Psychoactive Substances

Product Approval Guidelines

16 January 2015

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Glossary of terms

The Act The Psychoactive Substances Act 2013

Active ingredient The ingredient responsible for producing a psychoactive effect

API Active Pharmaceutical Ingredient

APLAC Asia Pacific Laboratory Accreditation Cooperation

The Authority The Director-General of Health or his/her delegate

CARM Centre for Adverse Reactions Monitoring

CHMP Committee for Medicinal Products for Human Use (formerly known as CPMP Committee for Proprietary Medicinal Products)

CoS Certificate of Suitability to the monographs of the European Pharmacopeia (also known as a CEP)

CoMP Code of Manufacturing Practice

CTD Common Technical Document (ICH format)

Day Calendar day

DMF Drug Master File

EC European Commission

EDQM European Directorate for the Quality of Medicines

EMA European Medicines Agency (formerly known as EMEA European Medicines Evaluation Agency)

EPA Environmental Protection Agency

Excipient Any non-psychoactive ingredient of a product (excluding the capsule)

EU European Union

FDA Food and Drug Administration (USA)

The fees regulations The Psychoactive Substances (Fees and Levies) Regulations

Finished product Psychoactive product that is packaged and ready for retail sale

GCRP Good Clinical Research Practice

GMP Good Manufacturing Practice

HSNO Hazardous Substances and New Organisms Act

IANZ International Accreditation New Zealand

ICH International Conference on Harmonisation

INN International Non-proprietary Name

Intermediate product Any isolatable partly processed material that is formed during the manufacturing process, but which must undergo further manufacturing steps before it becomes a finished product

JAS-ANZ Joint Accreditation System of Australia and New Zealand

ILAC International Laboratory Accreditation Cooperation

ISO International Organisation for Standardisation

NPC National Poisons Centre

NPPA New Psychoactive Product Application

NSPPA New Subsidiary Psychoactive Product Application

NZMT New Zealand Medicines Terminology

NZULM New Zealand Universal List of Medicines

The OPSRA The Office of the Psychoactive Substances Regulatory Authority

PBRER Periodic benefit-risk evaluation report

PDE Permitted Daily Exposure

Ph. Eur. European Pharmacopoeia

PIC/s The Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Cooperation Scheme

PSAC Psychoactive Substances Appeals Committee

PSEAC Psychoactive Substances Expert Advisory Committee

The PSR Guidelines The Psychoactive Substances Regulatory Guidelines

QOS Quality Overall Summary

The regulations The Psychoactive Substances Regulations 2014

RFI Request for Information

TSE Transmissible spongiform encephalopathy

US United States

USP United States Pharmacopoeia

WHO World Health Organisation

Working day Monday to Friday, not including public holidays or the period between 25 December and 15 January (inclusive)

1. Background

The [Psychoactive Substances Act 2013](http://www.legislation.govt.nz/act/public/2013/0053/latest/DLM5042921.html?src=qs) (the Act) came into force on 18 July 2013. The purpose of the Act is to regulate the availability of psychoactive substances in New Zealand to protect the health of, and minimise harm to, the individuals who use these substances. The Act sets up a system of pre-market approval for psychoactive products by requiring them to demonstrate that they pose no more than a low risk of harm to the individuals who use them, and by placing restrictions on how and to whom they can be sold.

The Act establishes the Psychoactive Substances Regulatory Authority (the Authority) within the Ministry of Health. The Authority is responsible for ensuring products meet adequate safety requirements before they can be distributed in New Zealand, and also licenses importers, researchers, manufacturers, wholesalers, retailers and sellers of unapproved psychoactive substances.

The Psychoactive Substances Regulations (the Regulations) further define the full regulatory requirements for psychoactive substances. The regulations specify

* the requirements for product approvals and licences to sell unapproved psychoactive substances and to import, research and manufacture psychoactive substances.
* the fee and levy structure and the penalties for infringements.
* the requirements for licences to wholesale and retail.

These guidelines (the Psychoactive Substances Product Approval Guidelines) are based on New Zealand’s approach to regulating pharmaceuticals.

1. Introduction to the legislative framework

Copies of all relevant legislation can be downloaded free of charge from [www.legislation.govt.nz](http://www.legislation.govt.nz).

### The Psychoactive Substances legislation and guidelines

Regulation of psychoactive substances is subject to the following legislation:

* The Psychoactive Substances Act 2013 (the Act)
* The Psychoactive Substances Regulations 2014 and 2015 (the regulations)
	+ The Psychoactive Substances (Fees and Levies) Regulations 2014 (the fees regulations)
	+ The Psychoactive Substances (Infringement Fees and Form of Notices) Regulations 2014 (the infringement regulations)
	+ The Psychoactive Substances Regulations 2015
* The Psychoactive Substances Regulatory Guidelines 2014 (the PSR Guidelines).

### Other relevant legislation to be read in conjunction with the PSR Guidelines:

* The Psychoactive Substances Act 2013
* The Psychoactive Substances Regulations 2014 and 2015
* The Misuse of Drugs Act 1975
	+ Schedules 1, 2 and 3 – list controlled drugs
	+ Schedule 4 – lists precursor substances
* The Medicines Act 1981
	+ Section 3 – defines a medicine
	+ Section 2(1) - defines a herbal remedy
* The Medicines Regulations 1984
	+ Schedule 1 – lists all prescription, restricted and pharmacy-only medicines
* The Dietary Supplements Regulations 1985
	+ Regulation 2(a) – defines a dietary supplement
* The Food Act 2014 and its associated Standards
	+ Section 9 – defines a food
* The Smoke Free Environments Act 1990
* Section 2(1) – defines a tobacco product
1. **Requirements to comply with other legislation and standards**
	* 1. *Consumer legislation*

Manufacturers must comply with consumer legislation administered by the Ministry of Business, Innovation and Employment, in particular the [Fair Trading Act 1986](http://www.legislation.govt.nz/act/public/1986/0121/latest/DLM96439.html?src=qs) and the [Consumer Guarantees Act 1993](http://www.legislation.govt.nz/act/public/1993/0091/latest/DLM311053.html?src=qs).

1. *Hazardous substances and new organisms legislation*

Manufacturers and importers are required to ensure that the ingredients contained in the psychoactive products they manufacture in New Zealand comply with HSNO legislation, administered by the Environmental Protection Authority. The web site <http://www.hsno.govt.nz> is dedicated to the HSNO legislation and its application.

The web site <http://www.epa.govt.nz> includes information on EPA procedures together with a searchable register of applications and approvals under the HSNO Act.

For further information about the HSNO and EPA requirements for obtaining consent to import and or release products controlled under the HSNO legislation, contact:

General Manager, Applications and Assessments

Environmental Protection Authority

Level 10, 215 Lambton Quay, 6011

Private Bag 63002, 6140

Wellington

Telephone: (04) 473 8426

Fax: (04) 473 8433

Web site: <http://www.epa.govt.nz>

# Principles of the Act

The three key principles in the Act are that:

1. Any psychoactive product that poses no more than a low risk of harm to individuals who use the product should be approved. (A product that poses no more than a low risk of harm is expected to have a risk profile similar to an over-the-counter or general sales medicine
2. Conversely, any psychoactive product that poses **more** than a low risk of harm to individuals who use the product should be prohibited
3. Animals must not be used for the purposes of assessing whether a psychoactive product should be approved.

Assessment of the risk of harm posed by a psychoactive substance requires the OPSRA to consider a range of pharmaceutical, toxicological and chemical factors. In making the assessment, the Act prohibits the OPSRA from considering any data derived from the use of the product in animals.

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| In the opinion of the Psychoactive Substances Expert Advisory Committee (PSEAC), it is unlikely that a product can be shown to pose no more than a low risk of harm without the use of animal testing. See Appendix 3 for the PSEAC Position Statement on animal testing |

# 4 A quick guide to the product application and approval process

The key steps in the product approval process are:

* receiving and screening for completeness
* invoicing and payment
* evaluation of information
* consideration by the Psychoactive Substances Expert Advisory Committee (PSEAC)
* notification of the outcome
	+ issuing of a product approval, or
	+ the opportunity to make a further submission if the outcome is negative
	+ the opportunity to lodge an appeal with the psychoactive substances appeals committee (PSAC) if the outcome is negative.

Figure A below provides an overview of the product approval process and the expected timeframes.

### Receiving and screening for completeness

Applications must include all of the required information in the format required to pass initial screening or they will be returned for resubmission. Initial screening will take place within 20 working days of receipt of the application

*4.1.1 Invoicing and payment*

Once an application has been screened for completeness, the OPSRA will issue the applicant with a tax invoice which will be included with the acknowledgement letter. It is the OPSRAs intent to complete screening and issue an invoice within 14 working days of receipt of the application. Payments are to be made on an invoice basis only – do not send payment with the application.

Payment can be made by Electronic Funds Transfer, or by cheque. Details on how to make a payment by these methods is listed on our invoice remittance advice.

Credit card payments with Visa or MasterCard can also be made. A 2% transaction fee on credit cards applies. You should also check with your card issuer for details about other fees or charges that may apply, as credit card transactions are carried out in terms of arrangement between you and your bank.

Payments are in New Zealand dollars. If payment is made using a credit card issued outside New Zealand, any currency conversion will be done according to the terms and conditions of the card.

From the invoice remittance advice you will require the customer number, invoice number, and invoice total to complete the payment transaction. Payments received up to 2230hrs New Zealand time will be applied the next business day.

The schedule of fees payable can be found in section 6 below.

### Evaluation of initial and additional information

A full evaluation will be completed within 300 days of receiving payment. If further information is required during evaluation a Request for Further Information (RFI) will be made. All information provided in response to a request from the OPSRA should be provided in hard copy and on disc in order to prevent the application from lapsing. An application lapses if the requested information is not supplied within 30 days of the request, or any further time the OPSRA may allow (by written notice). A lapsed application will need to be resubmitted and a full application fee paid.

Additional information provided in response to an RFI will be evaluated within 150 days of receiving the information. The OPSRA may issue up to two RFI rounds before making a recommendation on the application.

### Consideration by the Psychoactive Substances Expert Advisory Committee (PSEAC)

All product applications are referred to the PSEAC. The PSEAC is a committee made up of experts in relevant areas such as pharmacology, toxicology, neurosciences and medicine. The function of the PSEAC is to evaluate psychoactive products to assess whether they should pose no more than a low risk of harm to be approved for use by individuals and to advise the Authority accordingly. The final decision on whether to approve a product or not is made by the Authority on the basis of the recommendations made by the OPSRA and the PSEAC.

The PSEAC will meet not less than four times a year. Product applications must be ready to be referred to the committee at least one month prior to the date of the meeting Product applications that do not meet the one month cut off period will be referred to a subsequent meeting.

Meeting dates, agendas and minutes will be published on the PSRA website at www.psychoactives.health.govt.nz

### Notification of the outcome

If the outcome is positive, the applicant will receive the licence approval certificate and an outcome letter. Applicants should carefully read both the outcome letter and the certificate as these documents will describe the approved details, requirements and conditions that must be complied with. Any incorrect details should be notified to the OPSRA immediately.

If the outcome is negative, the applicant will receive an outcome letter which clearly explains the grounds for the proposed refusal. The letter will also advise the applicant of their right, under section 21(1)(b) of the Act, to make a written submission to the OPSRA to object to the Authority’s proposal to refuse product approval.

If the applicant chooses not to make a written submission within the required timeframe the Authority will refuse the licence application.

If the applicant chooses to make a written submission and it is received within the required timeframe the Authority will reconsider the proposal to refuse the licence based on the written submission. It is the OPSRAs intent to complete this process within 28 working days of receiving the written submission.

If the outcome is positive, the applicant will receive the licence certificate and an outcome letter. Applicants should carefully read both the outcome letter and the licence certificate as explained above.

If the outcome is negative, the applicant will receive notification that the licence application has been refused, and the grounds for this refusal. Applicants will also be advised of their right, under section 45 of the Act, to lodge an appeal with the PSAC. Specific conditions imposed on licences can be contested by the applicant with the OPSRA. If the applicant is not content with the outcome received from the OPSRA, they can appeal to the PSAC about the Authority’s decision to impose specific conditions on a licence

### Lodging an appeal with the PSAC

The PSAC is a committee made up of three members, at least one of which must be a lawyer with at least seven years’ experience. The function of the committee is to independently review any decision made by the Authority:

* to refuse to approve the psychoactive product
* to impose a condition on the approval of the psychoactive product
* to revoke the approval of the psychoactive product
* to issue a recall order for the approved product
* to refuse to grant the person a licence
* to impose a condition on the person's licence
* to suspend or cancel the person's licence

The committee cannot review any decision or part of a decision that is not appealed against. On hearing the appeal, the committee may:

* confirm, reverse or modify the decision appealed against
* make any other decision that the Authority could have made
* refer appeals back to the Authority to reconsider.

Appeals against an Authority decision should be accompanied by a detailed letter stating the decision to be appealed and the grounds on which it is to be appealed. The committee will meet as and when required.

Appeals should be sent to:

The Psychoactive Substances Appeals Committee Convenor

Governance & Crown Entities, Corporate Services

Ministry of Health

Po Box 5013

Wellington 6145

New Zealand

Appeals must be received no later than 60 days after the decision appealed against is given unless the committee allows a longer period. The decision being appealed remains in force throughout the appeal unless the committee orders otherwise.

For further information on the appeals process, please direct queries to psychoactiveappeals@moh.govt.nz.

Figure A: Overview of the product approval process



# When is an application required?

### Products

All psychoactive substances require consent from the Authority (as established by section 10 of the Act) before they can be sold in New Zealand.

1. *Definitions*

A psychoactive **substance** is anything that can be used to induce a psychoactive effect in humans by ingestion. A psychoactive **product** is a product containing a psychoactive substance and which is packaged and ready for retail sale. For the purposes of these guidelines the term’ psychoactive substance” is used to refer to both the substance and the product

The term ‘active ingredient’ is used to refer to the ingredient or substance which is responsible for producing a psychoactive effect.

*5.1.2 Exclusions*

The definition of a psychoactive substance under the Act does **not** include an alcohol or tobacco product (unless they contain a psychoactive substance), controlled drug or precursor substance, medicine, herbal remedy, dietary supplement or food. The definition also does not include anything that has been declared by the Governor-General, under Section 99 of the Act, not to be a psychoactive substance.

If, after reading these guidelines, it is still unclear whether a product meets the definition of a psychoactive product, prospective applicants should contact the OPSRA at [www.psychoactives@moh.govt.nz](http://www.psychoactives@moh.govt.nz).

###  Licences

Individuals or legal entities must have the Authority’s consent to perform each of the following activities:

* import psychoactive substances
* manufacture psychoactive substances
* research psychoactive substances
* sell psychoactive substances that are not approved products
* sell psychoactive substances by retail
* sell psychoactive substances by wholesale.

Further information on the requirements for these licences and how to apply for these licences can be found in the Guidelines to the Psychoactive Substances Regulatory Licensing Scheme.

# Claims of a psychoactive nature

Any product that is sold or promoted as being able to produce a psychoactive effect meets the definition of a psychoactive substance, irrespective of the ingredients of the product, and must have the Authority’s consent before it can be sold in New Zealand.

A claim of producing a psychoactive effect can be direct, implied or suggested. Such claims include terms such as “high”, “euphoria”, “mood altering”, “hallucinogenic” “vision inducing” and in some instances “stimulant”.

Consumers have the right to expect that any product claiming to produce a psychoactive effect will, in fact, produce a psychoactive effect in the user. Any product which claims to induce a psychoactive effect in the user, but does not induce the effect, may be subject to regulation under the [Fair](http://www.legislation.govt.nz/act/public/1993/0091/latest/DLM311053.html?src=qs) Trading Act 1986.

Claims of a psychoactive nature will be investigated as part of the application process and must be able to be supported.

# Unapprovable dosage forms

Psychoactive substances are prohibited if they are in a form that is:

* intended to be injected,
* a powder or liquid except where it is contained in a capsule or tablet, or
* is, or resembles, a food.

Where a psychoactive product is presented in any of these dosage forms, the product cannot legally be sold in New Zealand

### *Guidance on the information required to support an application for a smokeable psychoactive product*

The OPSRA is unaware of any suitable guidelines that describe requirements to support an application for registration of a smokeable product. This is because the smokeable dosage form is not a recognised pharmaceutical dosage form. The OPSRA is willing to consider any information an applicant is able to compile to justify the smokeable dosage form; however, this information would need to demonstrate that the dosage form is not carcinogenic. The OPSRA is unaware of any *in-vitro* tests which suitably demonstrate that a substance or dosage form is not carcinogenic.

Applicants should be aware of these difficulties when deciding whether to develop a psychoactive product as refunds are unlikely to be granted once an application has been accepted.

# What type of product application is required?

All psychoactive products and significant (material) changes to approved psychoactive products require the Authority’s consent before the products can be distributed in New Zealand.

Application forms can be found on [www.psychoactives.health.govt.nz](http://www.psychoactives.health.govt.nzan)

### New psychoactive product

A psychoactive product is considered to be ‘new’ if it has not previously been granted a product approval in New Zealand. Variations in the name, dose form, psychoactive ingredient or strength of an already approved product are also considered to be new products.

### New subsidiary psychoactive product

A new subsidiary product (NSPPA) is a product that varies from another approved product only in flavour or pack size. In this instance the original product is known as the parent product.

Applications for a subsidiary product can be submitted at the same time as the parent product or after the parent product has been approved.

### New psychoactive product and subsidiary product applications

A new psychoactive product application (NPPA) is an application for the Authority’s consent to distribute a new psychoactive product. A separate NPPA is also required for each subsidiary product.

New products are subject to the full product application fee. Subsidiary products attract a smaller subsidiary product fee.

To obtain the Authority’s consent an NPPA must be submitted to the OPSRA under section 30 of the Act.

### Changes to an approved product

When a material change to a previously approved product is proposed, the product is considered to be a new product, and an NPPA must be submitted to the OPSRA.

Material changes include, but are not limited to:

* the formulation (including changing the source of an ingredient)
* the container and/or closure
* the product labelling (including the pack insert)
* the product name
* the manufacturing site or process (for the substance and the product – this includes the intermediate manufacturing site)
* the specifications (for the substance, the product and any ingredient)
* the shelf life
* the packing site
* the testing site

If you wish to make a change that is not listed above, please contact the OPSRA (psychoactives@moh.govt.nz) to determine if the change requires an NPPA to be submitted.

For non-material changes, contact OPSRA to discuss the level of change. Based on the change, a fee reduction will be available.

# Product development

# The following information needs to be provided in **all** NPPA applications.

### Pre-market *in vitro* assessment

The researcher or manufacturer must provide the following pre-market safety information in order to demonstrate that a product poses no more than a low risk of harm:

* identify a range of potential candidate substances that may have psychoactive effects.
* determine the mode of action (eg, which receptors the ingredients target) and
* identify any potential risks associated with the substance, (eg, based on structural similarity to other molecules).

Any substance selected for potential development that demonstrates the potential for genotoxicity, immunotoxicity, mutagenicity, or acute cellular toxicity at low concentrations, cannot be considered as meeting the regulatory requirement that a product should pose no more than a low risk of harm.

Where possible and ethical, *in vitro* pre-clinical testing and human clinical trialsshould be used to determine risk. Animal testing is prohibited under the regime to demonstrate that a product poses no more than a low risk of harm. This includes animal testing conducted overseas.

### Pre-clinical safety assessment

Psychoactive ingredients that have successfully completed *in vitro* testing and are considered suitable for further product development should follow the ICH pre-clinical testing regimen set out in Appendix 1, except where the ICH guidelines suggest the use of animal models.

At this time, the OPSRA is unaware of any suitable non-animal alternatives for assessing the pharmacokinetics, metabolism, reproductive toxicity or addiction potential of a substance. These are key requirements in assessing risk.

See Appendix 3 for the Position Statement on Animal Testing by the Psychoactive Substances Expert Advisory Committee (PSEAC)]

Applicants should take this into consideration when deciding whether to submit a NPPA as no refunds will be given if an application is unsuccessful. The OPSRA is, however, willing to consider any and all information that an applicant chooses to submit as non-animal alternatives to address these safety issues.

If any aspect of the ICH or any other pre-clinical testing criteria indicates that any product or ingredient may pose more than a low risk of harm to humans its potential for development as a psychoactive substance must be reassessed. The OPSRA will not accept or approve any application where the active ingredient of a product has failed pre-clinical assessment, unless the applicant has provided appropriate and sufficient evidence to justify the safety of the product.

### Clinical safety assessment

Only products containing active ingredients that have completed and passed the pre-clinical safety testing regimen should be considered for use in human trials. The requirements for human research are set out in Part 11 of the New Zealand Regulatory Guideline for Medicines ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)) but applicants for psychoactive substances are not required to obtain approval under section 30 of the Medicines Act. Given the small study population required for the Phase I and Phase II studies required for approval, any report of a serious adverse reaction (including allergic reactions) will be sufficient evidence for the Authority to conclude that the product poses more than a low risk of harm to an individual user.

A **serious** adverse reaction is one which:

* results in death
* is life-threatening (NOTE: The term “life-threatening” in the definition of “serious” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe)
* requires inpatient hospitalisation or results in prolongation of existing hospitalisation
* results in persistent or significant disability/incapacity
* is a congenital anomaly/birth defect
* is a medically important event or reaction.

# How to prepare the content of an application

### Who should apply?

The Act allows a person who is a New Zealand resident to submit an NPPA. The person who submits the NPPA is the applicant.

Preparing an application for approval is complex. Some consultants and companies operate as regulatory consultants for the pharmaceutical sector and may be able to provide some assistance. A list of such consultants and companies is available on the Medsafe website ([www.medsafe.govt.nz/regulatory/consultants.asp](http://www.medsafe.govt.nz/regulatory/consultants.asp)).

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| **It is strongly recommended that you hire an experienced consultant to compile your product application.** |

**The application form includes the requirement for an individual or body corporate to assume the legal responsibility for all aspects of the product in New Zealand, including any regulatory action relating to it.**

The individual or company who assumes legal responsibility for the product is designated the “sponsor” or “licence holder” for the product. The sponsor is responsible for ensuring the accuracy of any information submitted to the OPSRA in support of any NPPA or NSPPA.

An overseas company wishing to market a psychoactive product in New Zealand therefore needs to have a New Zealand-based subsidiary or appoint a local individual or company as the New Zealand agent to act for them in New Zealand as the sponsor for the product concerned. **The New Zealand subsidiary or agent is the sponsor responsible for the product, including any recall of the product from the market.**

An NPPA or NSPPA is submitted to the OPSRA in the name of the sponsor, but may be submitted by an applicant. An overseas branch of the company or a local or overseas consultant may act on the sponsor’s behalf and prepare the paperwork for an application and submit it to the OPSRA. For administrative purposes, the identity of the “applicant” depends upon the circumstances.

* An application or notification may be prepared, signed and submitted to the OPSRA by an employee of the sponsor. In this case the applicant is the sponsor.
* An application or notification may be prepared and submitted on the sponsor’s behalf by an independent consultant who signs the documentation as if he or she was an employee of the sponsor. In this case the applicant is the sponsor.
* An application or notification may be 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.
* An application or notification may be prepared and submitted on the sponsor’s behalf by an overseas branch of the company. An employee of the overseas company may sign the documentation and submit it to the OPSRA. 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 NPPA, or an NSPPA, 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 the OPSRA, either with the application/notification or separately within 20 working days of the application being submitted.

All OPSRA 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 subsidiary product fee.

### Language

All applications and supporting data should be submitted in English Documents in languages other than English (eg, GMP certificates and manufacturer’s licences) may be included in the application provided they are accompanied by a notarised English translation.

### Format of application

A new psychoactive product application consists of two sections; the administrative information and the dossier of supporting data to establish the quality, safety and efficacy of the product. Both the administrative data and the supporting dossier should be divided into appropriately labelled sections using filing tabs.

The required format for the dossier of supporting quality, safety and efficacy data is the [ICH Common Technical Document (CTD)](http://www.ich.org/products/ctd.html) (www.ich.org/products/ctd.html). Electronic copies are required to be submitted in the [eCTD](http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html) format. The dossier should include the following:

* Overview and Summaries of the data (ICH Module 2)
* Chemical and Pharmaceutical quality documentation (ICH Module 3)
* Pre-clinical/Toxicology documentation (ICH Module 4)
* Clinical documentation (ICH Module 5)

A complete explanation of the ICH model and guidelines is provided in Appendix 1.

Incorrectly formatted dossiers will be returned to the applicant at the applicant’s expense at the screening stage.

### Administrative information

The administrative information consists of the following documents:

* a covering letter (template provided on www.psychoactives.health.govt.nz)
* a detailed Table of Contents
* a completed application form (accessible from www.psychoactives.health.govt.nz)
* evidence that all manufacturing sites are compliant with the NZ Code of Manufacturing Practice or Good Manufacturing Practice (accessible from www.psychoactives.health.govt.nz)
* labelling
* information leaflet/package insert

Dossiers must meet the following requirements.

* The proposed proprietary name for the product must be clear, unambiguous, and unlikely to be confused in any way (eg, in print or speech) with another psychoactive product, medicine, food or product currently approved in New Zealand.
* The proposed proprietary name also must not be misleading in any way with regard to the nature, composition, purpose, uses or effects of the product.
* The proposed proprietary name must also not be the same as a product that was formerly marketed.

*Site compliance*

All sites involved in the manufacture of a psychoactive product (this includes manufacture of the psychoactive substance, manufacture of the intermediate and final product, and packing and testing of the final product) must have either:

* certification or other evidence demonstrating that the site complies with the [New Zealand Code of Manufacturing Practice 2014](http://www.health.govt.nz/our-work/regulation-health-and-disability-system/psychoactive-substances-regulation/code-manufacturing-practice) (found on www.psychoactives.health.govt.nz) or
* Good Manufacturing Practice (GMP) certification or other evidence of GMP compliance that is accepted by the OPSRA.

In both cases, the documentation must:

1. be specific for the product or substance concerned, or psychoactive products or substances in general and
2. in the case of a product manufacturing site state the dosage form (eg, tablet)
3. be issued by authorities recognised by the OPSRA and
4. not have expired or be more than five years old by the time the product is likely to be approved for distribution in New Zealand.

A list of the authorities recognised by the OPSRA for the purpose of issuing GMP certificates can be found in Appendix 2.

Product labelling

* The product labelling must comply with the Psychoactive Substances Act 2013, Regulations and Guidelines (see 12.6 below for more detail).
* If applicable, the labels must allow easy discrimination between the different strengths of a product.
* Any package insert/information leaflet supplied with the product must be consistent with the product details approved by the Authority.
* If any excipients (eg, lactose) in the product are unsuitable for particular populations, appropriate information or warnings must be included on the label (or, when space on the label does not permit, in an information leaflet/ package insert).

### Dossier - Technical Guidelines to be Followed

The technical data requirements for applications for consent to distribute new psychoactive products in New Zealand are closely aligned with those currently applying in the European Union for medicines. Requirements may change in line with evolving “best international practice”.

The guidelines and standards that are accepted by the OPSRA in support of an NPPA are as follows:

* International Conference on Harmonisation (ICH) guidelines
* European Commission (EC) guidelines
* U.S. Food and Drug Administration (FDA) guidelines
* Pharmacopoeia
* World Health Organisation (WHO) guidelines
* Good Laboratory Practice (GLP)
* Good Clinical Research Practice (GCRP)
	+ 1. *ICH Guidelines*

The ICH has developed and published numerous guidelines relating to the quality, safety and efficacy of medicines. These guidelines are also relevant to psychoactive products. Copies of these guidelines may be obtained from:

ICH Secretariat

15, chemin Louis-Dunant

P.O. Box 195

1211 Geneva 20

Switzerland

email: admin@ich.org

ICH guidelines may also be obtained in electronic form (printable pdf format) from the following address: <http://www.ich.org/products/guidelines.html>.

Once ICH guidelines are formally adopted and come into force in the EU they are recognised by the OPSRA. Draft guidelines may also be referenced where the guideline is new (ie, there is no previous version of the guideline). A more complete explanation of the ICH model and guidelines is provided in Appendix 1.

Where an ICH guideline exists for a particular aspect of a product (eg, impurity limits, validation of analytical procedures, stability) conformity to this guideline is the minimum requirement for applications submitted to the OPSRA.

Where no ICH guideline exists for a particular aspect of a product, data will normally be acceptable if they comply with the requirements of the EC and/or FDA guidelines.

* + 1. *European Commission guidelines*

The European requirements for medicines are published by the European Commission (EC) as the [Rules Governing Medicinal Products in the European Union](http://ec.europa.eu/health/documents/eudralex/index_en.htm). Various other documents have been published as additions and amendments to these Rules by the [Committee for Proprietary Medicinal Products (CPMP) Working Parties](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb) as ‘Notes for Guidance’. These CPMP documents are listed on the [European Medicines Agency](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb) (EMA) web site (<http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb>).

The guidelines and rules are also relevant to psychoactive products.

Printed copies may be obtained from:

European Medicines Agency

30 Churchill Place

Canary Wharf

London E14 5EU

United Kingdom

Tel. +44 (0)20 3660 6000

Fax: +44 (0)20 3660 5555

In the absence of a relevant ICH guideline, the OPSRA accepts EC directives, guidelines and rules.

* + 1. *FDA guidelines*

The US [FDA](http://www.fda.gov/) has published numerous guidelines dealing with all aspects of medicines. Copies of FDA guidelines may be obtained from:

Office of Training and Communication

Division of Drug Information, HFD-240

Center for Drug Evaluation and Research

Food and Drug Administration

5600 Fishers Lane

Rockville, MD 20857

USA

Most FDA guidelines relevant to New Zealand requirements may also be obtained in printable electronic form (pdf format) from <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

FDA guidelines relating to biological and biotechnological products may be obtained from <http://www.fda.gov/cber/guidelines.htm>.

In the absence of a relevant ICH guideline, the OPSRA accepts FDA guidelines.

* + 1. *World Health Organisation guidelines*

In the absence of any relevant ICH, EC or FDA guidelines the OPSRA also recognises the guidelines published by the World Health Organisation.

* + 1. *Good Laboratory Practice and Good Clinical Research Practice*

The OPSRA expects toxico-pharmacological studies and clinical studies supplied in support of any NPPA to have been carried out in accordance with the internationally accepted standards of GLP (http://www.who.int/tdr/publications/documents/glp-handbook.pdf) and GCRP (www.medsafe.govt.nz).

* + 1. *Pharmacopoeia*

A pharmacopoeia is an official collection of standards for medicinal products and pharmaceutical substances. Each standard is called a monograph. Where a British, European or United States pharmacopoeial monograph exists for any ingredient in a psychoactive product, applicants must demonstrate compliance with the current version of the monograph or compliance to a higher standard. Where a product or ingredient is controlled according to a pharmacopoeial monograph, the specifications are to be updated to reflect any revisions to the monograph concerned. Where a pharmacopoeial monograph exists, this is considered to be the minimum requirements for the product or substance.

* + 1. *Alternative approaches*

It is recognised that, in some circumstances, a different approach from that described in a guideline may be appropriate. However, where an applicant chooses to submit a data package that does not meet the relevant guideline, that decision should be explained and justified in the dossier submitted in support of the application. The following situations are possible grounds for departing from current guidelines:

* scientific development
* circumstances unique to the product in question
* adoption by the company of an acceptable approach which had not previously been considered by the OPSRA
* sufficient alternative studies having been conducted which satisfy the criteria of quality and safety.

### Good Manufacturing Practice Documentation

*11.1 When is GMP Documentation Required?*

The OPSRA requires evidence of compliance with manufacturing practice for each active ingredient and finished product manufacturing site and packaging site specified in an NPPA or NSPPA.

For bulk active ingredients, the requirement for the manufacturing site is **GMP** certification issued by an OPSRA recognised regulatory authority.

For the finished product manufacturing site(s) and packaging site(s) the requirement is evidence that the site complies with the Psychoactive Substances [Code of Manufacturing Practice](http://www.health.govt.nz/publication/psychoactive-substances-code-manufacturing-practice) (CoMP certification, found at www.psychoactoves.health.govt.nz) or GMP certification, issued by an OPSRA recognised regulatory authority and stating the products or product classes for which it has been granted.

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 the site which manufactures any intermediate products, the finished product manufacturing site and which contributes to a packing operation which places the final dose form into its labelled primary or secondary (etc.) container. This includes a site where products are overlabeled.

Manufacturers with premises in New Zealand must hold an appropriate current licence to manufacture psychoactive products, issued by the OPSRA. The licence must have been issued before manufacture of the product for distribution can commence.

For overseas manufacturers and packers, the OPSRA requires that certification be included with each NPPA or NSPPA even if the site already supplies product to New Zealand and certification has been supplied previously with an earlier application or notification. This is desirable to ensure 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 the OPSRA. Details of the documentation that is acceptable are provided in section 11.1.2 below and a list of authorities whose competence to certify GMP compliance is provided in Appendix 2.

The certificate, licence or report should be no more than three years old when the NPPA is submitted, and must be no more than five years old at the time of approval of the new psychoactive product.

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, the OPSRA will require an audit of the site by OPSRA auditors to be arranged at the applicant's request and expense.

* + 1. *Recognised Documentation*

GMP certification recognised by the OPSRA can be any document issued by a recognised authority (see Appendix 2) which attests to GMP compliance. Legible photocopies of the documents are acceptable.

Documents should contain the following information:

* the street address of the site
* 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;
* 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.

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. *Classes of Product*

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.

* + 1. *Manufacturers of Bulk Active Ingredients*

Evidence of GMP (or at least evidence that a bulk active ingredient is manufactured consistently and to acceptable quality standards) is required for all sites which manufacture bulk active ingredients. Such evidence should be included with each application or notification.

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 ingredients:

* 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 (DMF) or equivalent data (ie, ICH module 3.2.S)
* a Certificate of Suitability (CoS) for a substance controlled according to the European Pharmacopoeia (Ph. Eur.)
* a DMF or CoS must be accompanied by batch analytical data demonstrating consistent quality of the substance produced. Product testing using a validated testing methodology must have been conducted by a testing facility that is accredited by an OPSRA recognised agency (ie, International Laboratory Accreditation Cooperation (ILAC) or Asia Pacific Laboratory Accreditation Cooperation (APLAC) as meeting International Accreditation New Zealand (IANZ) or Joint Accreditation System of Australia and New Zealand (JAS-ANZ) standards.

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

### Guidance on analytical procedure validation

The information that follows is guidance to industry on the OPSRA’s expectations with reference to analytical procedure validation. Departure from this guidance is permissible if sufficient justification is provided. Equally, the OPSRA may request additional information if it has concerns over an aspect of an analytical procedure’s use.

This guidance covers three topics, which address the OPSRA’s expectations regarding:

* the validation of pharmacopoeial methods
* the validation of non-pharmacopoeial methods
* the conduct of analytical procedure transfer.

In addition, each section includes the OPSRA’s data requirements as they pertain to the submission of an NPPA.

The OPSRA expects all analytical procedures, (pharmacopoeial, and non-pharmacopoeial) to have been verified as suitable for use at each site where testing is to occur. It also expects that method verification will have occurred before use.

The extent of verification required is determined by:

* whether the analytical procedure is in a recognised pharmacopoeia
* the type and complexity of the analytical procedure in question.

Verification encompasses a range of techniques including: full validation in accordance with ICH guidance, analytical procedure transfer validation, or conformance with system suitability criteria.

* + 1. *Validation requirements for pharmacopoeial analytical procedures*

The OPSRA expects pharmacopoeial analytical procedures to be verified as suitable for use at all sites of testing. In most cases this means conformance with system suitability criteria and does not involve full validation in accordance with ICH guidance.

Notable exceptions to this rule are:

* *Finished product assay procedures.* Evidence is required that the finished product excipients do not interfere with the procedure.
* *Impurity (in the active ingredient) analytical procedures.* Evidence of appropriate validation will be required where the active ingredient is made using a different route of synthesis from the route that underpins the pharmacopoeial monograph, or where a non-pharmacopoeial impurity is specified.
* *Biological tests eg, microbial quality, sterility, endotoxins.* Such tests require preparatory investigations to have been undertaken to ensure the analytical procedure is functioning correctly and is suitable for use. Evidence of this is required.

For standard pharmacopoeial analytical procedures, other than those specified above, no validation or analytical procedure transfer data is required to be submitted for sites of testing.

For non-standard pharmacopoeial analytical procedures, such as those specified above, validation reports are required from the site of analytical procedure development, but not from each proposed site of testing.

* + 1. *Validation requirements for non-pharmacopoeial analytical procedures*

The OPSRA expects non-pharmacopoeial analytical procedures to be validated in line with ICH guidance at the site of analytical procedure development.

Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process that is in-line with ICH guidance, or through use of an analytical procedure transfer process (see section 11.2.3 below for further details).

For a non-pharmacopoeial analytical procedure a validation report is required from the site of analytical procedure development.

A revalidation report or evidence of analytical transfer (see section 11.2.3 below for further details) is required for each additional site of testing.

* + 1. *Analytical Method Transfer*

Analytical method transfer is the process that qualifies a laboratory to use a particular test method that has been developed in another laboratory.

Fundamentally, test method transfer comprises repeated testing of common samples at the sending and receiving sites in order that comparative analysis may be undertaken.

Useful reference texts on the technical requirements for analytical procedure transfer are:

* J. Ermer, J. and Miller, J.H.McB (Eds). 2005. *Method Validation in Pharmaceutical Analysis. A guide to Best Practice.* WILEY-VCH Verlag GmbH & Co KGaA, Weinheim. ISBN 978-3-527-31255-9.
* ISPE. 2003. ISPE *Good Practice Guide: Technology Transfer.* ISPE. www.ispe.org. ISBN 1-931879-13-3

Test methods must have either been validated or successfully transferred to all testing sites and suitable evidence must be provided as part of the application.

Evidence of test method transfer should be in the form of a report and be accompanied by a justification for the extent of the analytical procedure transfer undertaken**.**

* 1. **Composition/formulation**

The dose form (eg, tablet, capsule, oral liquids, powders for inhalation, etc) and formulation must be adequately justified and be appropriate for the psychoactive product concerned.

All of the ingredients must be acceptable for use in humans and be compatible with each other. The Handbook of Pharmaceutical Excipients is a helpful list of ingredients that are acceptable in medicines and other products for human consumption. The Handbook also provides a guide to the uses, properties and safety of these ingredients. The Handbook can be accessed here: <http://www.pharmpress.com/product/MC_EX/handbook-of-pharmaceutical-excipients>.

**11.4 Dose form**

Potential doses forms of psychoactive substances include tablets, capsules, oral liquids, powders for inhalation, smokeable dose forms and products such as incense where inhalation to produce a psychoactive effect is intended. Note that dose forms that require combustion will require additional information to demonstrate that the dosage form is not carcinogenic.

Dose delivery must be consistent within and between batches. Any antioxidants and any chemical or anti-microbial preservatives included in the product must be adequately justified and their effectiveness established.

Adequate measures must be taken to ensure that any animal-derived ingredients (eg, gelatin, magnesium or calcium stearate, stearic acid) used in the product are free from Transmissible Spongiform Encephalopathy (TSE) contamination in accordance with European Commission (EC) or US requirements. Descriptions of these measures are required.

Different strengths of the product must be readily distinguished (e.g. by differences in size, colour, shape, markings, etc. or through prominent labelling if this is not possible).

The primary container (immediate) and secondary (outer) packaging and packaging materials, closures, induction or tamper-proof seals, pack sizes, any dosing device, and any desiccant or cotton wool contained in the package must be compatible with the product and fit for purpose.

### *Manufacture of Active Ingredients(s)*

Unless previously approved, information detailing the manufacture and quality control of the active ingredient(s) from each supplier of bulk active ingredient must be submitted.

This may be in the form of a DMF, ICH Module 3.2.S supplied as part of the dossier, or a Certificate of Suitability to the monographs of the European Pharmacopeia (CoS) issued by the European Directorate for the Quality of Medicines (EDQM).

Although it is likely that some psychoactive substances may not have a DMF or CoS, these documents may be available for other ingredients in the products.

The active ingredients found in psychoactive products may be manufactured by a company other than the manufacturer of the finished product. In such cases, the manufacture, quality control and stability of the active ingredient are usually described in a DMF, and submitted to the regulatory authority by the manufacturer of the active ingredient.

Where the active and finished product are manufactured by the same company, information on the production, quality control and stability of the active substance may be submitted as part of the dossier for the finished product as ICH module 3.2.S rather than in a separate DMF.

The DMF must describe in detail:

* the “route of synthesis”
* each step in the manufacturing and purification process
* the reaction conditions and in process controls for each step
* the quality control of starting materials, reagents, catalysts, solvents and any isolated intermediates
* any subsequent processing (eg, milling) of the bulk substance.

The DMF must also provide proof of the chemical and stereochemical structure of the substance (and of any significant impurities) using appropriate physical, chemical and spectroscopic methods.

Where relevant, adequate evidence of the crystalline form produced and control thereof must be provided.

This section provides details of the format and content of DMFs and CoSs.

**Guidelines to read in conjunction with this section:**

* CHMP*:* [*Guideline on Active Substance Master File Procedure*](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/01/WC500120687.pdf)
* FDA*:* [*Guideline for Drug Master Files*](http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm122886.htm)
* TGA*:* [*Guidance 11: Drug Master Files and Certificates of Suitability of a Monograph of the European Pharmacopoeia for drug substances*](http://www.tga.gov.au/industry/pm-argpm-guidance-11-00.htm)
* WHO*:* [*Guidelines for assuring the quality of pharmaceutical preparations made by recombinant DNA technology WHO/PHARM/89.542 BS/89.1609*](http://apps.who.int/iris/bitstream/10665/61578/1/WHO_PHARM_89.542.pdf?ua=1)

In order to refer to the DMF in an application, the applicant must have the written permission of the active ingredient manufacturer who submitted the DMF. A “letter of access” from the active ingredient manufacturer, addressed to the OPSRA and indicating clearly the applicant to which it applies must be sent to the OPSRA by the active ingredient manufacturer, either with the DMF or separately.

If an active ingredient manufacturer has supplied (or been asked to supply) a DMF to the OPSRA for the registration of a psychoactive product, it is not necessary for a further copy of the DMF (or part thereof) to be provided for the registration of another product sponsored by a different sponsor. However, the active substance manufacturer needs to provide the OPSRA with a new letter of access, referring to the previously supplied DMF and the new applicant.

Finished product manufacturers are responsible for the quality of their products and the raw materials used to manufacture them. Applicants should provide written assurance that there is a formal agreement between the active raw material manufacturer and the applicant which ensures that information will be communicated to the sponsor, and to the OPSRA, before any significant change is made to the method of manufacture or specifications of an active raw material used in a product distributed in New Zealand.

Quality control of the bulk active ingredient is carried out by both the manufacturer of the active ingredient and by the manufacturer of the finished product. Testing by the manufacturer of the bulk active ingredient is usually described in the DMF. GMP requires the finished product manufacturer to re-test the active ingredient’s identity, potency and purity before use in the manufacture of finished products. This testing is usually described in the application dossier for the finished product.

DMFs should be updated periodically to reflect any changes. The sponsor concerned should ensure that either the updated DMF (together with a detailed list of changes made), or details of any changes made, are forwarded to the OPSRA. Material changes include but are not limited to changes in the characteristics, manufacture or quality control of the substance concerned. Material changes require an NPPA to be submitted to, and approved by, the OPSRA before the changes can be implemented. Non-material changes should be notified to the OPSRA before being implemented but do not require an NPPA.

Quality testing for active ingredients should be conducted using validated testing systems by laboratories accredited IANZ or JAS-ANZ by ILAC or APLAC.

* + 1. *Quality Control of Active Ingredient(s)*

The quality control of the active ingredient is important if a DMF, or similar information, does not exist.

* + 1. *Controls applied by the bulk active ingredient manufacturer*

The active ingredient specifications applied by the manufacturer of the bulk active ingredient must be in accordance with a recognised pharmacopoeia (eg, European, British or United States pharmacopoeia or Ph. Eur., BP and USP respectively), where a relevant monograph exists.

If there is no relevant monograph, non-pharmacopoeial specifications may be applied, which must cover all of the relevant identity, organoleptic, physical (including crystalline form and particle size distribution, if applicable), chemical, stereochemical and microbiological quality parameters.

A manufacturer may choose to use non-pharmacopoeial specifications where a pharmacopoeial monograph exists but the non-pharmacopoeial specifications must be shown to be equivalent or superior to the pharmacopoeial monograph.

Justification must be given for the selection of any non-pharmacopoeial tests, test procedures, requirements and limits. If certain tests are not carried out routinely, adequate justification must be provided.

Physical, chemical and microbiological test procedures (whether pharmacopoeial or not) must be self-validating or have been validated in accordance with pharmacopoeial standards or ICH guidelines.

All assay and related product/degradation product and residual solvent impurity level tests must have been validated (as appropriate) for specificity/selectivity, limit of detection, limit of quantitation, accuracy, precision, repeatability, linearity, stability of solutions, and robustness/ ruggedness.

Proof must be provided that the related substance assay procedure is adequate to detect and control all of the related substance impurities actually or potentially present in the bulk substance produced using the intended manufacturing process.

Satisfactory representative batch analytical data must be supplied for at least three typical batches of bulk active substance. Any Certificates of Analysis submitted must have been signed. If a “house” reference standard is used in the assays, characterisation and analytical data confirming its suitability for use must be provided.

* + 1. *When is a DMF not required?*

A DMF is not required for:

* any active substance that is controlled according to the relevant monograph in the Ph. Eur. and for which a valid CoS is provided .
* common inorganic substances and simple organic compounds available commercially in high purity from chemical supply houses, eg, naturally occurring organic acids and their salts and amino acids (even though they may be synthesised rather than being extracted and refined)
* simple, unrefined extracts from plant materials
* plant materials

|  |
| --- |
| Although a DMF is not required for these active ingredients, evidence needs to be submitted by the finished product manufacturer that the substance is obtained from a reliable source and consistently complies with the applicable pharmacopoeial or non-pharmacopoeial specifications. Any non-pharmacopoeial specifications need to be assessed by the OPSRA to determine their appropriateness and adequacy to ensure the quality of the substance.  |

* + 1. *Format for a DMF*

DMFs compiled using the European or US format are acceptable.

The DMF may, if required, be presented in two sections, with the first (open) section containing information accessible to the finished dose form manufacturer and the second (closed) section containing information not accessible to the finished dose form manufacturer.

* + 1. *Certificate of Suitability (CoS)*

Where an active ingredient is described in the European Pharmacopoeia (Ph. Eur.), the manufacturer may submit the DMF (or equivalent documentation) to the European Pharmacopoeial Commission for assessment and issuance of a CoS. This certificate confirms that the purity of the substance, as produced by the manufacturer, is suitably controlled by the monograph in the Ph. Eur. This certificate may then be submitted in lieu of a DMF, obviating the need for regulatory authorities to carry out their own detailed assessment of the data. For details of the certifications scheme, contact the secretariat of the European Pharmacopoeial Commission. Some information is available on the internet site: <http://www.pheur.org>.

Where a CoS is submitted in lieu of a DMF, the sponsor must also provide a written assurance that any conditions attached to the CoS by the European Pharmacopoeial Commission, as well as any agreed additional tests and limits (eg, for polymorphic form, particle size distribution, impurities, etc.) are applied to each batch used in product intended for the New Zealand market.

The European Pharmacopoeial Commission also assesses and issues CoSs for substances used as active ingredients or excipients confirming that they comply with Ph. Eur. requirements for minimising the risk of transmission of animal spongiform encephalopathies. The OPSRA accepts these certificates.

Where a CoS is submitted in lieu of a DMF, the New Zealand product sponsor must ensure that the CoS is submitted with the written permission of the manufacturer of the bulk active ingredient to be used to manufacture the specified product for the New Zealand market. This is usually in the form of a letter of access from the active ingredient manufacturer, addressed to the OPSRA and clearly indicating the sponsor and, where possible, the products to which it applies. The letter of access should also confirm that the active ingredient manufacturer will, if requested, supply direct to the OPSRA data relating to the manufacture, quality control and stability of the substance concerned. To ensure the appropriate information is provided, the OPSRA has developed a template letter of access that can be downloaded at: www.psychoactives.health.govt.nz

* + 1. *Colouring Agents*

The colouring agents that are acceptable for use in psychoactive products are the same as those permitted in medicines and are listed in Table 1 below.

**Table 1: Colouring agents allowed in psychoactive products**

|  |  |  |  |
| --- | --- | --- | --- |
| **Name**  | **Synonyms** | **CI Number** | **INS Number** |
| Allura Red AC | CI Food Red 17 FD&C Red No. 40 | 16035 | 129 |
| Amaranth | CI Food Red 9 FD&C Red No. 2 | 16185 | 123 |
| Annatto | Natural Orange 4BixinNorbixinAnnatto Extracts (Oil and Alkali-extracted)Annatto Extracts (Solvent-extracted) | 75120 | 160b |
| Anthocyanins | Grapeskin extract(comprising Cyanidin, Peonidin, Malvidin, Delphinidin, Petunidin, Pelargonidin) | - | 163 |
| Betanin (name currently used in NZ)Beet Red (name currently used in Australia) | Beetroot Red | - | 162 |
| Beta -apo-8'-carotenal (C30) (name currently used in NZ)Food Orange 6 (name currently used in Australia) | Apocarotenal | 40820 | 160e |
| Beta -apo-8'-carotenoic acid ethyl ester (name currently used in NZ)Food Orange 7 (name currently used in Australia) |  | 40825 | 160f |
| Beta-carotene (name currently used in NZ)Betacarotene (name currently used in Australia) | CI Food Orange 5 | 40800 | 160a(ii) |
| Brilliant Black BN | CI Food Black 1Brilliant Black PN | 28440 | 151 |
| Brilliant Blue FCF | CI Food Blue 2FD&C Blue No. 1 Acid Blue 9 disodium salt | 42090 | 133 |
| Brown HT (name currently used in New Zealand)Chocolate Brown HT (name currently used in Australia) | CI Food Brown 3 | 20285 | 155 |
| Calcium carbonate | CI Pigment White 18Chalk | 77220 | 170 |
| Canthaxanthin | Food Orange 8 | 40850 | 161g |
| Caramel - Ammonia | Caramel III | - | 150c |
| