included</li> <li>• other details different from parent product</li> </ul>
Additional dose form - Grade 1	<ul style="list-style-type: none"> <li>• new and parent products have different dose forms and the same or different strengths</li> <li>• bioequivalence not relevant to new dose form</li> </ul>
Additional dose form - Grade 2	<ul style="list-style-type: none"> <li>• new and parent products have different dose forms and the same or different strengths</li> <li>• bioequivalence study or clinical data included</li> </ul>

### 3.2.5. New Lower-risk Medicine Applications

A **New Lower-risk Medicine Application (NMA-L)** is an application for consent to distribute a new medicine that:

- is not defined above as a Higher-risk or Intermediate-risk Medicine, and
- may be supplied without a prescription (i.e., an OTC product), and
- is recommended for indications that are already well documented for the active ingredient(s), and
- is presented in a pharmaceutical form that is monographed in a pharmacopoeia, and
- **either**
- contains active ingredients that are the subject of a pharmacopoeial monograph or
- contains active ingredients that have a well-documented history of use in OTC products (e.g., as evidenced by entries in Martindale etc.) or
- has active ingredients that are contained in one or more other products marketed OTC in New Zealand.

Lower-risk medicines may include products required to be sterile (e.g., eye drops).

A product containing a Controlled Drug for which a prescription is not required (e.g., pholcodine linctus or a codeine-containing combination analgesic) is evaluated using the New Lower-risk Medicine assessment procedure, provided it meets the criteria listed above.

New Intermediate-risk and Lower-risk Medicine Applications are sometimes referred to as “abridged” applications, because they do not contain the clinical and toxicological data required in a New Higher-risk Medicine Application. New Lower-risk Medicine Applications require less data as the medicine poses a lower-risk and can, therefore, safely be subjected to a lower level of regulatory control.

New Lower-risk Medicine Applications are further categorised into application types as detailed in Section 3.7 of this Guideline.

## 3.3. Abbreviated New Medicine Applications

### 3.3.1. Abbreviated evaluation process

Medsafe offers an abbreviated evaluation procedure in which review of overseas regulatory evaluation reports forms the basis of the evaluation. Therefore, the quality and availability of evaluation reports should be a fundamental consideration for applicants wishing to use the abbreviated evaluation process.

The abbreviated evaluation process is intended to be a simpler and quicker process than the standard evaluation process. This is reflected in the application fee.

The abbreviated evaluation process is not intended to be applicable to all medicine applications. For instance, it is known that the FDA does not issue evaluations reports for generic medicine applications. Consequently, it is not possible to submit a generic medicine application through the abbreviated evaluation route if it is based upon FDA approval.

The abbreviated evaluation process is not applicable to low-risk new medicine applications or Changed Medicine Notifications (CMNs). However, Medsafe strongly encourages applicants to consider providing international regulator evaluation reports and evidence of approval if this is available at the time of submission.

Applicants who are not eligible for the abbreviated evaluation process may submit via the standard evaluation process – by submitting a full dataset for assessment as required by the Medicines Act and the Guideline for the Regulation of Therapeutic Products in New Zealand (GRTPNZ).

### 3.3.2. Eligibility criteria

To be eligible for the abbreviated evaluation process the medicine must meet all of the following criteria:

- ☞ be an Intermediate-risk or High-risk medicine that has been approved by a recognised regulatory authority since 1 January 2001
- ☞ not be subject to any regulatory action that may result in a suspension or revocation of the market authorisation by any recognised regulatory authority
- ☞ have the same formulation as the product originally approved by the recognised regulatory authority
- ☞ have the same dosage and indications as the product originally approved by the recognised regulatory authority (does not apply to generic medicines which must be aligned with the NZ innovator)
- ☞ have current market authorisation issued by the recognised regulatory authority
- ☞ have undergone **NO MORE THAN TWO** of any of the following types of significant change and those changes must have been approved by the recognised regulatory authority:
  - ☞ significant changes in method of manufacture considered as a "Finished product manufacturing process – Grade 2" Changed Medicine Notification
  - ☞ addition of a new finished product testing site
  - ☞ addition of a new finished product manufacturing site
  - ☞ addition of a new active ingredient manufacturing site for which a Drug Master File is required
  - ☞ addition of a new primary packing site
  - ☞ extension of shelf-life (multiple extensions will be considered as one change as subsequent changes supersede earlier ones).

The application must be supported by a complete dataset as required by the Medicines Act and the GRTPNZ, consisting of Modules 1, 2, 3, 4, and 5 (as applicable). The dataset should reflect the product details being sought for registration

The original dossier submitted to the overseas authority must be in Common Technical Document (CTD) format and the dossier (submitted to Medsafe) must have been updated to incorporate the supporting data for any changes approved by the recognised authority.

The overseas evaluation report(s) must be in English, correspond to CTD structure and a complete record of the assessment (redacted reports are not acceptable).

Evidence of approval by the recognised overseas authority of the medicine and any of the above significant changes to it, is included in the application to Medsafe. Such evidence in



relation to applications from Europe can be in the form of either a marketing authorisation or notification from the authority of either a closed Centralised Procedure, Mutual Recognition Procedure, or Decentralised Procedure.

Note that a significant change that includes consequential changes can be counted as one change, providing that all changes were assessed and approved by the overseas authority at the same time as one application (e.g., a new finished product manufacturing site is consequentially registered as a finished product testing and primary packing site – all is considered one significant change).

Medsafe reserves the right to re-route any application to the standard evaluation process if the application does not fulfil the intent of the abbreviated evaluation process.

### 3.3.3. Recognised regulatory authorities

For the purposes of the abbreviated evaluation process, Medsafe recognises the following regulatory authorities:

- ☞ Australian Therapeutic Goods Administration (TGA) (excluding applications approved upon appeal)
- ☞ United States Food and Drug Administration (FDA)
- ☞ Health Products and Food Branch of Health Canada
- ☞ Medicines and Healthcare products Regulatory Agency (MHRA)
- ☞ European Medicines Agency (centralised procedure only)
- ☞ EU member states (decentralised or mutual recognition procedure only).

## 3.4. Applications for provisional consent

Provisional consent, under [section 23](#) of the Medicines Act, may be granted when it is desirable that the medicine be sold, supplied, or used on a restricted basis for the treatment of a limited number of patients. Provisional consent is only granted for a period not exceeding two years and will then expire.

Conditions may be included with a medicine that has provisional consent. These may relate to the person whom the medicine may be sold or supplied, the area in which the medicine may be distributed or other conditions. Any conditions relating to restrictions on supplying or prescribing the medicine are included in the *Gazette* notice.

Provisional consent is ideally suited to medicines still undergoing clinical assessment but where it is desirable that patients have early access. It is anticipated that the medicine will be used on a restricted basis until which time that the risks and benefits have been quantified and full consent can be granted.

In exceptional circumstances provisional consent may also be appropriate for medicines that will only be supplied in very limited circumstances for a period not exceeding two years.

### 3.4.1. Renewal of provisional consent

It is the sponsors' responsibility to ensure that provisional consent does not expire for the medicine. Applications for renewal of provisional consent must be submitted at least three months prior to the expiry of provisional consent. This is necessary to allow sufficient time for administrative processing, evaluation and publication of the *Gazette* notice.



If an application is received less than three months before the expiry of provisional consent there may be insufficient time to process a renewal of provisional consent and it will be required to be treated as a new provisional consent.

Renewal of provisional consent is for a period of up to two years from the date of expiry i.e., the current provisional consent expires on 30 October 2013 and the renewal of provisional consent is published on 22 August 2013, therefore provisional consent will now expire on 30 October 2015.

### **3.4.2. Conversion from provisional consent to full consent**

Sponsors of medicines with provisional consent should address the data deficiencies that were identified during the initial application to convert to full consent under [section 20](#) of the Medicines Act 1981.

It is expected that a sponsor should generally submit an application for full consent within five years of provisional consent initially being granted.

If a medicine has any conditions relating to restrictions on supplying or prescribing the medicine it is not considered suitable for full consent at this time.

Provisional consent must be maintained during the period that the application is undergoing evaluation for full consent. The evaluation timeframes will not be adjusted to avoid renewal of provisional consent being required.

## **3.5. Priority assessment of New Medicine Applications**

### **3.5.1. Criteria for priority assessment**

There are three eligibility criteria for granting priority assessment to a new medicine application. The criteria relate to medicines which address a significant clinical need, medicines which could deliver significant cost savings to the taxpayer, and medicines that are manufactured in New Zealand for export. The criteria are discussed below. Note that Changed Medicine Notifications are not eligible for priority assessment. Changed Medicine Notifications referred under [section 24\(5\)](#) of the Medicines Act 1981 are susceptible to the same eligibility criteria for priority assessments as NMAs.

#### **(A) Significant clinical need**

Requests for priority assessment on the basis of significant clinical need will be considered for applications for products containing new active substances or where alternative products are not available. Vaccines for the prevention of diseases are treated in the same way as other agents for the treatment of diseases. Cost saving does not constitute a significant clinical advantage, hence will not be taken into account when deciding whether a product meets the clinical criteria for priority assessment.

The sponsor of a medicine may request priority assessment if the medicine is indicated for the treatment or diagnosis of a serious, life-threatening or severely debilitating disease or condition for which other treatment options are limited. Sponsors may also request priority assessment to address an out-of-stock situation or withdrawal from the market of alternative medicines and it is essential that access to that treatment is maintained.

Medsafe has determined that there is capacity for up to four NMAs with priority assessment, on the basis of significant clinical need, to be undergoing evaluation at any one time. Requests for priority assessment on significant clinical need will only be granted if there is resource availability.

Requests for priority assessment can only be made by the New Zealand sponsor or distributor of the product.

Sponsors are encouraged to provide support for claims of significant clinical need by submitting material such as letters of support from PHARMAC, clinicians and consumer support groups.

### **(B) Significant potential cost savings**

A request for priority assessment of a medicine on the basis of potential cost savings can normally only be made by or with support from PHARMAC.

### **(C) Medicines manufactured in New Zealand for export**

A request for priority assessment of a medicine that is to be exported should be made by the sponsor at the time the application for consent is lodged. The request should include the following information:

- a statement that the medicine (prescription or non-prescription) is being manufactured in New Zealand for export (it is not necessary for the medicine to be produced exclusively for export)
- a declaration that early approval of the medicine in New Zealand would facilitate access to the intended export market(s).

Applications given priority assessment under the “exported medicines” criterion will have a lower priority than applications granted a priority under criteria A or B.

The Manager, Product Regulation decides which applications are accepted for priority assessment.

## **3.6. Application fees**

The Ministry of Health is responsible for administering the Medicines Act 1981 and Medicines Regulations 1984. Its functions in relation to this legislation are funded from a mixture of Crown funding and third party revenue collected from fees set under the Act.

The Act provides for the charging of fees in relation to applications for licences and for the approval of new and changed medicines and clinical trials. The schedule of fees payable is contained in regulation 61 of the Regulations.

Regulation 61A of the Regulations provides that the Director General of Health may waive or refund, in whole or in part, a fee otherwise payable under regulation 61.

In exercising this power the Director-General is obliged to have regard to the degree of complexity and time required to consider an application, and the interests of public health in New Zealand.

A ‘standard’ waiver is applied in a number of instances to reduce the fee for approval of a new or changed medicine in order to recognise the reduced time required to consider the application. For example, a partial waiver is routinely applied to applications for approval of new non-prescription medicines.

A partial fee waiver is also available for applications made under the abbreviated process for new prescription medicines already approved by a recognised overseas regulator.

The actual fee payable for an application of a particular type, after application of any applicable standard waiver, is set out in a [schedule of fees](#).

Applicants may request additional partial or fee waivers in accordance with [regulation 61A](#) of the Medicines Regulations 1984.

### 3.7. Further categorisation of New Lower-Risk Medicine Applications

New Lower-risk Medicine applications are further categorised as described below. A flow chart is also available in Appendix 2 to assist with categorisation.

#### N1 applications – clones

The N1 application category includes applications for ‘clones’. The term ‘clone’ is used in relation to OTC medicines that are identical in all respects to a previously approved ‘parent product’, apart from the aspects detailed below.

Where a product is accepted as a ‘clone’, reduced supporting data is required (limited to the proposed labelling, package insert, CMI and data sheet (where applicable), GMP and finished product specifications (specific for the product under evaluation)).

