MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Guideline on the Regulation of Therapeutic Products in New Zealand

Changed Medicine Notifications and Non-Notifiable Changes

Edition 1.3

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Contents

Abbreviations and definitions

Abbreviation or term	Definition
CEP	Certificate of Suitability
CoA	Certificate of Analysis
CMN	Changed Medicine Notification
CRPN	Changed Related Product Notification
CTD	Common Technical Document
DMF	Drug Master File
GMP	Good Manufacturing Practice
FDA	Food and Drug Administration (USA)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
NIBSC	National Institute for Biological Standards and Control (UK)
NMA	New Medicine Application
PMF	Plasma Master File
SACNs	Self-assessable Change Notifications
TSE	Transmissible Spongiform Encephalopathy
WCB	Working Cell Bank
WHO	World Health Organisation
WS	Working Seed

1. Introduction

A Changed Medicine Notification (CMN) is a notification to the Director-General of Health by the sponsor of a product, under section 24 of the Medicines Act 1981, of a planned change to an approved product (this includes prescription and non-prescription medicines), 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, a New Medicine Application (NMA) (not a CMN) is required. The NMA must be kept separate from and will be processed separately from any CMN. The new product cannot legally be distributed until consent has been granted and published in the New Zealand Gazette.

2. Notification of changes to medicines

A change to the regulatory file information of an approved medicine may require assessment by Medsafe or be self-assessable. 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).

Self-assessable changes are also notified through a CMN but there is no requirement to obtain consent prior to making the change, provided the self-assessable change is not part of a notification that includes an assessable CMN. For self-assessable changes that can be implemented without consent, the notification must precede the change.

Details of the various types of assessable and self-assessable changes and the applicable fees are given in the CMN forms available on the Forms and Templates page on the Medsafe website – see the 'Medicines – (Changed Medicine Notification forms)' section. There are two CMN forms, Form A and Form B:

- CMN Form A should be used for lower-risk, intermediate or higher-risk medicines (other than biological or biotechnological medicines) and these include antibiotics and like-substances derived from micro-organisms.
- CMN Form B is for biological or biotechnological products (eg, vaccines, allergens, products derived from human blood or plasma or serum, immunological products, and any product derived from biotechnology).

The CMN forms include categories for common changes (and changes consequent to these) and are designed to be as comprehensive as possible. The fee structure for the categories is reflective of the product types and the amount of Medsafe assessment required. If an intended change is not included in the relevant form, please seek advice from Medsafe.

3. Self-Assessable Change Notifications (SACNs)

Self-assessable changes (SACNs) are to be notified using the same CMN form as used for notifying assessable changes. Forms can be found on the Forms and Templates page of the Medsafe website.

No supporting data are required to be submitted with a SACN, except in the case of a changed label, updated specifications or data sheet, introduction of secondary reference standards, or extension of a reference standard shelf life/retest date. It is the responsibility of the sponsor to ensure that the data to support the change are held and are made available to Medsafe on request. Where supporting data are required, refer to the subsections below and to Appendix 1 of this guidance document for data requirements.

A SACN is able to be implemented when payment for the application has been received. Medsafe **acknowledges** but does not formally approve or issue a "consent notice" for SACNs

Sponsors should note that SACNs 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 SACNs 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.

3.1 Labels and data sheets

When a SACN is made to a label or data sheet, the appropriate checklist and /or declaration must be completed by the applicant and submitted with the CMN, along with copies of the previously approved data sheets or new labels. See 'Labelling of Medicines and Related Products' and 'Requirements for Information for Prescribers and Consumers' guidelines for further details.

A CMN is not required when the only change to a label is the classification statement (as long as no other changes to the label are required as a consequence of reclassification). In this case all that is required is a copy of the new label for inclusion in Medsafe's product file.

3.2 Changes to secondary reference standards

The quality control of biological/biotechnological products often includes assays for determination of biological activity, potency or other specific properties. The assay test methods may be based on comparative assessment of test samples against preparations of reference standards. Two types of standard preparations exist: primary standards, which are established and well characterised biological reference preparations (eg. those issued by international organisations such as the WHO and NIBSC, or those approved as primary standards as part of the NMA for the product);

and secondary standards, which are preparations with activity calibrated relative to the relevant primary standard. Secondary standards are variously referred to as in-house working/reference standards and subsidiary standards. A SACN is acceptable for the replacement of secondary standards used in biological assays for Type III (biological or biotechnological) products provided all of the following conditions are met:

- an assurance is provided that no other changes have been made, other than the replacement of the secondary (in-house) reference standards, or other self-assessable changes
- the use of the new in-house standard is qualified following a protocol previously approved by Medsafe. The protocol must have been approved as part of the NMA or as a subsequent (assessable) CMN to change the secondary (in-house) reference standard
- the currently approved dossier makes reference to the fact that self-assessable CMNs will be used to inform Medsafe of changes to secondary (in-house) reference standards, with Medsafe having the option to request and review additional supporting information or data as it sees fit
- an assurance is provided that Medsafe will be advised immediately of any aberrant results that arise during routine use of the secondary (in-house) reference standards, or GMP issues identified regarding management of in-house standards
- the self-assessable CMN confirms all of the above, and is sent, along with relevant data and Certificates of Analysis (CoAs), prior to routine use of the new secondary (in-house) reference standard.

A change of this kind should be submitted using CMN Form B, category 'Test methods and specifications – G1 (Self-assessable)'.

A CMN is required using CMN Form B category 'Test methods and specifications – G4' if any of the above requirements are not met.

3.3 Changes to reference standard shelf life/expiry date

Where a protocol for the retest/expiry date of a biological/biotechnological reference standard has been previously approved (via NMA or CMN), then a SACN (using CMN Form B category Shelf life/storage conditions – G1) may be used to extend the shelf life/expiry/retest date. Relevant data/CoAs should be included with the submission, along with an assurance that no other changes are made, and that Medsafe will be advised immediately of any aberrant results that arise during routine use of the standard. If a relevant protocol has not been approved, then the extension should be submitted as a CMN (using CMN Form B category Shelf life/storage conditions – Reference Standard), along with appropriate data. A protocol for subsequent use of SACNs may be included with the submission.

4. Making the same changes for multiple therapeutic products

A sponsor can submit a CMN for an identical change(s) to multiple medicines. This type of CMN applies **only** when the change(s) do 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 all changes are self-assessable and include a data sheet, products should be split on a per data sheet basis.

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 changes affecting the medicine in each of its presentations.

Where a medicine is distributed by a second sponsor as a ‘clone’, both sponsors are similarly responsible for ensuring 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.

6. Abbreviated and priority assessment of notifications

The statutory timeframe for CMNs requires that the initial Medsafe evaluation must be completed within 45 days (see Evaluation Timelines). Medsafe typically completes its initial evaluation in a shorter timeframe. CMNs therefore are not eligible for priority assessment.

Medsafe does not operate an abbreviated process for CMNs, except for section 24(5)(a) notifications, which are described further in section 7 of this guideline. If the same change(s) has been approved by a recognised regulatory authority and 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.

If an urgent CMN assessment is required due to a potential out of stock situation please refer to "What to do in the case of a potential out of stock" Medsafe webpage.

7. Referrals under section 24(5) of the Medicines Act 1981

Section 24 of the Medicines Act 1981 sets out restrictions on the distribution of changed medicines. Subsection 5 permits the Director-General (DG) 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 complexity that the medicine should not be distributed without consent of the Minister (section 24(5)(a)), or that the DG is insufficiently informed about the change proposal (section 24(5)(b)).

The following are examples of CMNs that are typically referred under Section 24(5):

- Additional indications or extensions to the current indication or dosing regime
- New sites of drug substance manufacture (involving a new Drug Master File or 3.2.S of the Common Technical Document (CTD))
- 'Grandmother's axe' products (when changes are so significant that the proposed product no longer resembles the approved product)
- Changes that are too complex and/or too numerous to be assessed by Medsafe within CMN evaluation timeframes.

The following are examples of CMNs that are typically referred under Section 24(5)(b):

- Failure to respond to requests for information
- The time required by a sponsor to provide additional information exceeds the legislative time allowed for CMNs.

The timeframe for a CMN referred under section 24(5) of the Medicines Act 1981 is the same as a New Medicine Application (NMA).

CMNs referred under section 24(5) of the Medicines Act 1981 are subject to the same eligibility criteria for priority assessments as NMAs (refer to section 7 of the New Medicines Applications guideline).

8. Abbreviated procedure for CMNs referred under section 24(5)(a)

An abbreviated evaluation procedure is available for section 24(5)(a) notifications (similar to the abbreviated procedure for NMAs), in which review of evaluation reports from Medsafe recognised regulatory authorities forms the basis of the evaluation. Although the abbreviated evaluation process places reliance on overseas evaluation reports, Medsafe undertakes an independent evaluation and makes an independent decision on whether consent should be granted for the distribution of the medicine in New Zealand.

The abbreviated evaluation process for CMNs referred under section 24(5)(a) is a quicker process than the standard evaluation process. This is reflected in the application fee and indicative timelines.

The acceptance of section 24(5)(a) notifications for the abbreviated pathway will be determined on a case-by-case basis at screening, based on the quality and extent of the evaluation reports available. Notifications that are not eligible for the section 24(5)(a) abbreviated procedure need to be submitted via the standard CMN process.

Multiple changes may be grouped together for a section 24(5)(a) notification submitted for the abbreviated procedure, provided those same changes were approved together by the overseas regulatory authority as part of the same application/notification.

8.1 Eligibility criteria

To be eligible for the abbreviated evaluation procedure, all the following criteria must be met:

- The proposed changes are identical to those approved by the recognised regulatory authority. This requires the pre-change aspects of the product, relevant to the changes being made, being identical to the details currently approved in New Zealand.
- The proposed changes have not been rejected or withdrawn by a recognised regulatory authority for quality, safety, or efficacy reasons.
- The formulation of the product(s) subject of the section 24(5)(a) notification is identical to that approved by the recognised regulatory authority.
- The product(s) must have a current market authorisation issued by the recognised regulatory authority from which the assessment reports are being provided.
- Full assessment reports from the recognised regulatory authority must be available.

- Any questions raised by the recognised regulatory authority and the company's responses, along with the regulatory authority's assessment of these responses must be available.
- If the section 24(5)(a) contains multiple changes, then all of the changes have been approved by the recognised regulatory authority together as part of the same application/notification.

8.2 Data requirements

The notification must be supported by a complete data set relevant to the proposed change(s), as would be expected if the notification was submitted via the standard notification process (i.e. include relevant sections of Modules 1, 2, 3, 4, and/or 5).

The data set must be updated to incorporate any revisions/changes that were requested by the recognised regulatory authority during their review of the proposed changes.

The recognised regulatory authority evaluation report(s) must be in English and be a complete record of the assessment. Any evaluation reports that have been translated must be certified translations. Redacted reports are not acceptable. The following recognised regulatory authority reports and approval documentation must be provided:

- All evaluation reports that have been completed by the recognised regulatory authority for their assessment of the change(s).
- All questions raised by the recognised regulatory authority during their review of the proposed change(s), the company's responses to these questions, and the subsequent assessment by the overseas regulatory authority of the responses to these questions.
- Evidence of the recognised regulatory authority's approval of the proposed change(s).
- If the notification was subject to a joint regulatory authority work sharing process (eg, Access Consortium) then evaluation reports must be submitted from all the regulatory authorities that contributed to the assessment of the change(s). All regulatory authorities associated with the work sharing process must be Medsafe Recognised Regulatory Authorities (refer to section 8.3 of this guidance).

Some regulatory authorities may prefer to provide their evaluation reports directly to Medsafe, rather than to the sponsor. In this situation, it is the responsibility of the sponsor to organise the regulatory authority to provide its reports to Medsafe. Medsafe can provide a letter to the sponsor that can be forwarded on to the regulatory authority advising how to submit their reports directly to Medsafe. These reports are required before the CMN 24(5)(a) can be accepted for the abbreviated pathway.

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

Although an abbreviated application is based on recognised regulatory authority approval, Medsafe reserves the right to request modifications to any part of the dossier relevant to the proposed change(s) during the evaluation process, including to the indications and dosage information, or other data sheet sections.

8.3 Recognised regulatory authorities

For the purposes of the abbreviated pathway for CMNs referred under section 24(5)(a), Medsafe recognises the following regulatory authorities:

- Australian Therapeutic Goods Administration (TGA) (excluding applications approved upon appeal)
- European Medicines Agency (EMA) (centralised procedure only)
- European Union (EU) member states (decentralised procedure only)
- Health Products and Food Branch of Health Canada
- Singapore Health Sciences Authority (HSA)
- UK Medicines and Healthcare products Regulatory Agency (MHRA)
- Swissmedic
- United States Food and Drug Administration (FDA) .

9. Changing the market availability or consent status of a medicine

Sponsors of medicines can choose to designate their consented products 'not available' if they wish to communicate the unavailability of medicine in the market to the public and healthcare professionals. Sponsors do not have to maintain published data sheets for prescription and restricted medicines if the medicine is designated '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 not been generally available for more than five years as described in section 1 of the New Medicines Applications guideline.

A change in the market availability to 'not available' or consent status to 'approval lapsed' can be made 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 available on the Forms and Templates page on the Medsafe website – see the 'Administration and Maintenance of Product Files' section. Sponsors should advise when the product was last marketed in New Zealand.

There is no cost associated with updating the market availability to 'not available' or consent status to 'approval lapsed'.

When changing the market availability information from 'not available' to 'consent given' or 'provisional consent', the sponsor should ensure that the regulatory file information approved by Medsafe for the product is up-to-date and consistent with the product being reintroduced into the New Zealand market. If the regulatory file information needs to be updated, a CMN must be submitted and granted consent prior to the market availability information being updated and the product being reintroduced into the market. When requests to update the market availability status are submitted as part of a CMN this should be clearly identified in the CMN cover letter. For prescription or restricted medicines, the CMN must include a revised data sheet to demonstrate that any 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 to change the market availability information to 'consent' because the regulatory file has been kept up to date, a justification letter along with a completed Product Status Change Request form should be provided to Medsafe. (The form is available on the Forms and Templates page on the Medsafe website – see the 'Administration and Maintenance of Product Files' section.) Medsafe will review the justification letter and form to ensure that any requests for CMNs have been addressed prior to the market availability information being updated and the product is able to be reintroduced into the market.

CMNs, justification letters and Product Status Change Request Forms must be submitted at least 90 days prior to the intended date product distribution will commence. Justification letters should be addressed to the Manager, Product Regulation (medsafeapplications@health.govt.nz).

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 1.2 of the New Medicine Applications guideline.

10. Non-notifiable changes

The following are examples of changes to the regulatory file information that are considered a non-notifiable change (ie, a CMN or SACN 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 market availability or consent status (see section 8 of this guideline).
- Change in proprietary ingredient subject to the following conditions:
  - the new proprietary ingredient is the same type (ie, black ink, orange flavour)
  - the new proprietary ingredient is already registered.
- New or changed site for New Zealand product release (see section 9.5 of this guideline).
- Change in excipient supplier, with no change to excipient specifications.
- Change in name of a manufacturing or packing site (see section 9.2 of this guideline) subject to the following conditions:
  - there is no change of ownership
  - the change in name affects the whole site (ie, name change is not restricted to selected buildings)
  - a Good Manufacturing Practice (GMP) certificate has been provided with the new site name.

10.1 Changes in pharmacopoeial specifications

A CMN is not required to update the 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*).

10.2 Changes in names of manufacturers or packers

When the name of a manufacturer, testing site, or packer is changed but there are no changes to the address or the manufacturing or packing processes, a CMN is not required. Instead, the sponsor should advise Medsafe (medsafeapplications@health.govt.nz) in writing 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, testing, or packer, each sponsor that uses the site is responsible for notifying the change to Medsafe.

10.3 Updates to Drug Master Files

Drug Master Files (DMFs) should be updated periodically to reflect any changes that are made to the active ingredient manufacturing process, controls, or stability. Sponsors should ensure that such DMF updates and details of any changes made are forwarded to Medsafe.

If Medsafe receives a DMF update from a DMF holder, Medsafe sends "Request for CMN" letters to the sponsors of medicines that use that DMF.

The sponsor should determine whether any changes that have been made to the DMF require submission of a CMN to Medsafe. Submission of a CMN is required for Medsafe to assess DMF updates. The sponsor should ensure the version of the DMF referenced in a CMN is the same version which is submitted by the DMF holder that is subject to the changes being notified.

During Medsafe assessment of an updated DMF, any questions that relate to the DMF are sent directly to the DMF holder. The sponsor receives a Request for Information letter stating that this has occurred and requests that the sponsor contact the DMF holder to advise of a timeline for the response. Consent letters for DMF updates are issued to the sponsor that has submitted the CMN for the DMF update. The DMF holder does not receive a separate consent letter. It is the responsibility of the sponsor to advise the DMF holder if any updates have received Medsafe consent. DMF updates generally are not referred under section 24(5), unless the update is introducing new sites of manufacture or a new manufacturing process.

10.4 Changes to Working Cell Banks or Working Seeds

Manufacturing of many biological or biotechnological products involves the use of cultured cells, either as hosts for propagation of viruses (eg, mammalian cell culture), or for production of active molecules (eg, 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 prepare 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 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 International Council for Harmonisation of Technical Requirements for Human Use (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 (eg, 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 (Form B: Active ingredient method of manufacture – Grade 3) is required to submit the above information, and to propose the future use of advisory letters, unless this is covered in the NMA.

A CMN (Form B: Active ingredient method of manufacture – Grade 3) 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.

10.5 Addition of 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 (medsafeapplications@health.govt.nz) in writing so that Medsafe can update its records.

11. Change of Sponsor

A change of sponsor should be notified using the relevant CMN category and include letters or other evidence from both the proposed and current sponsors 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 notification 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 existing product in the distribution chain with the previous contact details.

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 to the new sponsor.

New sponsors should ensure that they meet the requirements as detailed in section 2.1 of the Overview of Regulatory Processes for New and Changed Medicines guideline.

12. Updating Plasma Master Files

Plasma Master Files (PMF) should be updated at least annually. For guidance regarding the content of the update, refer to the EMA Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) Revision 1 (EMEA/CHMP/BWP/3794/03 Rev.1), also the EMA Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010). The update may be submitted by a PMF holder, or by the sponsor of a product that relies upon the PMF, but must be accompanied by or associated with a CMN from a NZ sponsor (or their representative).

The revised PMF (plus any associated overseas evaluations and approvals) should be submitted to Medsafe in electronic form (see Section 3.2 of Overview of Regulatory Processes for New and Changed Medicines, Fees, and Timelines), along with:

- a cover letter
- a completed "Application to Accompany a Plasma Master File" Form (DOC/PR/01/15)
- a letter of access from the PMF holder
- a CMN Form B - the change category should be Active ingredient method of manufacture, Grade 2 or Grade 3 (depending on whether or not new plasma supply organisations are introduced), even if the PMF describes plasma used to manufacture an excipient).

If a sponsor wishes to refer to a current PMF already approved by Medsafe, then they need not submit the entire PMF. Instead, they may submit a letter of access from the PMF holder along with a completed CMN Form B using the self-assessable change category Active ingredient method of manufacture - Grade 1. This submission should be made even if the PMF describes plasma used to manufacture an excipient.

The letter of access should clearly state the Medsafe approval date and file reference for the PMF that it covers, and confirm that all details (eg. supply organisations, countries of plasma origin) are as approved by Medsafe.

13. Introducing changed medicines into the marketplace

It is expected that 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 changeover 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.

Sponsors considering longer change-over times should include a justification in the CMN. Consideration should be given to any potential impacts of extended change-over times, eg, discrepancies between labels and data sheet information.

Sponsors 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 occur rapidly and in conjunction with a product recall.

14. Preparing a Changed Medicine Notification for submission

CMNs 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". Only the CTD sections relevant to the change need to be submitted.

Each CMN must be accompanied by a cover letter and a completed CMN form. The cover letter should briefly summarise the changes being notified and the changes should also be clearly described in section 4 of the CMN Form.

There are two CMN forms published on the Forms and Templates page of the Medsafe website, and the correct CMN form should be used:

- CMN Form A is for lower-risk, intermediate or higher-risk medicines, (other than biological or biotechnological medicines) and these include antibiotics and like-substances derived from micro-organisms.
- CMN Form B is for biological or biotechnological products (eg, vaccines, allergens, products derived from human blood or plasma or serum, immunological products, and any product derived from biotechnology).

A separate CMN form should be completed for each product and all sections of the CMN form must be completed. Applicants should submit one copy of each completed CMN form and any supporting documentation.

It is not acceptable to combine a CMN with an NMA. CMNs can only be submitted after a NMA has been consented. Any supporting documentation that is referred to in a CMN must be provided with the CMN; it is not appropriate to reference supporting information that was submitted in the product's 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) regulatory file information changes are intended, a new CMN and fee are required.

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

Consequential changes are grouped within some CMN category 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 specific 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.

Appendix 1: Data requirements for Changed Medicine Notifications

The data required to support a CMN or Changed Related Product Notification (CRPN) are essentially the same as that required for the corresponding section(s) of a NMA.

The following data should be provided, and if not provided, may be requested by Medsafe.

Formulation

CoAs issued by the finished product manufacturer for two or three representative batches of any new excipient if that excipient is not controlled in accordance with a recognised pharmacopoeial monograph.

Comparative dissolution data for the proposed new and currently approved finished products using a discriminatory test, must be supplied for tablets and capsules. The data need to establish that there are no significant differences between the new and original formulations.

CoAs for the finished product manufactured using the proposed new formulation. At least one batch should be at full production scale unless otherwise justified, while the other batches should be at least pilot scale manufactured using full production scale equipment.

Bioequivalence data if required (see note below).

Stability data if required (see note below)

If the formulation involves a change to the preservative system, then additional data may be required such as:

- Proof of anti-microbial efficacy of the finished product at expiry.
- Test methods (and validation data) for the determination of preservative content at finished product release.
- Stability data (including microbial quality).

Note: The following changes are considered unlikely to have an impact on the stability or bioavailability of an immediate release or modified release solid oral dose form:

- Removal, replacement or reduction in the amount of a colouring or flavouring agent.
- A change in the percentage content of any of the following excipients provided that:
    - the change in the amount of an individual excipient does not exceed the maximum allowable change for that excipient as shown in the table below, and

- the total additive change to all non release-controlling excipients is not more than 5% of the total formulation, and
- the total additive change to all release-controlling excipients in a modified release dose form is not more than 5% of the total formulation, and
- the total weight of the dosage form is still within the previously approved range.

Excipient		**Maximum allowable change** (as a percentage of total weight)
Filler		5%
Disintegrant:	Starch	3%
	Other	1%
Binder		0.5%
Lubricant:	Calcium stearate	0.25%
	Magnesium stearate	0.25%
	Other	1%
Glidant:	Talc	1%
	Other	0.1%
• **Film coat**		1%

If a product undergoes a series of stepwise formulation changes, bioavailability data will be required if the overall change exceeds the limits stated above.

When an application is made for approval of a change to the formulation of a solid oral dose form, and the change falls *within* the criteria above, a bioequivalence study and stability study are not required to be submitted with the change notification. For any formulation change that falls *outside* the criteria given above, the applicant must either provide stability and bioavailability data, or provide adequate justification for not doing so.

Site of manufacture (active ingredient)

Either a Drug Master File with accompanying "letter of access", or a European Pharmacopoeial Commission "Certificate of Suitability" (CEP) with an accompanying "letter of access". If the finished product is a "low risk" medicine then CoAs for representative batches of active ingredient issued by the finished product manufacturer are sufficient instead of a DMF or European Pharmacopoeial Commission CEP.

For prescription medicines, acceptable evidence of GMP (from a Medsafe-recognised authority – see Guideline on the Regulation of Therapeutic Products New Zealand (GRTPNZ) "Manufacture of medicines") for the new active ingredient site of manufacture must also be submitted.

Certificates of analysis are required for at least three production-scale drug substance batches manufactured at the new site, **issued by the finished product manufacturer**.

A comparison should be provided of the impurity profiles and other relevant features (particle size, polymorphism) of the active ingredient manufactured by the new and existing sites.

Data should be provided that demonstrates the suitability of the active ingredient from the new site for use in the finished product (e.g. batch data for finished product manufactured using active ingredient from the new site, or comparative dissolution profiles), or a justification given for not providing such data (e.g. active ingredient from the new manufacturing site is controlled according to the same pharmacopoeial monograph as active ingredient from the existing site(s), has a similar impurity and stability profile, and physical and chemical characteristics are unlikely to be impacted by the finished product manufacturing process).

Site of manufacture (finished product)

GMP certification for the new site, if available, or other acceptable evidence of GMP compliance at the site (see GRTPNZ "Manufacture of medicines").

Appropriate validation of the process at the new site must be submitted to demonstrate that product manufactured at this site meets the currently registered requirements for in process controls and the finished product specifications.

Description and validation of quality control test methods where there is a change in test procedures or the laboratory testing the product.

CoAs for representative batches of finished product manufactured at the new site. The batch sizes for the representative batches should be in accordance with the recommendations of European Medicines Agency (EMA) guidance "Guideline on process validation for finished products – information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1).

Comparative dissolution data using a discriminatory test, must be supplied for tablets and capsules. The data need to establish that there are no significant differences between product made at the old and new sites.

Relevant stability data must be generated for batches produced at the new site as required by GMP. Medsafe may request the sponsor to provide accelerated stability data for a particular medicine where stability is known to be a problem or where changes in stability could have clinical consequences. The relevant stability data need not necessarily be supplied prior to the issue of consent for the change of site. However, if stability data are not supplied, the sponsor must complete the Declarations and Commitments section of the Medsafe CMN form to confirm that stability data will be generated and Medsafe notified immediately if there are any significant problems identified or if the data indicate that the stability of product from the new site is different from that made at the original site to the extent that the shelf life of the medicine would be affected.

If the new finished product manufacturing site complies with the Food and Drug Administration (FDA's) Guidance for Industry on Scale-Up and Post-Approval Changes (SUPAC) requirements, this is also acceptable.

Manufacturing process (active ingredient)

Description of changed manufacturing process and in-process controls.

Process validation data for sterile active ingredients, biological, or biotechnological products.

CoAs for representative batches of active ingredient manufactured using the new process.

Manufacturing process (finished product)

Description of the changed manufacturing process and in-process controls.

Process validation data.

CoAs for representative batches of finished product manufactured using the proposed process. The batch sizes for the representative batches should be in accordance with the recommendations of EMA guidance "Guideline on process validation for finished products – information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1).

Comparative dissolution data for representative batches of the finished product using a discriminatory test, must be supplied for tablets and capsules. The data needs to establish that there are no significant differences between the product manufactured using the new and original manufacturing processes.

Stability data or confirmation that stability data will be collected. Relevant stability data must be generated for batches produced using the new process as required by GMP. Medsafe may request the sponsor to provide accelerated stability data for a particular medicine where stability is known to be a problem or where changes in stability could have clinical consequences. The relevant stability data need not necessarily be supplied prior to the issue of consent for the change of process. However, if the data are not supplied, the sponsor must complete the relevant

Declarations and Commitments section of the Medsafe CMN form to confirm that stability data will be generated and Medsafe notified immediately if there are any significant problems identified or if the data indicate that the stability of product from the new process is different from that made at the original process to the extent that the shelf life of the medicine would be affected.

Bioequivalence data if required.

Biosimilarity data for biological or biotechnological products if required.

Specifications/test methods (active ingredient and finished product)

Justification for specification changes.

Validation of any new or changed test methods, except where the test method performed on the active ingredient is pharmacopoeial **and** the method is subject of a pharmacopoeial update.

If a new testing site is being introduced for a non-pharmacopoeial method, then evidence of analytical method transfer or revalidation at the new site is required. Analytical procedure transfer is the process that qualifies a testing site to use an analytical procedure that has been developed and/or validated at another testing site.

CoAs for the active ingredient or finished product demonstrating the ability of the company to meet specifications.

Packaging

Packaging materials specifications.

Stability data if the primary packaging has a different composition or is expected to be less protective than the currently approved packaging.

Changes to dose delivery devices (eg, automated pens) will require evidence of appropriate dosing capability.

New and extended indications

Justification or supporting clinical data (as appropriate) and a draft revised data sheet.

Datasheets

Supporting information required for safety related changes to the data sheet and a draft revised data sheet.

1. **Generic medicine data sheets**

The revised data sheet should align with the innovator data sheet. Provide the New Zealand innovator data sheet to support the proposed changes. If the New Zealand innovator is not marketed, or has approval lapsed, provide the SmPC/PI for the overseas innovator that is being referenced.

2. Innovator medicine data sheet

Include a signal review/clinical overview and the company core data sheet. Additional supporting information can also be provided.

3. Data sheet update requested by Medsafe Pharmacovigilance

No additional documentation is required to be provided for data sheet changes that only include updates that have been requested by the Medsafe pharmacovigilance team. On submission of the CMN, refer to the data sheet request that was sent by Medsafe, for example by including the corresponding letter or PBRER assessment, a Medsafe reference number or requestors name, if known.

Summary of major changes and rationale

Proposed changes	Rationale
Section 6 (Abbreviated and priority assessment of notifications): Amending wording to allow for section 24(5)(a) notifications to use an abbreviated procedure.	Introduction of an abbreviated procedure for section 24(5)(a) notifications.
Section 7 (Referrals under section 24(5) of the Medicines Act: Amending wording to differentiate between section 24(5)(a) and section 24(5)(b) notifications.	Provide clarity to sponsors about the different types of section 24(5) notifications.
Section 8 (Abbreviated procedure for CMNs referred under section 24(5)(a)): This is a new section that includes a description of the abbreviated procedure for section 24(5)(a) notifications, associated eligibility criteria and data requirements, and the recognised regulatory authorities that can be used for this procedure.	Introduction of an abbreviated procedure for section 24(5)(a) notifications to create a procedural pathway with reduced Medsafe evaluation timeframes for these types of notifications.