



MEDSAFE

NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY

A BUSINESS UNIT OF
THE MINISTRY OF HEALTH

Guideline on the Regulation of Therapeutic Products in New Zealand

Part 4:

Manufacture of medicines

Edition *Draft*

October 2014

Section 1: Good Manufacturing Practice Documentation

Section summary

- *This section explains when evidence of compliance with GMP is required and what evidence is acceptable.*
- *This section is copied from section 5 of Part D of the New Zealand Guidelines for Regulation of Medicines and is currently under review.*

1.1. When is GMP Documentation Required?

Medsafe requires evidence of **Good Manufacturing Practice** (GMP) compliance for each finished product manufacturing site and packaging site specified in a New Medicine Application or Changed Medicine Notification.

Evidence of GMP compliance is required for products regarded as medicines in New Zealand, whether or not they are considered medicines in the country of origin.

In the case of related products, evidence of compliance with GMP is required for NRPA's and CRPNs for products taken internally (eg, throat lozenges, and vitamin and mineral tablets).

Evidence of GMP is **not** required for related products used externally. However, evidence is still required to show that the manufacturer complies with an internationally recognised quality system (eg, ISO accreditation).

For bulk active pharmaceutical ingredients evidence that the material is manufactured consistently and produced with acceptable quality is required.

GMP certification, or equivalent documentary evidence, stating the products or product classes for which it has been granted is required for all:

- ☞ manufacturers of the finished product (including manufacturers of intermediate products)
- ☞ sterilisers of the finished product
- ☞ packers of the finished product
- ☞ sites where products are overlabeled

A manufacturing site for a finished product is any site which contributes to a manufacturing operation which converts bulk raw materials to a finished dose form.

This includes sterilising sites. A packing site means any site which contributes to a packing operation which places the final dose form into its labelled primary or secondary container.

Manufacturers and/or packers with premises in New Zealand must hold an appropriate current licence to manufacture and/or pack medicines. The licence must have been issued for the site for the manufacture and/or packaging of the type of product or packaging operation before manufacture or packaging of the product for distribution can commence. Provided they hold such current licences, certification need not be provided with each application or notification.

For overseas manufacturers and packers, Medsafe requires that certification be included with each NMA or CMN which relates to a change of site, even if the site already supplies product to New Zealand and certification has been supplied previously with an earlier application or notification. This reduces delays associated with locating other files, and because it is desirable for the certification to be product-specific and up-to-date.

Acceptable evidence of GMP compliance normally consists of copies of appropriate certificates, manufacturing licences or reports issued by a regulatory authority whose competence is recognised by Medsafe. Details of the documentation that is acceptable and a list of authorities whose competence to certify GMP compliance is recognised by Medsafe is given below in Section 1.5.

The certificate, licence or report should be no more than 3 years old when the NMA or CMN is submitted, and must be current at the time of approval of the new or changed product for distribution in New Zealand.

If the original documentation was in a language other than English then copies of both the original documents and a certified English translation must be submitted.

If acceptable evidence of GMP compliance is not available, an audit of the site by Medsafe auditors can be arranged at the applicant's request and expense.

1.2. Recognised Documentation

GMP certification recognised by Medsafe can be any document issued by a recognised authority which attests to GMP compliance. Legible photocopies of the documents are acceptable.

Documents should contain the following information:

- ☞ the street address of the site concerned
- ☞ reference to the product or product class
- ☞ reference to GMP acceptability and/or to a GMP audit
- ☞ name and address of the issuing authority
- ☞ date and signature.
- ☞ date of expiry of the certification or licence

The following are examples of acceptable evidence of GMP certification:

- ☞ licence to manufacture issued by a recognised authority where such a licence is issued only where the site is inspected and regularly re-inspected for GMP compliance
- ☞ current registration and entry (for the product, product class or process concerned) of the site in the Australian Register of Licensed Manufacturers
- ☞ United Kingdom Product Licence or Product Licence Variation where name and address of site is shown
- ☞ certification of pharmaceutical product issued under the WHO scheme by a recognised authority which certifies the quality of pharmaceuticals moving in international commerce
- ☞ Canadian Drug Plant Inspection Rating Report
- ☞ a letter or file note from a recognised authority which attests to GMP compliance. The most usual example seen is an extract from FDA files obtained by the manufacturer under the US Freedom of Information Act. It usually states that an audit occurred on the given date and gives the outcome of the audit
- ☞ a certificate issued by the Australian TGA confirming that it has confirmed (eg, with the US FDA) that GMP compliance at the particular site is satisfactory. Note that Medsafe also has access to the FDA's electronic GMP database and can check the GMP status of manufacturing sites inspected by the FDA.

The following are NOT acceptable as evidence of GMP compliance:

- ☞ a licence to manufacture which is not issued by a recognised authority
- ☞ certification issued by a pharmaceutical company - even if the company certifying is not the same as the manufacturer or packer
- ☞ Annual Registration of Drug Establishment (USA). This document is not indicative of GMP compliance.

1.3. Classes of Medicine

Certification should preferably be product-specific. Certification in the WHO format or a manufacturing or product licence listing the product are the most easily obtained examples of this type.

If product-specific certification cannot be obtained, the certification must relate to a medicine or medicines of the same class(es) (see below) as the one which is the subject of the application or notification. A medicine may belong to more than one class. In such cases, the certification should be for a product belonging to the same classes.

- I Medicines containing penicillin

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| II | Medicines containing cephalosporin |
| III | Vaccines or sera |
| IV | Sterile medicines |
| V | Hormones and steroids |
| VI | Microdose preparations (other than vitamins), ie, containing 5 mg or less per unit dose |
| VII | Antineoplastic agents and immunosuppressant agents (other than steroids) |
| VIII | Solid dose forms |
| IX | Recombinant DNA medicines |
| X | Metered dose aerosol preparations |
| XI | Liquids, creams, ointments |
| XII | Non-metered dose aerosols |
| XIII | Powders |
| XIV | Wound dressings |
| XV | Transdermal patches |

1.4. Sites which Manufacture Bulk Active Pharmaceutical Ingredients

Evidence of GMP is required for *all sites* which manufacture bulk active pharmaceutical ingredients. Such evidence should be included with each application or notification which relates to a change of site.

Applications and notifications must include the name and address of the *actual site of manufacture* and applicants should ensure that there is no confusion between sites of manufacture and addresses of company head offices or brokers. Any documentary evidence of GMP must refer to the actual site of manufacture.

Any of the following are acceptable as evidence for manufacturers of bulk active pharmaceutical ingredients used in OTC medicines and related products.

- ☞ A GMP certificate or inspection report issued by a recognised authority. Note that not all authorities issue certification for sites manufacturing bulk active substances.
- ☞ A Drug Master File or equivalent data submitted as part of the dossier for a new chemical entity or new biological entity medicine.
- ☞ A European Pharmacopoeial “Certificate of Suitability” for a substance controlled according to the European Pharmacopoeia.
- ☞ Batch analytical data demonstrating consistent quality of the substance produced (accepted as adequate evidence only for lower risk medicines and related products).

Note: A GMP certificate alone is not acceptable as a substitute for a DMF, Certificate of Suitability or batch analytical data where these are normally required.

1.5. Recognised Authorities

GMP certification issued by the authorities listed below is recognised by Medsafe. The authorities listed include the competent authorities in the European Community, member authorities of the PIC and/or PIC/S organisations, and other authorities where Medsafe has information that GMP assessment systems that are compatible with New Zealand expectations exist. The inclusion of all the European Community competent authorities is a consequence of the Mutual Recognition Agreement in Relation to Conformity Assessment that became effective between New Zealand and the European Community on 1 January 1999. Omission of an authority from the list generally indicates that Medsafe has not assessed that authority's systems, and should not be construed in any way as an adverse reflection on the competence of the authority itself. The inspectorates recognised by Medsafe are listed below.

Australia

Therapeutic Goods Administration, Commonwealth Department of Health and Family Services

Austria

Pharmaceutical Division, Federal Ministry of Health, Sports and Consumer Protection (Bundesministerium für Gesundheit und Konsumentenschutz)

Belgium

Inspection general de la Pharmacie, Ministère de la Santé Publique et de la Famille

Canada

Therapeutic Products Directorate, Health Product and Food Branch, Health Canada

Czech Republic

State Institute for Drug Control

Denmark

Medicines Division, Danish Medicines Agency (Sundhedsstyrelsen)

Finland

National Agency for Medicines

France

Agence du Médicament, Ministère de la Santé

Germany

Bundesministerium für Gesundheit

(The individual medicine inspectorates for the different German states and cities, as listed in the Pharmaceutical Inspection Convention List of Inspectors Employed by the PIC/S Competent Authorities, [State, Name of Authority (City)] are as follows:

Baden-Württemberg

Regierungspräsidium Tübingen, Leitstelle Arzneimittel-überwachung Baden-Württemberg (Tübingen)

Bayern

Regierung von Mittelfranken (Ansbach)
Regierung von Niederbayern (Landshut)
Regierung von Oberbayern (München)
Regierung von Oberfranken (Bayreuth)
Regierung der Oberpfalz (Regensburg)
Regierung von Schwaben (Augsburg)
Regierung von Unterfranken (Würzburg)

Berlin

Landesamt für Gesundheitsschutz, Arbeitsschutz und technische Sicherheit
(Berlin)

Brandenburg

Landesamt für Soziales und Versorgung (Wünsdorf)

Bremen

Senator für Gesundheit, Jugend, Soziales und Umwelt-schutz (Bremen)

Hamburg

Behörde für Arbeit, Gesundheit und Soziales (Hamburg)

Hessen

Regierungspräsidium Darmstadt (Darmstadt)

Mecklenburg-Vorpommern

Arzneimittelüberwachungs- und –prüfstelle Mecklenburg-Vorpommern
(Schwerin)

Niedersachsen

Bezirksregierung Braunschweig (Braunschweig)
Bezirksregierung Hannover (Hannover)
Bezirksregierung Lüneburg (Lüneburg)
Bezirksregierung Weser-Ems (Oldenburg)
Bezirksregierung Arnsberg (Arnsberg)
Bezirksregierung Detmold (Detmold)
Bezirksregierung Düsseldorf (Düsseldorf)
Bezirksregeirung Köln (Köln)

Nordrhein-Westfalen

Bezirksregierung Münster (Münster)

Rheinland-Pfalz

Landesamt für Soziales, Jugend und Versorgung (Koblenz)

Saarland

Ministerium für Frauen, Arbeit, Gesundheit und Soziales (Saarbrücken)
Regierungspräsidium Chemnitz (Chemnitz)
Regierungspräsidium Dresden (Sachsen)
Regierungspräsidium Leipzig (Leipzig)

Sachsen-Anhalt

Landesamt für Versorgung und Soziales Sachsen-Anhalt (Halle a.d. Saale)

Schleswig-Holstein

Landesamt für Gesundheit und Arbeitssicherheit des Landes Schleswig-Holstein (Kiel)

Thüringen

Thüringer Landesverwaltungsamt (Weimar)

For immunologicals: Paul-Ehrlich-Institut, Federal Agency for Sera and Vaccines

Greece

National Drug Organisation (E.O.F.)

Hungary

Drug Inspectorate, National Institute of Pharmacy

Iceland

State Drug Inspectorate

Ireland

Irish Medicines Board

Italy

Pharmaceutical Division, Ministry of Health (Ministero della Sanita, Direzione Generale del Servizio Farmaceutico)

Japan

Pharmaceutical Affairs Bureau, Ministry of Health and Welfare

Liechtenstein

Kontrollstelle für Arzneimittel, Amt für Lebensmittelkontrolle

Luxembourg

Division de la Pharmacie et des Medicaments

Netherlands

Pharmaceutical Inspectorate, Section Pharmaceutical Industry and Trade (Ministerie van Volksgezondheid, Welzijn en Sport, Inspectie voor de Gezondheidszorg)

Norway

Pharmaceutical Inspectorate, Pharmaceutical Department, (Helsedirektoratet Legemiddelavdelingen)

Portugal

Pharmacies and Pharmaceutical Inspections Department (Instituto Nacional da Farmacia e do Medicamento - INFARMED)

Romania

State Institute for Drug Control and Pharmaceutical Research

Singapore

Ministry of Health, National Pharmaceutical Administration

Slovak Republic

State Institute for Control of Drugs

Spain

Ministerio de Sanidad y Consumo, Subdirección General de Farmacéutico

Sweden

Pharmaceutical Inspectorate, Medical Products Agency (Läkemedelsverket)

Switzerland

For sera and vaccines:

Office Federal de la Santé Publique

For other pharmaceutical products:

Office Intercantonal de Contrôle des Médicaments

United Kingdom

Medicines Control Agency, Department of Health

USA

Food and Drug Administration