‘Clone’ applications must comply with the following requirements:

- the ‘clone’ must be identical to the ‘parent product’ in all respects other than the product name and labelling. Note: the acceptability of the proposed name and labelling will be fully assessed as part of the evaluation of the ‘clone’ application
- the ‘parent product’ must have been previously approved and comply with all current regulatory requirements, including the Medsafe Label Statements Database
- the sponsor of the ‘parent product’ must authorise Medsafe to access the ‘parent product’ information
- if the sponsor of the ‘parent product’ is not the same as the clone the sponsor must hold a full copy of the supporting data from the dossier
- the product name cannot include an umbrella segment that is restricted to a higher category assessment. Guidance on umbrella branding and the placement of umbrella branded products in the risk categorisation frameworks can be found in the appendix 3 of this document and the Guideline on the Regulation of Therapeutic Products in New Zealand, Part 5: Labelling of medicines and related products.
- if the ‘clone’ product name contains an umbrella segment where there is no restriction on application category, the sponsor must make their own assessment of the labelling including the unique segment of the medicine name to ensure consumers can easily differentiate the medicine from other medicines in the range.

The ‘clone’ application needs to include:

- a letter from the sponsor of the ‘parent product’ authorising Medsafe to access information on the ‘parent product’ to support the ‘clone’ application
- the cover letter for the application must include assurances that:
  - all quality aspects of the proposed ‘clone’ product are identical to the ‘parent product’, and that the sponsor will ensure that the ‘clone’ product will comply with all applicable regulatory requirements and
  - the ‘clone’ will comply with any specific conditions imposed by Medsafe on the ‘parent product’

- ☞ marked up and clean copies of all 'clone' labels, package inserts, data sheet and CMI (where applicable)
- ☞ the 'clone' labels, package insert, CMI and data sheet (where applicable) need to comply with current regulatory requirements, including the Medsafe Label Statements database
- ☞ copies of the most recently approved labels, package insert, CMI and data sheet (where applicable) for the 'parent product'. These must comply with current regulatory requirements, including the Medsafe Label Statements Database
- ☞ evidence of current GMP certification
- ☞ details of New Zealand site of batch release
- ☞ if the 'clone' product name contains an umbrella segment where there is no restriction on application category, labels for other medicines in the umbrella range should be provided to demonstrate that consumers can easily differentiate the medicines from other medicines in the range
- ☞ a copy of the finished product specification, specific for the product under evaluation, and stating the proposed clone name, complies with current regulatory requirements
- ☞ if a different pack size is proposed, an assurance that the container type is unchanged and the container material is unchanged.

## N1 applications – flavour/fragrance/colour variants

The N1 application category also includes extension applications for flavour/fragrance/colour (FFC) variants, where the medicine meets all of the requirements applying to a 'clone' (refer Section 3.7 of this Guideline) except for the inclusion of a different FFC.

A FFC extension application can only be submitted as an N1 application if it complies with the following:

- ☞ all of the requirements applying to 'clones', with the exception that the FFC may differ from the 'parent product'.

A FFC extension application must include all of the information and assurances required for a 'clone' application, together with the following:

- ☞ the cover letter for the application should include an assurance that all quality aspects, other than those directly related to the FFC, of the proposed 'clone' product are identical to the 'parent product', and that the sponsor will ensure that the 'clone' product will comply with all current regulatory requirements
- ☞ a copy of the raw material specifications for the 'parent product' FFC and the new FFC variant
- ☞ confirmation that any proprietary ingredients have been added to the Medsafe Proprietary Ingredient Register (and the reference number provided). Note, new Proprietary Ingredients should be added to the register following the process outlined in this Guideline.

## N1 applications – new pack size/classification

The N1 application category also includes NMAs for an additional pack size, where an active ingredient has been down-scheduled and/or the classification is dependent on pack size. The application must meet all of the requirements applying to other 'clone' applications except for the resultant change in pack size, classification statement and labelling.

An additional pack size/classification application can only be submitted as an N1 application if it complies with the following:

- ☞ all of the requirements applying to 'clones', with the exception that the pack size and classification may differ from the 'parent product'.

An additional pack size/classification application must include all of the information and assurances required for a 'clone' application, together with the following:

- ☞ the cover letter for the application should include an assurance that all quality aspects, other than those directly related to the pack size/classification change, of the proposed 'clone' product are identical to the 'parent product', and that the sponsor will ensure that the 'clone' product will comply with all current regulatory requirements.

## N1 applications – new combination pack

The N1 application category also includes NMAs for a new combination pack containing two or more previously approved 'parent products' when both products are contained within a fully labelled outer container (e.g., carton). The container for each component of the combination pack must be unchanged from that previously approved, and being in a combination pack must not affect the stability or shelf life of each component. There cannot be any change to indications or dosage of any component of the combination. The application must meet all of the requirements applying to other 'clone' applications except for resultant labelling.

## N2 applications – OTC monograph

Note: Category N2 is not currently applicable in New Zealand.
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## N3 – N5 applications

Applications for NMAs within the N3 – N5 categories are more complex than N1 and N2 applications and have different data requirements depending on the nature of the particular application. A summary of the data requirements for OTC medicine applications are described in appendices 6, 7 and 8. Applicants submitting via the N3 – N5 routes to approval should note the following requirements in addition to the generalised dossier requirements.

- ☞ Module 3 in CTD format is required to support the quality of the product. However, where all quality aspects of the product are identical to a 'parent product' that has been previously approved by Medsafe then the sponsor may provide an abbreviated Module 3 dossier. Where an abbreviated Module 3 dossier is submitted, the sponsor must provide:
  - ☞ a letter from the sponsor of the 'parent product' authorising Medsafe to access information on the 'parent product' to support the application

- ⌚ finished product specifications for the proposed product, specific for the product under evaluation, and stating the proposed clone name
  - ⌚ evidence of current GMP certification
  - ⌚ proposed labels
  - ⌚ details of New Zealand site of batch release
  - ⌚ an assurance in the cover letter that all quality aspects are identical to the 'parent product', and identifying the areas of difference (note: dependent on the areas of difference additional information may be required).
- ⌚ CTD Module 4 and Module 5 may be required for N4 and N5 applications to support the safety and efficacy of the product.
  - ⌚ If the product name contains an umbrella segment where there is no restriction on application category the sponsor must make their own assessment of the labelling, including the unique segment of the medicine name, to ensure consumers can easily differentiate the medicine from other medicines in the range. Labels for other medicines in the umbrella range should be provided in order to demonstrate that consumers can easily differentiate the medicines from other medicines in the range.

### N3 – products

New application for a 'generic' medicine other than those 'generic' applications in categories N1, N2 or N4. Typically this application type derives the evidence for safety and efficacy by comparison to previously approved products.

### N4 – products

The risk categorisation framework for NMAs in Appendix 5 details safety and/or efficacy data requirements for lower risk medicines for which safety and efficacy cannot be derived from the formulation alone.

These medicines include:

- ⌚ modified release products (excluding enteric coated tablets/capsules)
- ⌚ generic versions of a registered product where bioequivalence data are required or where a justification for not providing bioequivalence is required
- ⌚ products that include a new excipient or an excipient with a new route of administration
- ⌚ products where an equivalence statement is requested and where bioequivalence evaluation is required or where a justification for not providing bioequivalence is required
- ⌚ formulation dependent topical products
- ⌚ an application for an OTC product as a result of a change in scheduling for a particular product from the 'Prescription Only Medicine' schedule to a lower (OTC) schedule, where no such products are previously approved as an OTC medicine.

## N5 – Generic extension / new chemical entities

In general OTC medicines should only contain active ingredients that have a long history of use in medicines. However there are circumstances where a new OTC medicine may contain a new chemical entity. To be eligible for assessment as an OTC medicine all of the following conditions must apply.

- ☞ The active ingredient is classified as an OTC medicine or has been confirmed by the Medicines Classification Committee (MCC) as suitable for general distribution (i.e. agreed that the substance need not be scheduled).
- ☞ The overall presentation of the product is suitable for OTC sale, i.e. indicated for self-limiting, self-diagnosed conditions and suitable for self-selection by consumers.
- ☞ The active ingredient is widely used in New Zealand, Australia or the United Kingdom as an OTC medicine or in New Zealand as a food ingredient (including dietary supplements).

The N5 route may also be used for a new OTC medicine that is an extension of an N3 product including:

- ☞ new therapeutic indications
- ☞ new strengths
- ☞ new dose forms
- ☞ new directions
- ☞ new combination products
- ☞ different patient population.



## Section 4: Changed medicine notifications

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A CMN is a notification to the Director-General of Health by the sponsor of a product, under [section 24](#) of the Act, of a planned material change to an approved product (this includes prescription and non-prescription medicines and related products), and the reasons for the change.

If any change to a product results in a new active ingredient, new combination of active ingredients, new strength, new dose form, new flavour or new trade name an NMA (**not a CMN**) is required. The NMA must be kept separate from and will be processed separately from any other CMN. The new product cannot legally be distributed until consent has been granted and published in the [New Zealand Gazette](#).

### 4.1 Risk-based notification categories

A material change to an approved medicine may require evaluation (in which case an evaluation fee is payable) or be self-assessable (in which case an administrative fee is payable).

Assessable changes are notified through a CMN and consent must be obtained before the changed product can be distributed. Often one change in a medicine leads automatically to other changes (e.g., a change in formulation will often result in changes in manufacture, quality control and stability).

CMNs that require evaluation are categorised into three types and the fees applied depend upon the type of product and the amount of evaluation involved.

- |           |   |
|-----------|---|
| Type I:   | Lower-risk medicines  |
| Type II:  | Intermediate-risk or Higher-risk medicines other than biological or biotechnological products (but including antibiotics and like substances derived from micro-organisms)  |
| Type III: | Biological, or biotechnological products (i.e., vaccines, serums and allergens, medicinal products derived from human blood or plasma, immunological medicinal products, and products derived from biotechnology) |

Details of the various types of assessable and self-assessable changes and the applicable fees are given in the [CMN forms](#). The forms include common material changes (and changes consequent to these) and are designed to be as comprehensive as possible. If an intended change is not included in the relevant form, seek advice from Medsafe.

### 4.2 Self-assessable changes

For self-assessable changed medicine or related product notifications (SACNs), there is no requirement to obtain consent prior to making the change. However, the notification must precede the change. The onus is on the sponsor to ensure that data to support the change are held and are made available on request. Such changes are to be notified using the same [CMN form](#) as used for notifying assessable changes.

A SACN is considered validated when payment for the application has been received. Formal consent letters are not issued for SACNs.

Sponsors should note that self-assessable changes submitted within the same application as an assessable change must not be implemented until the entire CMN is approved.



Medsafe carries out random audits of self-assessable changes and, where any significant problems are identified the sponsor is required to rectify them. Where a CMN rather than a SACN should have been submitted, the sponsor will be required to submit a new notification, without refund of the cost of the SACN.

### **4.3 Making multiple changes for the same therapeutic products**

Where more than one change type is being proposed within a single CMN, the application category is determined by the highest application category.

### **4.4 Making the same changes for multiple therapeutic products**

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

If a sponsor puts in the same change for multiple products with different classifications (i.e., prescription and restricted versions of the same medicine; or different medicines with different classifications (e.g., sponsor changes)) the whole application will be treated as a prescription medicine CMN.

If all changes are self-assessable and include a data sheet, products should be split on a per data sheet basis.

### **4.5 Combination packs and 'mixed' sponsorship**

Where a medicine is distributed as a complete finished product by one (primary) sponsor and the same finished product is also distributed by a second sponsor in a combination pack together with other product(s), both sponsors are responsible for ensuring that the Director-General of Health is notified of any material changes affecting the medicine or related products in each of its presentations.

Where a medicine is distributed by a second sponsor as a 'clone', both sponsors are similarly responsible for ensuring material changes are notified.

There should be a commercial agreement between the two sponsors ensuring that the necessary information is exchanged between them and the necessary CMNs are lodged with Medsafe. The primary sponsor may lodge the appropriate CMNs for both presentations. A separate notification is required for each presentation of the product as consent must be issued for each.

### **4.6 Abbreviated and priority assessment of notifications**

The statutory timeframe for CMNs is that the initial evaluation must be completed within 45 days. Medsafe typically completes its initial evaluation in a shorter timeframe (see Section 11 of this Guideline). CMNs therefore are not eligible for priority assessment.

