MEDSAFE

New Zealand Medicines and Medical Devices Safety Authority

Guideline on the Regulation of Therapeutic Products in New Zealand

Overview of Medicine Regulation

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Contents

1. Introduction

1.1 Overview of the approval of new and changed medicines

New Zealand's medicine legislation requires that, in most circumstances, medicine distributors need to obtain Ministerial consent before commencing distribution of a new medicine or related product.

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 standards expected of medicines are briefly outlined in the Medicines Act 1981 and associated Medicines Regulations 1984. 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.

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

The risk profile of a medicine is generally 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.

1.2 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*

1.3 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
- Guidelines for the Regulation of Therapeutic Products in New Zealand

2. Who can submit an application?

The Medicines Act 1981 requires that a **New Medicine Application** (NMA), **New Related Product Application** (NRPA), **Changed Medicine Notification** (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 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 a 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 (eg, 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

An important part of being a sponsor is product stewardship. 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:

- staff available to engage with Medsafe (in New Zealand business hours) on quality issues, including any potential market actions
- 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)
- arrangements with overseas principles/suppliers (eg, quality and commercial agreements) to ensure the New Zealand dossier accurately reflects the product marketed in New Zealand
- staff are available and protocols are in place for responding to consumers, healthcare professionals and other interested parties (eg, 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
- procedures to routinely monitor Medsafe's website to ensure timely response to safety communications or consultations when applicable.

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.

3. Submitting an application or notification

3.1 How to submit an application or notification

Applications and notifications must be submitted electronically.

Medsafe uses a secure electronic file transfer system (EFT) to enable companies to submit medicine and related product applications and notifications. The EFT is a secure system as the file is encrypted in transit and then stored on a secure server within the Ministry of Health.

To use the EFT, a New Zealand sponsor, pharmaceutical company, or consultancy firm will first need to receive set up instructions from Medsafe. To receive set up instructions the following information should be provided to Medsafe:

- the name of the contact person
- the company of the contact person, such as the NZ sponsor, pharmaceutical company or consultancy firm if multiple sponsors will be represented
- the contact person's email address (preferably with a company email domain)
- the contact person's mobile number (with country code) to receive a password
- the contact person's IP address (this is required for security measures and can be found at whatsmyip.com)

Please send this information to eft@health.govt.nz and copy to medsafeapplications@health.govt.nz with **EFT Set Up** in the subject line. Once set up, Medsafe will provide further information to the contact person on how to use the EFT system, the name conventions required, and the file format.

There are no restrictions on the number of people from each company who can submit electronically

DMFs and PMFs must also be submitted through the EFT. However, it is up to sponsors to make their DMF/PMF holders aware of the process and direct them to medsafeapplications@health.govt.nz to receive EFT set up instructions. Please ensure your DMF/PMF holders send their email requests with **EFT set up – DMF or PMF** in the subject line.

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

3.2 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 Common Technical Document (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 the CTD sections and other various documentation provided in the submission

- allow information (including images) to be copied and pasted into other common word 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 rather than be structured to correspond with CTD format.

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:

- Good Manufacturing Practice (GMP) certificates
- Certificates of Analysis
- European Pharmacopoeial Commission Certificates of Suitability
- manufacturer's licences
- documents in foreign languages and for which a translation is provided as searchable text
- literature references (expect those in bibliographic applications)
- handwritten documents such as batch records and operating logs.
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3.3. 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 without 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 within these guidelines. 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 Guidelines may email Medsafe (medsafeapplications@health.govt.nz) 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.

4. Administrative processes for medicine applications

4.1 Monitoring the application process

Sponsors can monitor the workflow status of NMAs and CMNs through the Product/Application search function on the Medsafe website.

4.2 Application screening

NMAs, NRPAs, CMNs and CRPNs will be screened upon receipt to check that the sponsor has identified the correct application category and provided the required data and administrative information for the application to proceed through to the next phase of the process. For CMNs consideration for referral under section 24(5)(a) will occur as part of the screening process. After a notification has been referred to the Minister under section 24(5) of the Medicines Act it will be processed according to NMA processes.

The NMA/NRPN or CMN/CRPN must:

- have the correct application or CMN/CRPN category(ies) identified
- have a submission dossier that is:
    - in CTD format
- include all of the required data, information and/or assurances
- have current and valid evidence of GMP where applicable
- include a cover letter describing the nature and scope of the NMA/NRPA or CMN/CRPN, the reason for selecting the application category(ies) and any relevant background information. For CMNs/CRPNs, 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 Medsafe has determined that the application is complete.

An NMA/NRPA or CMN/CRPN will not be processed until screening has been completed and a complete data package has been received.

Unaccepted applications

If during the screening phase it is determined that the application is not complete the sponsor will be notified.

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

- application submitted using the incorrect NMA/NRPA or CMN/CRPN category(ies)
- incorrect format
- deficiency in any of the required data and information.

4.3 Payment of fees

If the NMA/NRPA or CMN/CRPN 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, NRPAs, CMNs, and CRPNs can be found in the fees schedule.

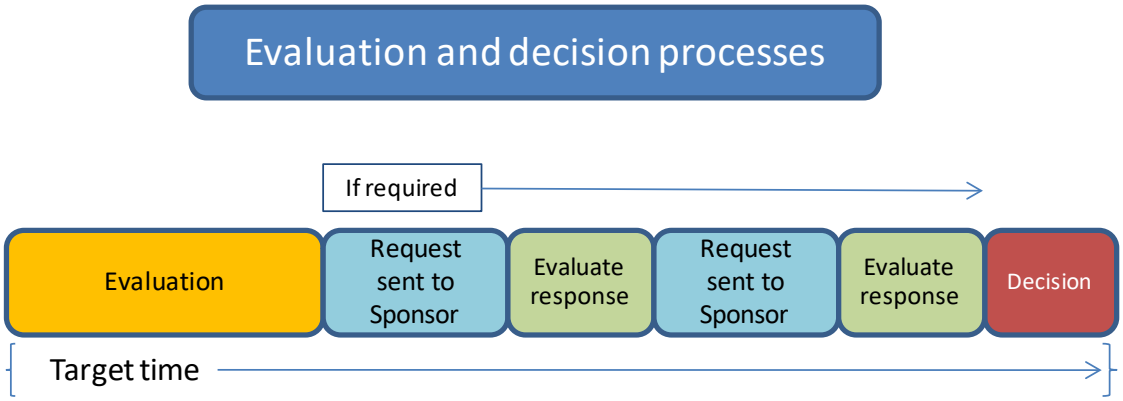
4.4 Medsafe evaluation

The evaluation phase consists of:

- Medsafe evaluation of the data and information that has been provided by the sponsor
- if required, up to two RFI letters (general limit for NMAs/NRPAs) to clarify specific aspects of the application
- if required, up to two rounds of Evaluation of Additional Information (EAI) (general limit for NMAs/NRPAs) provided by sponsor in response to the RFI letters
- written report of the evaluation and a final recommendation.

The Medsafe evaluation and decision phases are shown in greater detail in Figure 1 below.

Figure 1: Evaluation and decision processes



4.5 Requests for 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 an RFI letter.

In general, a maximum of two RFIs is permitted for NMAs/NRPAs, after which the application will proceed to the decision phase. There is no limit to the number of RFIs issued for a CMN/CRPN.

The RFI letter will specify the maximum number of calendar days allowed for the sponsor to provide a formal response. The CMN RFI letter will clearly detail the issues and concerns, whereas 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 an 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.

4.6 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 new chemical entities (NCEs) and new biological entities (NBEs)
- new vaccines indicated for children
- novel technologies such as medicines derived from stem cells and nano-technology
- 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 an NMA (see section 4.7 for more information on applications referred under section 24(5) of the Act).

4.7 Withdrawal

The sponsor may withdraw an application at any time during the process. Requests to withdraw applications must be submitted via email to medsafeapplications@health.govt.nz.

4.8 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, enabling 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.

5. 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 Medicines Regulations 1984.

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.
Fee waivers are rarely granted for changed medicine notifications especially when the change notified relates to multiple products. This is because the change must be added to each regulatory file and the administrative cost must be recovered.

6. Timelines

6.1 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.

6.2 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.

Document history

Revision Date	Version Number	Summary of Changes
January 2023	New	New document following major review and restructure of GRTPNZ Part 2, which has been obsoleted.