Medsafe does not operate an abbreviated process for CMNs. If the same change(s) has been approved by a recognised regulatory authority that authority's evaluation report is available, a copy should be included with the CMN. The overseas evaluation report will be considered during Medsafe's evaluation.

## 4.7 Referrals under Section 24(5) of the Medicines Act 1981

[Section 24](#) of the Act sets out restrictions on the distribution of changed medicines.

Subsection 5 permits the Director-General of Health to refer a medicine (that is the subject of a CMN) to the Minister in certain circumstances. Such a referral occurs when a CMN is of such a character or degree that the medicine should not be distributed without consent of the Minister or that the DG is insufficiently informed about the change proposal.

Examples of CMNs that are typically referred under Section 24(5) include:

- additional indications or extensions to the current indication or dosing regime
- new sites of drug substance manufacture (involving a new Drug Master File)
- 'Grandmother's axe' products (when changes are so significant that the proposed product no longer resembles the approved product)
- failure to respond to requests for information.

The timeframe for a CMN referred under section 24(5) of the Medicines Act is the same as a new intermediate-risk medicine application.

Changed Medicine Notifications referred under section 24(5) of the Medicines Act 1981 are susceptible to the same eligibility criteria for priority assessments as NMAs (see Section 3.5 of this Guideline).

## 4.8 Changing the registration situation

Sponsors of medicines can choose to designate their products 'not available' if they wish to communicate the unavailability to the public and healthcare professionals. Sponsors who do not wish to maintain published data sheets for prescription and restricted medicines can designate their medicines 'not available' in the therapeutic products database.

Sponsors who wish to surrender consent because they do not intend marketing the medicine again in New Zealand may notify Medsafe and the status will be updated to 'approval lapsed'. Approval lapsed is also used to denote medicines that have been not been generally available for more than five years as described in Section 3.1.

A change in the registration situation to 'not available' or 'approval lapsed' can be effected either by notification as part of a CMN/SACN or notified to Medsafe at any other time. Sponsors should use the [Product Status Change Request form](#). Sponsors should include advice as to when the product was last marketed in New Zealand.

There is no cost associated with updating the registration situation to 'not available' or 'approval lapsed'.

To change the registration situation from 'not available' to 'consent given' or 'provisional consent', a CMN is required to be submitted and granted consent prior to the registration situation being updated and the product being reintroduced into the market. When requests are submitted as part of a CMN it should be clearly identified in the cover letter. For prescription or restricted medicines the CMN must include a revised data sheet to demonstrate that all required updates have been included. The CMN must undergo evaluation and self-assessable change notifications will not be accepted.

If a sponsor determines that a CMN is not required because the regulatory file has been kept up to date, a justification letter or [Product Status Change Request form](#), for the registration situation to be changed to 'consent given' or 'provisional consent' should be provided to Medsafe. Medsafe will review the justification letter or form to ensure that all requests for CMNs have been addressed prior to the registration situation being updated and the product being reintroduced into the market.

CMNs, justification letters or [Product Status Change Request Forms](#) must be submitted at least 90 days prior to the intended date distribution will commence. Justification letters should be addressed to the Manager, Product Regulation.

If approval has lapsed, consent to the distribution of a new medicine needs to be granted before the product can be reintroduced onto the New Zealand market as described in Section 3.

## 4.9 Non-notifiable changes

The following are examples of changes to the registered particulars that are not regarded as a material change (i.e., a CMN is not required). Sponsors can request the file to be updated at no charge.

- Removal of manufacturing/packing sites. A [Request for Removal of Manufacturing, Testing or Packing Site from Therapeutic Product Database Report](#) must be completed.
- Change in registration situation (see Section 4.8).
- Change in proprietary ingredient subject to the following conditions:
  - the new proprietary ingredient is the same type (i.e., black ink, orange flavour)
  - the new proprietary ingredient is already registered.
- New or changed site of New Zealand batch release.
- Change in excipient supplier.
- Routine maintenance of processing equipment.
- Change in name of a manufacturing or packing site subject to the following conditions:
  - there is no change of ownership
  - the change in name affects the whole site (i.e., name change is not restricted to selected buildings)
  - a GMP certificate has been provided with the new site name.

### 4.9.1 Changes in pharmacopoeial specifications

A CMN is **not** required for updating of specifications for an active ingredient, excipient or finished product to conform to the most recent edition of the relevant pharmacopoeial monograph. Manufacturers are expected to keep their specifications in line with any revisions to those monographs.

However, a CMN **is** required if there is a change from the specifications of a monograph in one pharmacopoeia to that in another pharmacopoeia, or from in house specifications to a pharmacopoeial monograph (or *vice versa*).

#### 4.9.2 Changes in names of manufacturers or packers

When the name of a manufacturer or packer is changed but there are no changes to the address or the manufacture or packing processes a CMN is not required. Instead, the sponsor should advise Medsafe by letter so that Medsafe can update its records. A CMN is required if the change in name is a result of a change in ownership.

When there is a change in name of a manufacturer or packer, each sponsor that uses the site is responsible for notifying the change to Medsafe.

#### 4.9.3 Updates to Drug Master Files

Drug Master Files (DMFs) should be updated periodically to reflect any changes. Sponsors should ensure that such updated DMFs (together with a list of changes made), or (at least) details of any changes made, are forwarded to Medsafe. The sponsor should determine whether any material changes have been made to the product and submit the CMN to Medsafe (if required).

#### 4.9.4 Updates to Plasma Master Files

Plasma Master Files should be updated at least annually. For guidance regarding the content of the update, refer to EMEA/CHMP/BWP/3794/03 Rev.1 (Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) Revision 1). The sponsor is required to forward a hard copy of the revised PMF (plus any associated evaluations and approvals) to Medsafe which then considers the changes and, if action is required, advises the sponsor accordingly. This will include a request for submission of a CMN to cover introduction of new establishments for supply of plasma.

#### 4.9.5 Changes to Working Cell Banks or Working Seeds

Manufacture of many Type III (biological or biotechnological) products involves the use of cultured cells, either as hosts for propagation of viruses (e.g., mammalian cell culture), or themselves to express active molecules (e.g., recombinant mammalian cell culture, recombinant or wild type bacteria or fungi). These cells are often passaged from the Master Seed (or Master Cell Bank) to give a Working Seed (WS) or Working Cell Bank (WCB). The same strategy is used to lay down Working Seeds for bacteria and viruses used in manufacture of vaccines.

An advisory letter (with no payment), rather than a CMN, is required for production (and use) of a new lot of WCB or WS (henceforth referred to simply as WCB) **if all of the following conditions are met.**

- ☞ The currently approved dossier does not dictate use of a particular lot or batch of the WCB.
- ☞ The new WCB is derived from the previously approved Master Cell Bank, is manufactured using facilities, materials and processes already approved by Medsafe for this purpose, and meets a specification approved by Medsafe when tested following methods approved by Medsafe. Current pharmacopoeial requirements for the WCB, and its methods of manufacture and testing, must also be met.
- ☞ The use of the new WCB is qualified following a protocol already approved by Medsafe for this purpose, and the company provides an assurance that any apparent aberrant results seen during routine full-scale use will be communicated immediately to Medsafe.

- ☞ No deleterious changes to the product's adventitious agent safety profile are introduced by use of the new WCB. Current Notes for Guidance and ICH Guidelines concerning minimising contamination with adventitious agents (viral and TSE) are complied with.
- ☞ The currently approved dossier makes reference to the fact that advisory letters (rather than CMNs) will be used to inform Medsafe of changes to WCB, with Medsafe having the option to request and review further information as it sees fit. It could be that the dossier includes a commitment to provide certain data (e.g., results of testing and/or preliminary qualification) with the advisory letter.
- ☞ The advisory letter confirms all of the above, and is sent, along with any relevant data, prior to routine use of the WCB commencing.

A CMN (Bulk active methods of manufacture) is required to lodge the above information, and to propose the future use of advisory letters, unless this is covered in the NMA.

A CMN (Bulk active methods of manufacture) is also required if any of the above requirements are not met, or if changes are to be made to any details of manufacture or testing, or if any changes are to be made to Master Seed or Master Cell Bank.

#### **4.9.6 Addition or change to New Zealand Site of Product Release**

To add or change the New Zealand Site of Product Release a CMN is not required. Instead, the sponsor should advise Medsafe in writing so that Medsafe can update its records.

#### **4.10 Change of sponsor**

A change of sponsor should be submitted in the relevant application category and include letters or other evidence from both the proposed and current sponsor accepting and relinquishing sponsorship of the product(s). Additional changes to the product label and data sheet (if applicable) should be included as part of the same application whenever possible.

If the change in sponsor requires a change in contact details on the medicine label, it is acceptable for the sponsor to manage a transition period to allow time to generate new labels and sell through product in the distribution change.

Transition periods should be minimised to prevent confusion. As a general guide an acceptable transition for product in the distribution chain is three months for wholesale and six months for retail.

During the transition period the sponsors must have an agreement in place whereby any correspondence received by the relinquishing sponsor relating to the medicine is promptly forwarded.

New sponsors should ensure that they meet the requirements as detailed in Section 2.1.

#### **4.11 Fees for changed medicine notifications**

Fees for CMNs are contained in the notification form and the [fees schedule](#). Fee waivers are rarely granted for changed medicine notifications especially when the changed notified relates to multiple products. This is because the change must be added to each regulatory file and the administrative cost must be recovered.

## 4.12 Effecting a change in the market place

It is anticipated that, in usual circumstances, a change to a marketed medicine will be introduced into the market in a timely manner with time allowed to sell through existing stock. An acceptable change over in the market is medicine dependent as low volume or seasonal medicines may take longer to sell through.

In general Medsafe expects changed medicines to be presented to the market within the following time periods:

- ☞ 3 months for new stock from wholesalers
- ☞ 6 months for new stock from retailers.

Companies considering longer lead times should include a justification in the CMN.

Companies should not request a deletion of any approved regulatory information (data sheets, manufacturing sites etc) until stock has exited the New Zealand market.

Changes to existing products that have been initiated for safety concerns may need to be effected rapidly in conjunction with a product recall.

## Section 5: Guide to preparing new medicine applications

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### 5.1 Formats for New Medicine Applications

Applications for consent to distribute a new medicine must use the Common Technical Document (CTD) format as described in the ICH Guideline [“Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use”](#)

The CTD format is comprised of

- Module 1 Administration information and prescribing information for New Zealand
- Module 2 Overviews and Summaries of the Quality, Non-clinical and Clinical data
- Module 3 Quality
- Module 4 Non-clinical Study Reports
- Module 5 Clinical Study Reports

The expectation of the quality, safety and efficacy data is further described in the following ICH guidelines:

- ICH M4Q common technical document for the registration of pharmaceuticals for human use: Quality. Overall summary of Module 2 Module 3
- ICH M4S the common technical document for the registration of pharmaceuticals for human use: Safety. Nonclinical overview and nonclinical summaries of Module 2 organisation of Module 4
- ICH M4E the common technical document for the registration of pharmaceuticals for human use: Efficacy. Clinical overview and clinical summary of Module 2 Module 5: clinical study reports.

It is not necessary to include modules and documents that are not required for a specific application.

It is the applicant's responsibility to ensure the application is complete and contains sufficient evidence to attest to the safety, quality and efficacy of the medicine in accordance with international and national guidelines.

Medsafe's advice regarding acceptable evidence and the guidelines it prefers to during its assessment is in Appendix 8 of this Guideline.

If a module or document is required but cannot be provided or the information therein does not comply with the requirements outlined in the guidelines utilised by Medsafe, a robust scientific justification must be provided instead.

New medicine or related products applications may be submitted only partially in hard copy providing that the entire application is provided in electronic medium. CMNs may similarly be provided only partially in hard copy. Further information on the requirements for e-submission is in Section 9.2 of this Guideline.

### 5.2 New Zealand Module 1 requirements

The **administration and prescribing information for New Zealand** consists of the following documents (as applicable for the particular type of product):



- ☞ covering letter
- ☞ completed NMA form(s)
- ☞ signed declaration and commitments form
- ☞ EDQM Certificates of Suitability
- ☞ Good Manufacturing Practice (GMP) documentation
- ☞ labelling (see [Part 5: Labelling of Medicines and Related Products](#))
- ☞ information leaflet/package insert/CMI (See [Part 10: Requirements for Information for Prescribers and Consumers](#))
- ☞ data sheet (see [Part 10: Requirements for Information for Prescribers and Consumers](#))
- ☞ copies of overseas evaluation report(s) and approval documentation.

Each new medicine application must be accompanied by an [application form and a signed declaration form](#). A separate form should be completed for each separate medicine (name, dose form, drug substance, strength, classification and flavour as applicable).

### 5.3 General data requirements

An application for a new higher-risk medicine needs to be accompanied by an extensive **dossier of supporting quality, safety and efficacy data**. Safety and efficacy data is typically generated from randomised, placebo controlled clinical trials conducted in accordance with [ICH Guidelines](#).

New intermediate-risk and lower-risk medicines usually contain active ingredients that are listed in a pharmacopoeia and claim indications for which there is sufficient supportive published literature. In general the safety and efficacy can be demonstrated by reference to other approved medicines and as such are sometimes referred to as ‘abridged’ applications.

In some cases, a new intermediate-risk or new lower-risk medicine application may need to contain clinical documentation to support the proposed indications, and also possibly relevant toxicological and pharmacological documentation. This is generally applicable to new intermediate or lower-risk medicine applications that include novel indications.

While an application for provisional consent need not contain the same detail of safety and efficacy data as that required for full consent, all available information should be included, along with an explanation of the type of data still being collected and when these data will be available.

When the product that is the subject of an NMA is closely related to an existing product, such as a new strength, the applicant is only required to submit data relevant to the introduction of the new product. The application must specify all differences between the new and existing products and provide data to support the safety, quality and efficacy of the new product. A complete dossier duplicating data already supplied by the applicant for an existing product is not required.

Different pharmaceutical forms and strengths or flavours of a medicine require separate application forms, but may be supported by reference to the same dossier of information.

Where a medicine has been evaluated and approved in Australia, Europe, Canada or the USA, and the overseas approval documentation and evaluation reports are available, sponsors should provide copies of those reports along with an indication as to whether the supporting data submitted overseas was identical or not to the data submitted with the New Zealand application.



Product Development Pharmaceuticals are not normally required for lower-risk medicines. They may be required for unusual dose forms or formulations.

Where pharmacopoeial test methods are used to control a finished product, sufficient validation data should be provided to confirm that the test methods work satisfactorily for the product concerned.

Applications to distribute medicines described as biosimilars need to be accompanied by data according to annexes to the [CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues](#). Applications must also include any additional data as required by the Medicines Act 1981 and the NZRGM and a risk management plan covering the introduction of the product to New Zealand. Further information about Medsafe's position on biosimilars is available on its website at [www.medsafe.govt.nz/profs/Rlss/Biosimilars.asp](http://www.medsafe.govt.nz/profs/Rlss/Biosimilars.asp).

Additional information on the data requirements for specific application types is available in the appendices.

## 5.4 Formatting of documents

- ☞ All information in the dossier is to be in English, legible and easily located.
- ☞ Abbreviations and acronyms must be defined and included in a glossary.
- ☞ The documents must be numbered.
- ☞ The dossier must be divided into documents using tabs.
- ☞ Each part of the application must contain a detailed Table of Contents.

## 5.5 Older dossier formats

In exceptional circumstances Medsafe also accepts the EU format for the dossier as detailed in the European Commission's Rules Governing Medicinal Products in the European Union, Volume 2B: Notice to Applicants, 1998 edition, in cases where the dossier has previously been assembled and submitted in that format to a regulatory authority in Europe or Australia and the product has not undergone significant post-approval modification.

Medsafe does not expect applicants to re-format such material to the CTD format. If an application dossier in EU format is available, this should be submitted unchanged **except** for "Part IA" (Administrative Data) which must be replaced with the New Zealand NMA form so that all information relevant to the New Zealand application is presented and that specific to EC administrative requirements is omitted. The accompanying "Part IB" documents (GMP documentation, data sheet, labelling, etc.) should be submitted as they are or adapted to New Zealand requirements, as appropriate.

The application must be accompanied by a complete dataset as required by the Act and the GRTPNZ, consisting of the equivalent data as described in CTD Modules 1, 2, 3, 4, and 5 (as applicable). The dataset must reflect the product details being sought for registration. In cases where the product details have been changed post-approval, the original dossier must be updated with all changes incorporated.

A detailed Table of Contents must be provided with any dossier, regardless of the format, to assist evaluators in their assessment. It is expected that non-CTD format are cross-referenced to CTD format to assist with the location of information.

## **5.6 General requirements for applications based on a ‘parent product’**

The name and TT50 file reference number of the parent product must be provided.

The relationship between the two products should also be detailed in the cover letter. Full access rights to the parent product must be provided (if the parent product is owned by another sponsor).

The differences between the parent product and new product determine the type of application category and associated evaluation fee.

## **5.7 Format for RFI responses**

The only allowable exemption to using the CTD format is for responses to requests for further information (RFIs), but only when the additional information or data is limited in volume. It is important for all RFI responses that the additional information or data be cross-referenced to the outstanding questions/issues in the RFI letter in numerical order.

## Section 6: Proprietary Ingredients

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Medsafe has generated a register of Proprietary Ingredients to ensure accurate and up-to-date information is held on Proprietary Ingredients used in pharmaceutical products marketed in New Zealand.

### 6.1 Registration of a Proprietary Ingredient with the database

The Act requires sponsors to disclose all ingredients in a product including the formulation and manufacturing controls on Proprietary Ingredients. This information is used to register Proprietary Ingredients within the Medsafe database. The database is independent of product files thereby allowing several sponsors to quote a common Proprietary Ingredient in their formulations.

The following information is required to register a Proprietary Ingredient:

- the full name of the Proprietary Ingredient
- any unique identification number associated with the Proprietary Ingredient
- the manufacturer name
- the qualitative formulation
- the quantitative formulation
- a copy of the specifications from either the sponsor or the manufacturer.

The following information will not be acceptable in fulfilling the above requirements:

- material safety data sheets – these do not list all the ingredients
- the Proprietary Ingredient's ARTG number from Australia's TGA – Medsafe cannot obtain the required information from the TGA.

The sponsor can request the supplier of the Proprietary Ingredients to provide the information directly to Medsafe for confidentiality. The information can be submitted electronically (to [medsafeapplications@moh.govt.nz](mailto:medsafeapplications@moh.govt.nz)) or by post.

Any Proprietary Ingredient that is notified to Medsafe is registered with the database and allocated a unique reference number. This reference number can be quoted in all subsequent applications instead of submitting the required information. Reference numbers are sent to companies upon registration.

### 6.2 Proprietary Ingredient form

The [Proprietary Ingredient form](#) has been developed to act as an 'audit trail' between companies that market registered medicines, the Proprietary Ingredient supplier and Medsafe to assist all parties in monitoring the information flow. Medsafe regards the use of the form as voluntary.

The form has been prepared in response to difficulties in collecting the confidential information from Proprietary Ingredient suppliers. The sections to be completed in the form have been developed based on the information required to register a Proprietary Ingredient in the database.

## 6.3 Registration search

Proprietary Ingredients can be checked for registration by searching the 'ingredient field' in the Medsafe Product/Application database. [This is accessed on the Medsafe website.](#)

The Proprietary Ingredient name can be entered to search for registration.

- Colours, coating agents and inks are registered as brand name, colour, ID number e.g., Opadry white 123456.
- If the colour or ink does not have a brand name, special categories or colour and inks are used to register them e.g., Edible ink 123456.
- Flavours are registered as type, flavour, ID number e.g. Orange flavour 123456.

Alternatively, the finished product name can be searched in the Medsafe Product/Application Search database under the 'trade name' field to check for Proprietary Ingredient registration. The information for registration will appear in the product details under the excipient section.

Registered Proprietary Ingredients have a reference number alongside the Proprietary Ingredient name. If a Proprietary Ingredient is registered but is not linked to your product, please contact Medsafe to confirm the use of the Proprietary Ingredient in your product.

## Section 7: Guide to preparing a changed medicine notification

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### 7.1 Formats for changed medicine notifications

Changed medicine notifications must also use the CTD format as described in the ICH Guideline [“Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use”](#). Only the sections relevant to the change need to be completed

CMN forms and fee schedules are published on the Medsafe website. CMN Form A should be used for Type I and Type II products while CMN Form B should be used for Type III products.

Each CMN involving a material change must be accompanied by a CMN form and summary sheet, providing administrative details and outlining the changes being notified. A separate sheet should be completed for each product and all sections must be completed. Applicants should submit one copy of the form, summary sheet and any supporting documentation.

Where an applicant applies for consent to distribute a new medicine or related product and notifies the Director-General of changes to a currently marketed product at the same time the documentation must be kept separate. It is not acceptable to combine a CMN with an NMA.

Medsafe will not accept further changes to a CMN after it has been submitted (except, perhaps, to indicate or clarify changes consequential to the changes notified in the original CMN). If further (non-consequential) material changes are intended a new CMN and fee are required.

Note that when Medsafe issues formal consent for a change to a medicine or related product, only those changes specifically identified and applied for in the CMN form are covered by the consent. Material changes included in any accompanying documentation but not specifically identified in the CMN form and consequently not assessed as changes, are not included in any consent that may be granted for the CMN.

Consequential changes are grouped with some material changes for the purpose of fees calculations. However, these changes must be identified separately and supported by appropriate data or documentation, if relevant.

Each change included in a CMN is assessed separately. In some cases, Medsafe may consider that only some of the proposed changes can be approved. This may be because the supporting data submitted with the CMN do not justify the other changes proposed.

In this situation, if the sponsor is unable to supply acceptable data to support the proposed change(s), a recommendation to withdraw those changes from the CMN will be made to the sponsor. This will enable consent to be granted for the approvable changes.

Partial consent for some of the changes, with other changes assessed later, is not Medsafe's current practice. Any proposed changes withdrawn from a CMN can be resubmitted as a new CMN at a future date when the required supporting data are available. New fees will apply to this new notification must be accompanied by a new fee applying to those particular changes.

If a CMN consists of a number of grouped changes, the applicant must obtain consent for all the changes before any are implemented. This applies even if some of the changes could be self-assessed if submitted separately.

## Section 8: New and changed related products

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### 8.1 New related products data requirements

A new related product application (NRPA) is also lodged under [section 20](#) of the Medicines Act. An application for consent to distribute a new related product must be lodged using the [New Related Product application form](#) and accompanying [Declarations and Commitments form](#).

Applications should be compiled as described for new medicines in Section 5 and accompanied by the following data as described for new medicine applications but appropriate for the type of related product.

#### Summary of the Dossier

- ☞ Administrative data, including purpose and directions for use
- ☞ Labels
- ☞ Manufacturing Quality Assurance
  - ☞ (Note that GMP certification is required for related products intended to be taken internally but need not be provided for other dose forms).

#### Chemical, Pharmaceutical & Biological Documentation

- ☞ Composition and presentation of product
  - ☞ (Note: Product Development Pharmaceuticals are not required.)
  - ☞ Method of preparation
- ☞ Specifications for active ingredients
  - ☞ (Control tests on excipients need not be supplied.)
- ☞ Quality control of the active ingredient(s) both as the raw material and in the finished dose form.
- ☞ Specifications for the finished product
  - ☞ (Validation data should be provided to confirm that the proposed test methods work satisfactorily for the characteristics that establish the therapeutic nature of the product concerned.)
- ☞ Representative batch analytical data for the finished product.
- ☞ Stability (required only for products taken internally, or otherwise, if relevant)
- ☞ Other information (if relevant)

NRPA are processed as if they were a new lower-risk medicine application. The assessment considers the aspects relevant to the Act. However the product is expected to also comply with other relevant legislation applicable to the type of product e.g., cosmetic standards, dietary supplements regulations, food legislation.

### 8.2 Changed related product notifications

Changes to related products are made using the [Changed Related Product Notification form](#).

Data to support the proposed change must be provided as if the change was a change to an approved lower-risk medicine as described in Section 4. It is not necessary to notify a change to data that was not submitted in the original application.

### **8.3 Fees for related products**

Fees for new or changed related products are charged in accordance with the policy outlined for medicines in Sections 3 and 4. The actual fee payable for a new related product application, after application of any applicable standard waiver, is set out in a [schedule of fees](#).

Fees for changed related product notifications are contained in the notification form and in the [schedule of fees](#) .

## Section 9: Submitting an application or notification

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### 9.1 How to submit an application or notification

All data required to be submitted in hard-copy, including supplementary data, must be submitted on A4 sized paper and should be bound in sturdy ring-binders (or other types of binders from which pages can be removed and replaced) that do not spill their contents when opened.

One copy of all applications or notifications and supporting data should be submitted.

Send completed applications to the Manager:

Postal Address: Medsafe  
PO Box 5013  
Wellington 6145

Street/Courier Address: Medsafe  
Freyberg House  
20 Aitken Street  
Wellington 6011

Boxes containing volumes of data must be sturdy enough to provide adequate protection to their contents. They should also not exceed the weight that can be comfortably lifted.

When sending dossiers please ensure that:

- ☞ all dossiers that are delivered in boxes are labelled clearly on at least two sides that are visible when the box is stacked
- ☞ the box is sturdy enough to provide adequate protection to their contents
- ☞ the label includes:
  - ☞ the box number and the total number of boxes associated with the application (e.g., Box 1 of 5)
  - ☞ the name of the product
  - ☞ the TT50-file number (if applicable)
- ☞ the contents of each box by module and volume number
- ☞ Modules 1 & 2 are included in Box 1 (if more than one box), together with a cover letter if there is one, and the payment details. If possible, the label of box 1 is identifiable by colour.
- ☞ each box only contains documentation relating to one NMA.
- ☞ each box weighs less than 15 kg.

Applicants should contact Medsafe prior to submission of their medicine dossier if they have any questions.

Dossiers that are incorrectly labelled, paginated or indexed; and/or overweight or damaged boxes, will be returned at the applicant's expense.



Applicants are responsible for:

- ☞ transport and delivery of the application to Medsafe, including any border control/Customs requirements
- ☞ the physical security of the application during transportation
- ☞ ensuring the application arrives undamaged
- ☞ collection of applications that do not comply with Medsafe's application requirements.

## 9.2 Electronic submissions

### 9.2.1 Higher-Risk application requirements

All High-risk NMAs are required to be submitted with two copies of an electronic dossier. This is to allow the clinical and pharmaceutical chemistry evaluators to simultaneously evaluate the application.

### 9.2.2 Lower-Risk application requirements

Inclusion of two copies of an electronic dossier has been mandatory for all OTC medicine submissions since 1 September 2013.

### 9.2.3 All other applications

For all NMAs applicants are encouraged to submit two copies of an electronic dossier, in preference to a hard copy of Modules 2, 3, 4 and 5 of the dossier. Applicants should also consider electronic dossiers for CMNs that contain substantial supporting data.

### 9.2.4 Submission process

One hard copy of Module 1 is required plus process flow diagrams and finished product specifications. However, Modules 2, 3, 4 and 5 can be submitted solely in electronic format. A hard copy of the contents pages must be provided in Module 1 when submitting additional modules solely in electronic format.

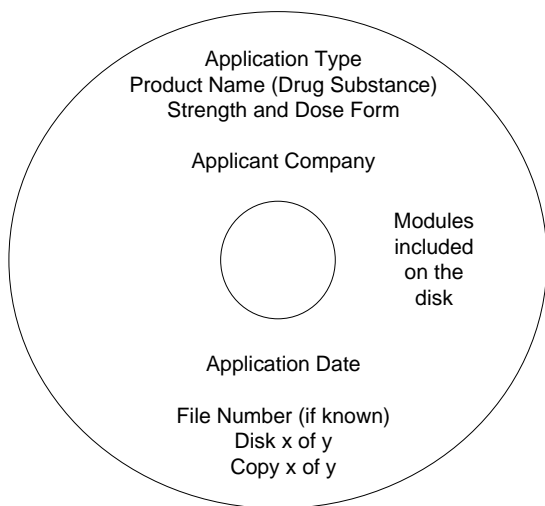
Two copies of the electronic dossier should be provided on CD or DVD in the required format (see below). Medsafe cannot accept electronic dossiers on a data stick, hard drive, rewritable disk or similar media. Before accepting the electronic dossier, it will be checked for compatibility with Medsafe systems. A replacement copy may be requested at any point during the duration of consent.

The physical disks should be clearly labelled with the following:

- ☞ application type
- ☞ product name (drug substance)
- ☞ strength and dose form
- ☞ applicant company
- ☞ application date
- ☞ file number (if known)

- ⌂ disk and copy number
- ⌂ modules included on the disk.

A suggested format is graphically represented below.



If a sticker is used to label the disk it must not impact on the ability for the disk to be read. An additional label is not required on the CD or DVD case.

Electronic dossiers should be packaged carefully and securely to ensure they arrive in a usable condition. In Medsafe's experience a courier bag by itself does not provide adequate protection for shipping. If the electronic dossier is being provided separately from the hard copy it should be sent in a secure package with an accompanying letter; loose disks are not appropriate.

Applicants submitting electronic dossiers must provide an assurance that the content of the electronic copies is identical to that of the paper. As with all applications submitted to Medsafe, applicants must also commit to holding a complete hard copy of the data set for the duration of consent and for a period not less than five years from the date approval lapses. The complete data set may be requested at any time.

### 9.2.5 Formatting of electronic submissions

Medsafe does not require dossiers to be prepared with eCTD software or in NeeS format, but electronic format should:

- ⌂ be in PDF except the application form which may be in MS Word
- ⌂ have files and folders structured to correspond with CTD format
- ⌂ be readable in Acrobat Reader version X (10)
- ⌂ enable the user to easily view a clear and legible copy of the information
- ⌂ enable the user to print each document page by page maintaining fonts, orientation, formats and page numbers
- ⌂ include a well-structured table of contents with hyperlinks to sections
- ⌂ allow information (including images) to be copied and pasted into other common programmes
- ⌂ contain hyperlinks and bookmarks to cross-reference information

- ☞ virus checked using up to date programmes (with confirmation of this to be provided in the cover letter)
- ☞ not have any security settings or password protection enabled.

Organisation of any electronic response to a request for information (RFI) should follow the same principles as the initial electronic submission. However, responses can be aligned with the questions (as currently occurs in hard copy responses) rather than be structured to correspond with CTD format.

### 9.2.6 Source of electronic document

It is preferable that dossiers are created from an electronic source document so they can be searched and copied to other documents.

Scanned paper documents are inferior to those produced from an electronic source document as they are more difficult to read and do not allow search function capability. If scanning is essential then optical character recognition software (OCR) is required and text verified as accurate prior to submission. Scanning must be at resolutions to ensure the document is legible on screen and when printed. As a guide, text documents should be scanned at 300 dpi and photographs at 600 dpi.

The following documents do not have to be converted to searchable text:

- ☞ GMP certificates
- ☞ Certificates of Analysis
- ☞ Certificates of Suitability
- ☞ manufacturer's licences
- ☞ documents in foreign languages and for which a translation is provided as searchable text
- ☞ literature references (except those in bibliographic applications)
- ☞ handwritten documents such as batch records and operating logs.

This guidance is based on *Providing Regulatory Submissions in Electronic Format - General Considerations* issued by the US Food and Drug Administration.

For complete details refer to the [FDA guidance](#).

## 9.3 Pre-submission meetings

Pre-submission meetings are not mandatory in New Zealand. As a small regulator, Medsafe is limited as to the advice it can give prior to lodgement of an application for consent before compromising its ability to undertake independent assessments on behalf of the New Zealand public.

Instead Medsafe encourages applicants to read the Guidelines for the Regulation of Therapeutic Products in New Zealand and the international guidance referred to. For applicants who wish to obtain regulatory advice regarding applications in New Zealand, there is a list of [regulatory consultants](#) on the Medsafe website.

Applicants who have specific questions regarding the Guidance may [email Medsafe](#) for advice.

Companies who wish to meet with Medsafe to discuss their applications for consent may [email](#) a meeting request. Requestors must provide a full agenda (including company representatives attending) and a list of specific issues that they wish to discuss.

Medsafe reserves the right to determine the most efficient and effective method of providing the information requested. Typically Medsafe only accepts requests for meetings which are mutually beneficial and the best use of its resource.

## Section 10: Administrative processes for new and changed medicines or related product applications

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### 10.1 Monitoring the application process

Sponsors can monitor the workflow status of applications through the [Product/Application search function](#) on the Medsafe website.

### 10.2 Application screening

Applications will be screened upon receipt to check that the sponsor has identified the correct application category and provided the required data and additional information for the application to proceed through to the next phase of the process. Consideration for referral under [section 24\(5\)\(a\)](#) will occur as part of the screening process.

The application must:

- have the correct application category identified
- have a submission dossier that is:
  - in CTD formats
  - have the specified material in hard copy
  - have two copies in an electronically enabled format (on a DVD or CD)
- include all of the required data, information and/or assurances
- have current and valid evidence of GMP
- include a cover letter describing the nature and scope of the application, the reason for selecting the application category and any relevant background information. For CMNs, the change(s) must be described.

Sponsors will be given the opportunity to remedy minor errors that are identified during the screening step. If minor errors are identified the sponsor will be advised and given a specific time period to rectify the deficiencies. Screening will resume only when the application errors have been rectified and a complete application confirmed.

An application will not be processed until screening has been completed and a complete data package has been received.

#### 10.2.1 Unaccepted applications

If during the screening phase it is determined that the application is not complete the sponsor will be notified and the application returned at the applicant's expense.

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

- application submitted using the incorrect application category
- incorrect format
- deficiency in any of the required data and information.

### 10.3 Payment of fees

If the application meets all the relevant requirements an invoice will be issued. Upon payment of the invoice the application will proceed to the evaluation phase. To avoid delays, the evaluation fee should be paid immediately following receipt of the invoice. Additional information on the fees for NMAs and CMNs can be found in the [fees schedule](#).

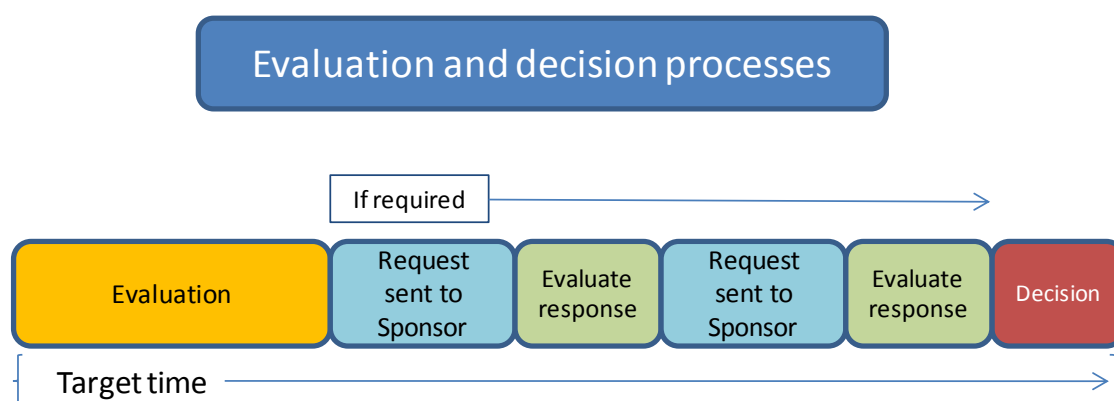
### 10.4 Evaluation

The evaluation phase consists of:

- € evaluation of the data and information that has been provided by the sponsor in accordance with the applicable application category
- € if required, up to two RFIs (dependent on application category) to clarify specific aspects of the application
- € if required, up to two rounds of evaluation of additional information (EAI) (dependent on application category) provided by sponsor in response to the RFI(s)
- € documentation of findings and a final recommendation.

The evaluation and decision phases are shown in greater detail in Figure 5 below.

**Figure 5: Evaluation and decision processes**



### 10.5 Requests for further information (RFI)

The evaluation phase allows Medsafe to seek clarification or further information about any component of the application that affects the safety, quality or efficacy of the product, and the risks and benefits to consumers. In cases where clarification is needed, a consolidated set of questions will be prepared by Medsafe and sent to the sponsor as a RFI letter.

A maximum of two RFIs is permitted for new medicine applications, after which the application will proceed to the decision phase. There is no limit to the number of RFIs issued for a CMN. After a notification has been referred to the Minister under [section 24\(5\)](#) of the Act it will be processed according to new medicine processes.

The RFI letter will clearly detail the issues and concerns. It will also specify the maximum number of calendar days allowed for the sponsor to provide a formal response. In the case of NMAs, the accompanying evaluation report will further document the outstanding issues.

The sponsor's response will need to address all issues raised, and if it is not received within the specified timeframe or is not complete, the evaluation and decision processes will proceed on the basis of the information previously supplied.

Once the application has been submitted, the sponsor will not be able to make changes to the application or submit additional data or information, other than that as requested as part of an RFI letter.

If sponsors are unable to respond to a RFI within the maximum number of allowable calendar days they must contact Medsafe immediately to negotiate an extension to the response time. Extensions may be granted if the sponsor cannot provide the information due to unforeseen circumstances. Typically extensions will be for a maximum of two weeks. Sponsors should note that extensions in excess of two weeks seriously impacts on Medsafe's ability to assess medicines in a timely manner, and has flow on effects to the evaluation of all new and changed medicine applications.

If sponsors are unable to respond to an RFI for a CMN the application will be referred under [section 24\(5\)](#) of the Act.

If sponsors do not respond to RFIs, Medsafe will conclude the assessment by considering the safety, quality and efficacy of the proposed medicine, based on the information already submitted, and make a recommendation on whether or not to approve the application.

## 10.6 Decision and finalisation

If Medsafe concludes that the application includes sufficient data to attest to the safety, quality and efficacy of the medicine and that the benefits outweigh the risk of harm to the patient, a recommendation that consent should be granted will be made to the Minister's delegate.

In the case of NMAs, and CMNs referred under [section 24\(5\)](#), if the recommendation is accepted, then consent for the new medicine will be notified through publication of the decision in the *New Zealand Gazette*.

If Medsafe concludes that the application **does not** include sufficient data to attest to the safety, quality and efficacy of the medicine and/or that the risks outweigh the benefits to the patient, the Minister's delegate may refer the application to an advisory committee.

Advice on specific issues relating to the application will be sought from the [Medicine Assessment Advisory Committee \(MAAC\)](#) which has expertise in the safety, quality and efficacy of medicines. Where an application is referred to the MAAC for advice, application processing timelines will be adjusted accordingly. The Committee typically meets three times per year and decisions are notified seven weeks following a meeting.

[Section 22](#) of the Medicines Act also permits the Minister's delegate to refer any new medicine application to the MAAC for advice where he is not satisfied that the medicine should be approved for use in New Zealand.

The following types of medicines will typically be referred to the MAAC irrespective of whether Medsafe has concluded that the application includes sufficient data to attest to the safety, quality and efficacy of the medicine and that the benefits outweigh the risk of harm to the patient:

- World-first NCEs and NBEs
- new vaccines indicated for children
- novel technologies such as medicines derived from stem cells and nano-tech
- medicines that have been withdrawn or refused consent by a recognised regulator.

Consent for changes to existing medicines and related products will be notified by letter from the DGs delegate, unless the application has been referred under [section 24\(5\)](#) of the Act. In this latter case the application will be processed as a NMA (see Section 4.7 for more information on applications referred under [section 24\(5\)](#) of the Act).

## **10.7 Withdrawal**

The sponsor may withdraw an application at any time during the process. Requests to withdraw applications must be made in writing.

## **10.8 Processing of priority assessment applications**

Applications that have been accepted for priority assessment will be processed earlier and faster than normal applications. Applications granted priority assessment on clinical grounds or on cost saving grounds will be given a higher priority than applications granted priority assessment on export grounds.

Applications granted priority status are allocated to an evaluator and becomes that evaluator's next piece of new work.

If deficiencies are identified during the evaluation, an RFI will be issued. Maintaining priority assessment status is conditional on applicants providing a complete response to an RFI within 28 days. If a sponsor considers that Medsafe's request cannot be responded to within 28 days, they should first contact Medsafe to ensure that the request has been correctly interpreted. In cases where the sponsor cannot obtain the information requested within the 28 day timeframe, it can still be provided after this deadline but the priority status of the application will be revoked.

Medsafe considers the 28 day response time to be reasonable as applications should be complete before lodgment. A further benefit of truncating the response time is that the application can be referred back to the original evaluator in most circumstances, with increased efficiency in concluding the evaluation.

The 28 day timeframe will be applied to applications that meet the significant clinical need but have been declined due to resource availability.



## Section 11: Timelines

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### 11.1 Target timelines

To provide sponsors with predictable timelines, Medsafe has used historical data to forecast the percentage of applications through each application category in order to determine realistic [target timelines](#).

It is important to note, however, that Medsafe can only commit to meeting target timelines where the sponsor has provided a complete and high quality application. Performance against target timelines is [published annually](#).

### 11.2 Clock stops

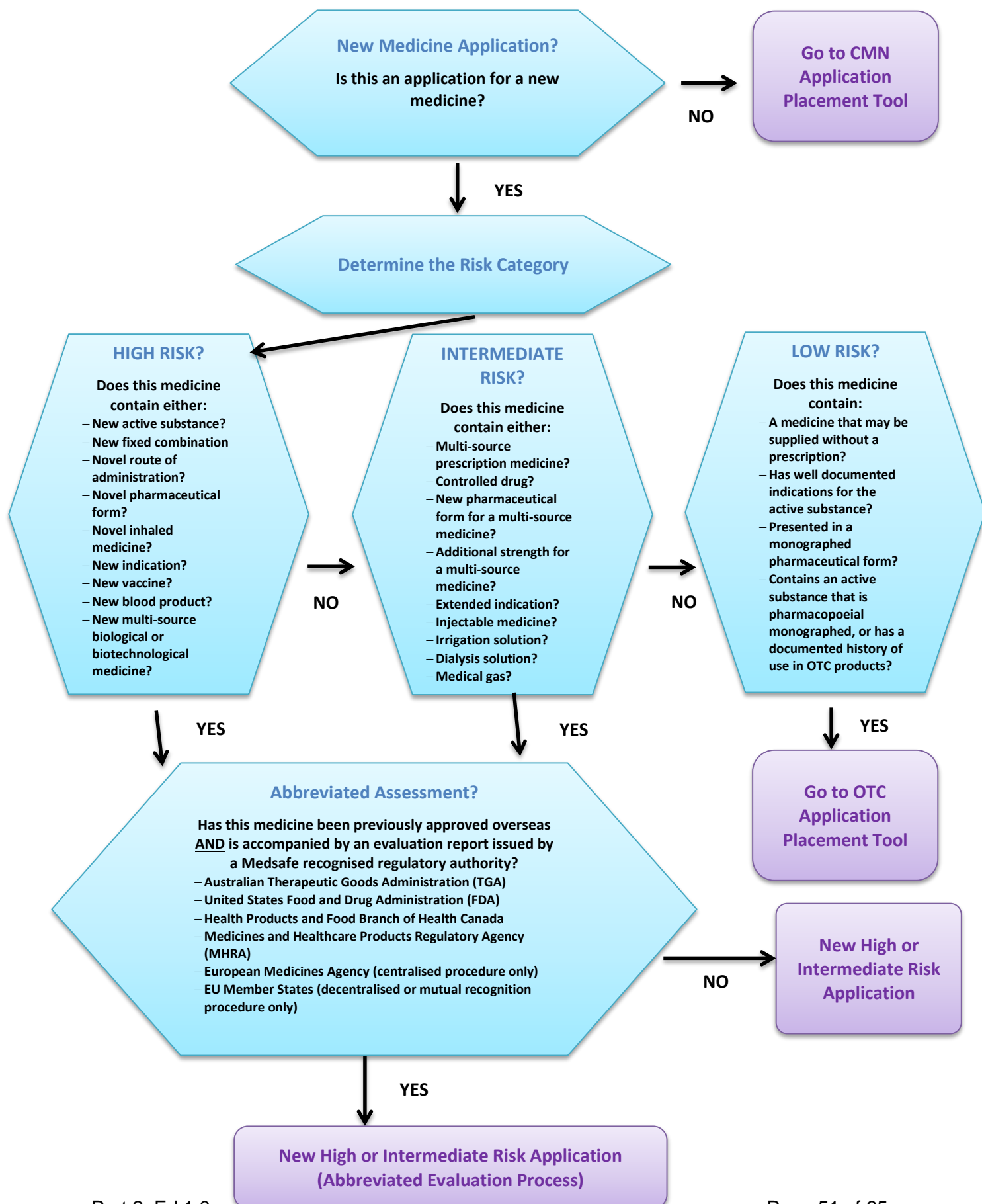
Target timelines are expressed in calendar days and the total time includes the time taken for sponsors to respond to RFI questions. Medsafe **does not** have a 'stop clock' policy, and will include the sponsor response time in reporting performance for the total evaluation time.

## Appendix 1: Glossary of terms

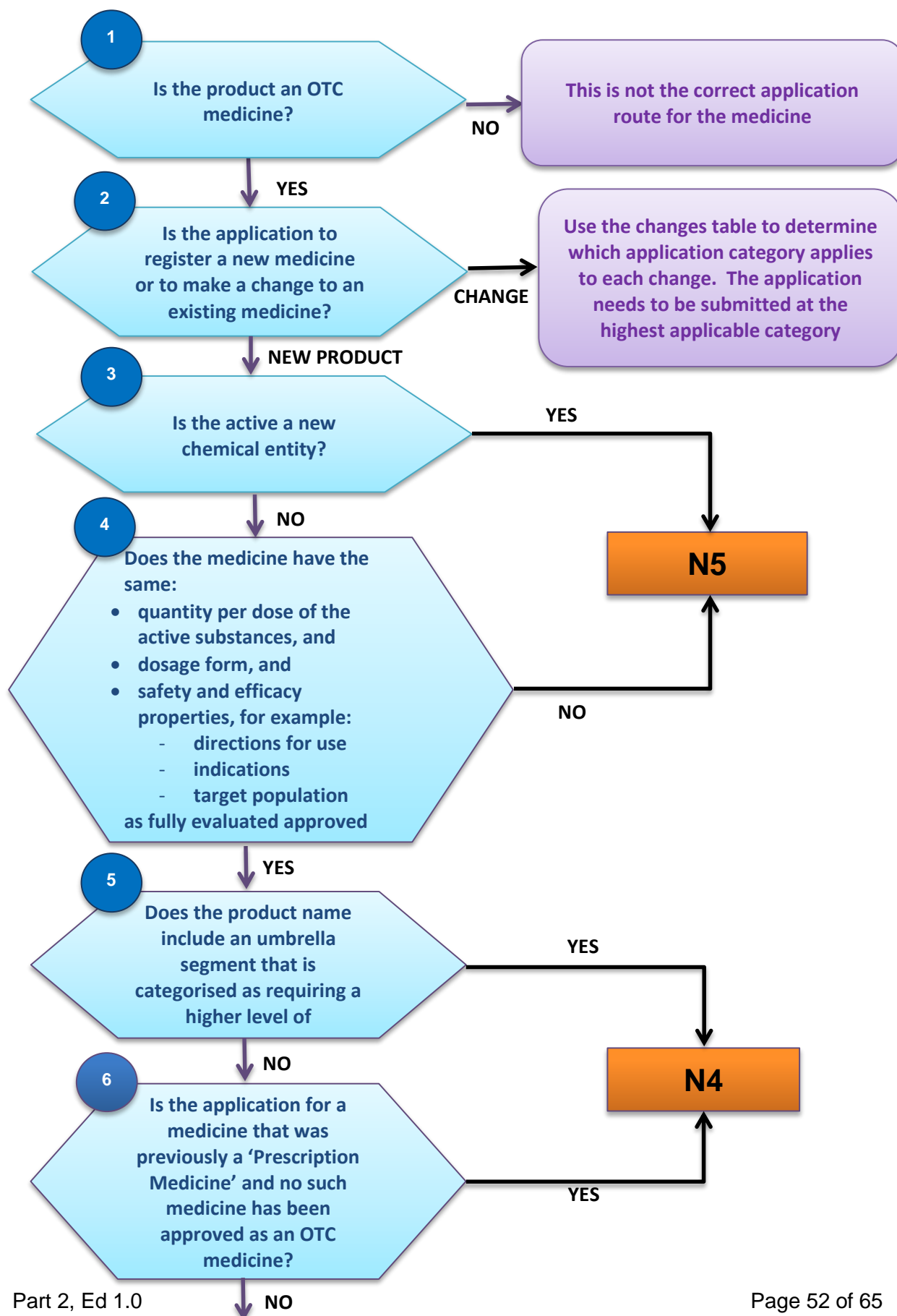
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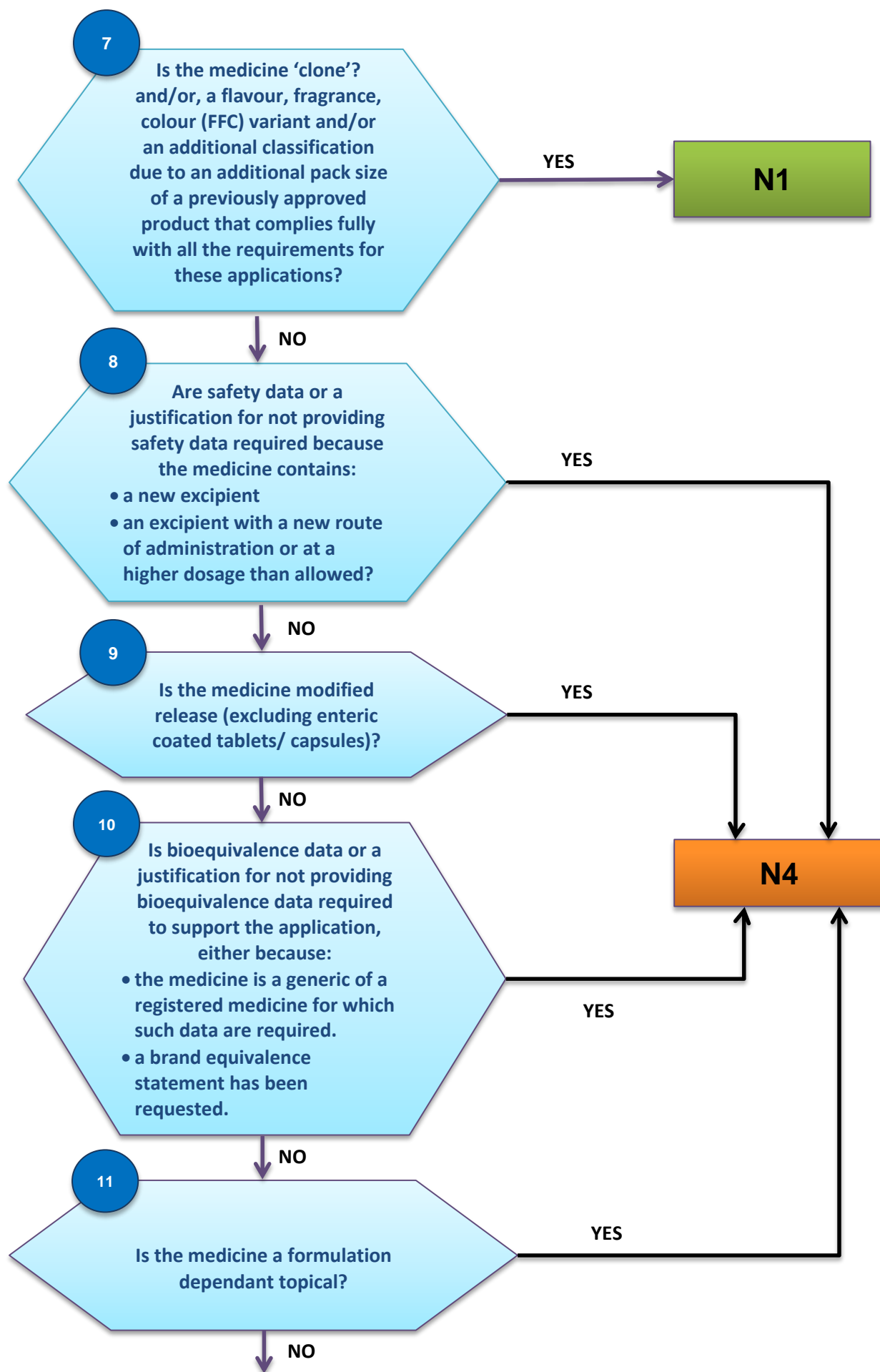
CMN	Changed Medicine Notification	CRPN	Changed Related Product Notification
DMF	Drug Master File		
NMA	New Medicine Application		
NRPA	New Related Product Application		
PMF	Plasma Master File		
RFI	Request for Further Information		
SACN	Self-assessable Change Notification		

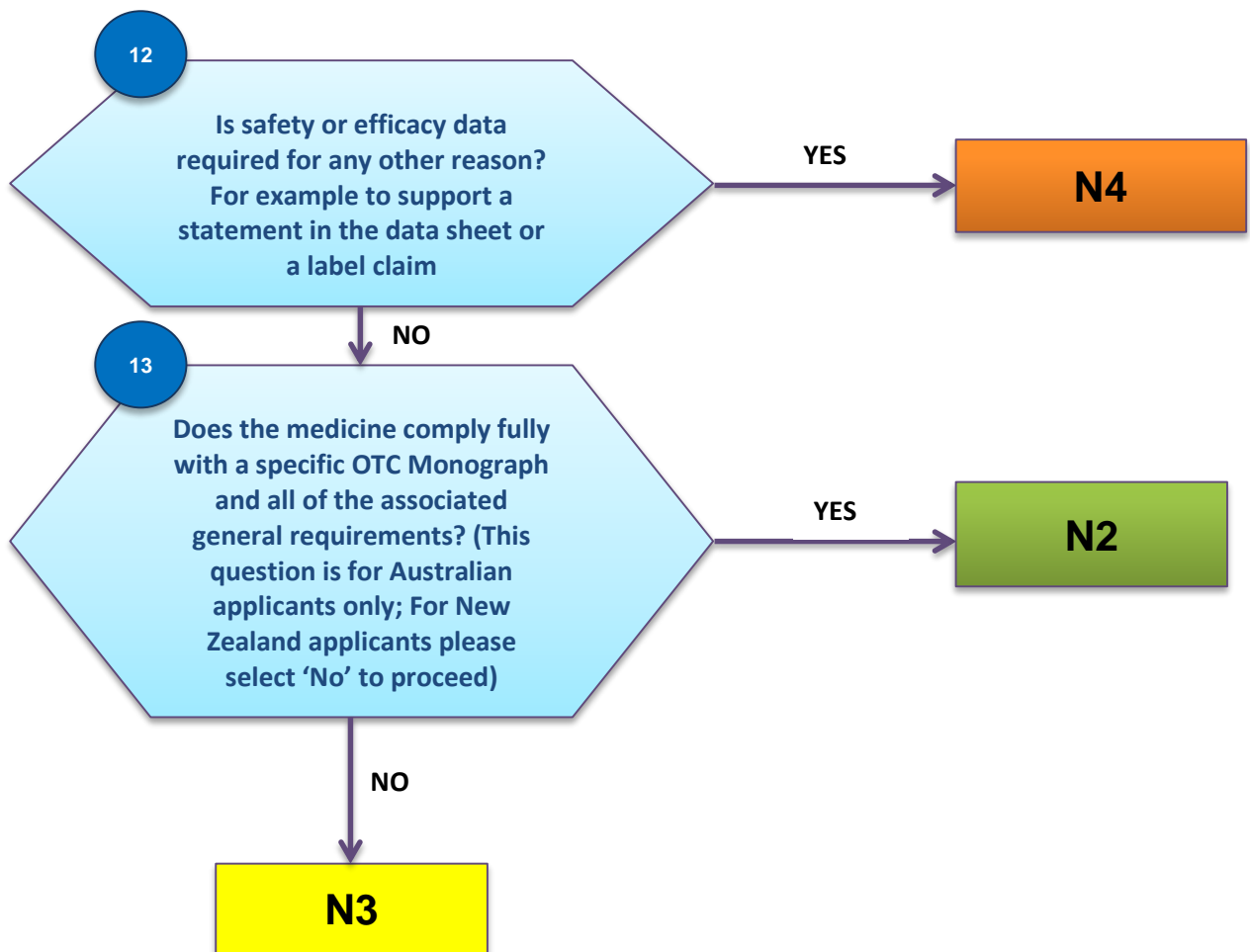
## Appendix 2: Application categorisation tool



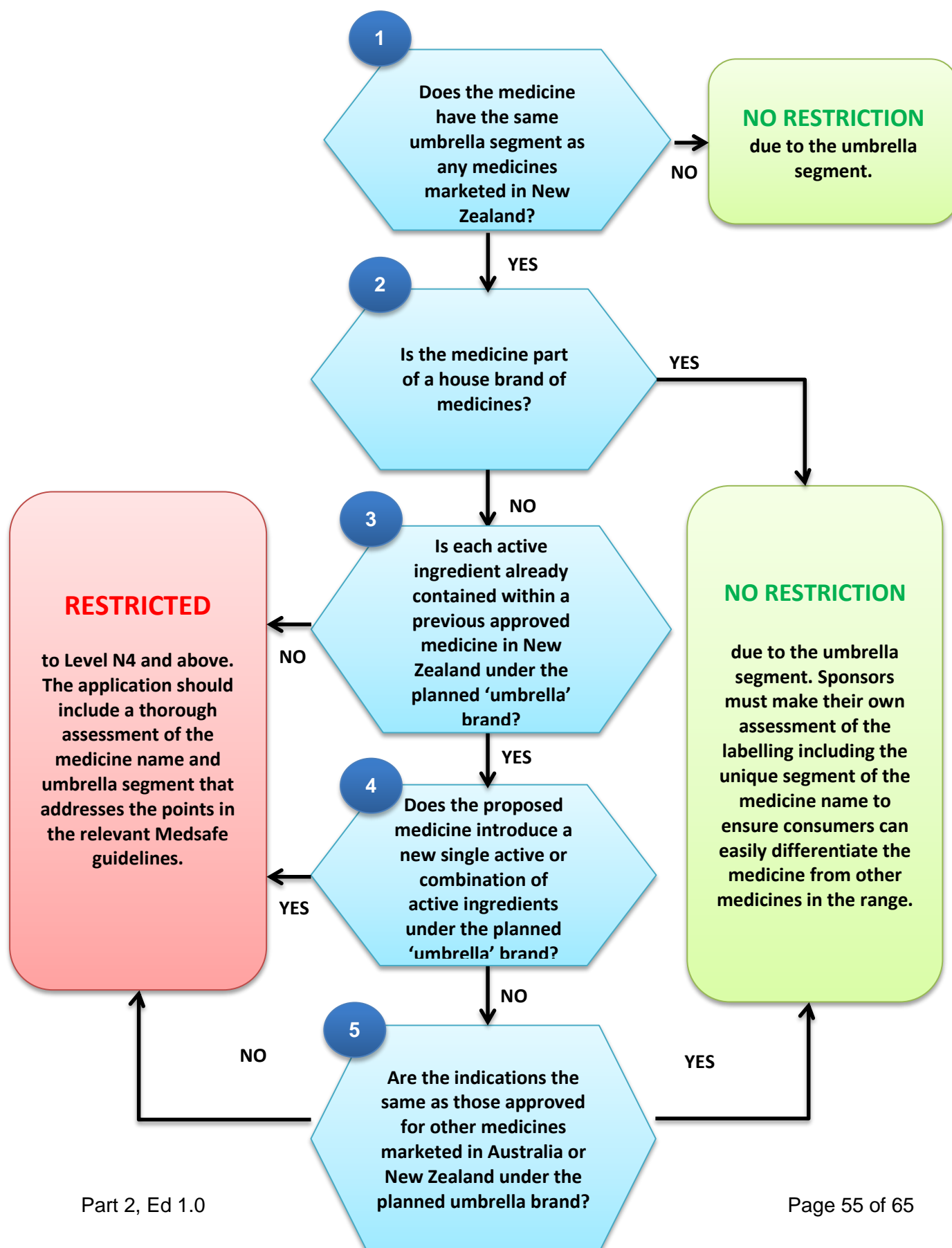
## Appendix 3: OTC placement tool







## Appendix 4: Decision tree for umbrella branded OTC medicines



## Appendix 5: Additional notes on categorisation of applications for new OTC medicines

Risk Rating	Application Level		Sponsor Definition/Mitigation Path	Application Criteria	CTD Module	Information Requirements
Negligible	Generics	N1	<p>Product is identical to parent product other than product name, and/or classification statement and pack size.</p> <p>The product name does not include an umbrella segment categorised as requiring a higher level of assessment.</p>	<p>Parent product must have been fully evaluated (safety, efficacy and quality)</p> <p>Full access to the rights of the product must be provided</p> <p>Evaluation includes compliance with Medsafe Labelling Statements Database</p>	<p>Module 1</p> <p>Module 3</p>	<p>Application / Assurances / Letter of authorisation / Evidence of GMP / Labels (PI/Data sheet and CMI as required)</p> <p>Finished Product Specification (FPS)</p>
		N2	<p>Complies fully with an OTC Medicine Monograph</p> <p>Does not include products in N4</p> <p>The product name does not include an umbrella segment categorised as requiring a higher level of assessment.</p>	<p>Supporting information to demonstrate compliance with OTC Medicine Monograph</p>	<p>Module 1</p> <p>Module 3</p>	<p>Application / Assurances / Evidence of GMP / Labels (PI/Data sheet and CMI as required)</p> <p>FPS and Certificates of Analysis (minimum of two)</p>



Low		<b>N3</b>	<p>All generic applications other than those in levels N1, N2 or N4 Does not comply with an OTC Medicine Monograph.</p> <p>Does not include products specified below as requiring assessment via the N4 route (See note at end of this table).</p> <p>The product name does not include an umbrella segment categorised as requiring a higher level of assessment.</p>	<p>Quality data to be evaluated</p> <p>Does not entail evaluation of safety and efficacy data as data previously evaluated and approved for such generics</p> <p>no safety and efficacy data provided</p>	<p>Module 1</p> <p>Module 3</p>	<p>Application / Assurances / Evidence of GMP / Labels (PI/Data sheet and CMI as required)</p> <p>Complete Module<sup>2</sup> (except where ARGOM / NZRGM specifies that a complete module is not required)</p>
		<b>N4</b>	<p>Any product specified below as requiring assessment via the N4 route (excluding those in level N5), and/or</p> <p>Any product with an umbrella branded product name where the umbrella segment is categorised as requiring a higher level of assessment.</p>	<p>Quality data to be evaluated</p> <p>Safety and/or efficacy data (supporting clinical and/or toxicological data) provided or justification for not providing the data</p>	<p>Module 1</p> <p>Module 2</p> <p>Module 3</p> <p>Module 4</p> <p>Module 5</p>	<p>Application / Assurances / Evidence of GMP / Labels (PI/Data sheet and CMI as required)</p> <p>As applicable</p> <p>Complete Module<sup>2</sup> (except where GRTPNZ specifies that a complete module is not required)</p> <p>As applicable</p> <p>As applicable</p>

<b>Moderate</b>	<b>Extensions / NCE</b>	<b>N5</b>	<p>New products that are an extension to a 'Generic category' product including:</p> <ul style="list-style-type: none"> <li>• new therapeutic indications</li> <li>• new strengths</li> <li>• new dosage forms</li> <li>• new directions</li> <li>• new combination products</li> <li>• different patient population</li> </ul> <p>New products containing a new chemical entity as an active ingredient</p>	<p>Quality data to be evaluated</p> <p>Safety and/or efficacy data (supporting clinical and/or toxicological data) provided or justification for not providing the data</p>	Module 1	Application / Assurances / Evidence of GMP / Labels (PI/Data sheet and CMI as required)
					Module 2	Complete Module
					Module 3	Complete Module <sup>2</sup> (except where GRTPNZ specifies that a complete module is not required)
					Module 4	As applicable
					Module 5	As applicable

### OTC medicines to be assessed via the N4 route

- Modified release products (excluding enteric coated tablets/capsules)
- Application for a generic of a registered product where bioequivalence data are required or where a justification for not providing bioequivalence is required
- Product includes a new excipient or an excipient with a new route of administration
- Applications for products where a brand equivalence statement is requested and where bioequivalence evaluation is required or where a justification for not providing bioequivalence is required
- Formulation dependent topical products
- An application for an OTC product as a result of a change in scheduling for the particular product from the 'Prescription Only Medicine' schedule to a lower (OTC) schedule, where no such products are previously approved as an OTC medicine

## Appendix 6: Summary of data requirements for new medicine applications

### Module 1

Module 1		Higher risk	Intermediate risk	Lower risk
1.0.0	Electronic lodgement Cover sheet	Not required	Not required	Not required
1.0.1	Letter of application	Mandatory	Mandatory	Mandatory
1.0.2	Responses to questions for information	Not required	Not required	Not required
1.1	Comprehensive table of contents	Mandatory	Mandatory	Mandatory
1.2.1	Application form	Mandatory	Mandatory	Mandatory
1.2.2	Pre-submission details	Not required	Not required	Not required
1.2.3	Patent certification	Not required	Not required	Not required
1.3.1	Data sheet and package insert	Data sheets are Mandatory	Data sheets are Mandatory	Data sheets may be required
1.3.2	Consumer medicine information	Desirable	Desirable	Desirable
1.3.3	Human embryo/embryonic stem cell declaration	Mandatory	Mandatory	Not required
1.3.4	Label mock-ups and specimens	Mandatory	Mandatory	Mandatory
1.4	Information about experts & expert declarations	Mandatory	Mandatory	Not required
1.5.1	Literature-based submission documents	May be required. Refer to Module 1 requirements.	May be required. Refer to Module 1 requirements.	May be required. Refer to Module 1 requirements.
1.5.2	Orphan drug designation	May be required. Refer to Module 1 requirements.	May be required. Refer to Module 1 requirements.	Not applicable
1.5.3	Genetically modified organisms consents	May be required	May be required	Not applicable
1.5.4	Additional trade name declarations	Not required	Not required	Not required
1.5.5	Co-marketed medicines declarations	May be required	May be required	May be required
1.6	Drug and plasma master files and certificates of suitability	May be required	May be required	May be required
1.7	Good manufacturing practice	Mandatory	Mandatory	Mandatory

<b>1.8</b>	Compliance with meetings and pre-submission processes	Not applicable	Not applicable	Not applicable
<b>1.9</b>	Individual patient data declaration	May be required	May be required	Not applicable
<b>1.10</b>	Overseas regulatory status	Mandatory	Mandatory	Mandatory
<b>1.11</b>	Summary of biopharmaceutical studies	Mandatory	Mandatory	Optional
<b>1.12</b>	References to paediatric development program	Optional	Optional	Not required
<b>1.13</b>	Information relating to pharmacovigilance	Mandatory	Mandatory	Not required
<b>Annex I</b>	Antibiotic resistance data	May be required	May be required	Not required
<b>Annex II</b>	Overseas evaluation reports	Desirable/ Mandatory for abbreviated route	Desirable/ Mandatory for abbreviated route	Desirable

## Module 2

Module 2 summarises the information that will be provided in the quality (Module 3), nonclinical (Module 4) and clinical (Module 5) modules of the dossier.

There is no single document that explains the content of Module 2 for the registration of pharmaceuticals for human use. The ICH documents for Modules 3, 4, and 5 include a section on the information that must be provided in Module 2.

<b>Module 2</b>	<b>Higher risk</b>	<b>Intermediate risk</b>	<b>Lower risk</b>
<b>2.1</b> Table of contents	Mandatory	Mandatory	Mandatory
<b>2.2</b> Introduction	Mandatory	Mandatory	Mandatory
<b>2.3</b> Quality overall summary	Mandatory	Mandatory	Mandatory
<b>2.4</b> Nonclinical overview	Mandatory	Mandatory	Not required
<b>2.5</b> Clinical overview	Mandatory	Mandatory	Desirable
<b>2.6</b> Nonclinical overview	Mandatory	Mandatory	Not required
<b>2.7</b> Clinical overview	Mandatory	Mandatory	Not required

## Module 3

[Module 3](#) describes the format and organisation of the chemical, pharmaceutical and biological data relevant to the application. New Zealand specific information required in Module 3 is available in Appendix 8.

## Module 4

[Module 4](#) describes the format and organisation of the nonclinical (pharmacologic, pharmacokinetic, toxicological) data relevant to the application.

## Module 5

[Module 5](#) describes the format and organisation of the clinical data relevant to the application.

**Table 1 Summary of data requirements Modules 3, 4 and 5**

	<b>Higher risk</b>	<b>Intermediate risk</b>	<b>Lower risk</b>
<b>Module 3: Quality</b>	Mandatory	Mandatory	Mandatory
<b>Module 4: Nonclinical</b>	Mandatory	Mandatory	Not required
<b>Module 5: Clinical</b>	Mandatory	Mandatory	May be required depending on specific application types
<b>Module 5.3.1: Reports of biopharmaceutic studies</b>	May be required	May be required	May be required
<b>Module 5.3.2: Pharmacokinetic studies using human biomaterials</b>	May be required	May be required	May be required

## Appendix 7: OTC dossier documents matrix

The OTC dossier documents matrix provides a summary of which documents are required for each application category. The matrix is expected to be used after a sponsor has determined the appropriate application category for their application and is intended to provide 'at a glance' an indication of which documents are to be provided.

The document requirements are described as:

**M:** where the stated document(s) are mandatory and are required to submit a valid application.

**D:** where the provision of the document(s) is dependent on regulatory requirements for the particular submission.

**O:** where the provision of the document(s) is optional. That is to say, there is no requirement or expectation from the regulator that the document(s) will be submitted with the application but that the document(s) could be provided where a sponsor considers the provision of the information may assist in the assessment of the application.

**NA:** where the document(s) are not relevant and should not be submitted with the application.

**\*:** Where an asterisk is included, documents are to be provided to Medsafe if available.

**Table 2: OTC dossier documents matrix**

		N1	N2	N3	N4	N5
Mod. 1.0.1	Letter of Application (cover letter)	M	M	M	M	M
Mod. 1.0.2	Responses to screening questions	D	D	D	D	D
Mod. 1.0.4	Letters of Authorisation	M	D*	D*	D*	D*
Mod. 1.1	Table of Contents	M	M	M	M	M
Mod. 1.2.1	Application Form (where a paper copy of dossier provided)	M	M	M	M	M
Mod. 1.2.3	Patent certification	D	D	D	D	D
Mod. 1.3.1	Product Information / Data Sheet	D	D	D	D	D
Mod. 1.3.1	Pack Insert	D	D	D	D	D
Mod. 1.3.2	Consumer Medicine Information	D	D	D	D	D

		N1	N2	N3	N4	N5
Mod. 1.3.4	Mock-ups and labelling specimens	M	M	M	M	M
Mod. 1.4	Info on Experts & Expert Declarations	NA	NA	D	D	D
Mod. 1.5	Categories N1 & N2: Finished product specification	M	M	NA	NA	NA
Mod. 1.5	Category N1: raw material specifications	D	NA	NA	NA	NA
Mod. 1.5	Category N2: Certificates of Analysis of finished product	NA	M	NA	NA	NA
Mod. 1.5	Category N2: OTC new product applications category N2 - assurances	NA	M	NA	NA	NA
Mod. 1.5	OTC Medicine Evaluation Analytical Validation Summary	NA	NA	D*	D*	D*
Mod. 1.5.1	Literature-based submissions document	NA	NA	NA	D	D
Mod. 1.6	Drug and Plasma Master Files and Certificates of Suitability	NA	NA	O*	O*	D

Mod. 1.7	GMP	D	D	D	D	D
Mod. 1.9	Individual Patient Data Declaration	NA	NA	NA	D	D
Mod. 1.10	Overseas Regulatory Status	O*	O*	O*	D*	D*
Mod. 1.11	Summary of Biopharmaceutic Studies	NA	NA	NA	D	D
Mod. 1.13	Information relating to pharmacovigilance	O	O	O	D	D
Mod. 1 Annex II	Overseas Evaluation Reports	NA	NA	O*	O*	O*
Mod. 2.1	Table of Contents	NA	NA	D	D	D
Mod. 2.2	Introduction	NA	NA	D	D	D

		N1	N2	N3	N4	N5
Mod. 2.3	Quality Overall Summary	NA	NA	D	D	D
Mod. 2.4	Non-clinical Overview	NA	NA	NA*	D	D
Mod. 2.5	Clinical Overview	NA	NA	NA*	D	D
Mod. 2.6	Non-clinical Summary	NA	NA	NA	D	D
Module 2.7	Clinical Summary	NA	NA	NA	D	D
Mod. 3	Quality	NA	NA	M	M	M
Mod. 4	Non-clinical	NA	NA	NA	D	D
Mod. 5	Clinical	NA	NA	NA	D	D
Mod. 5.3.1	Reports of Biopharmaceutic Studies	NA	NA	NA	D	D



## Appendix 8: Data requirements for new medicine applications

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Under development.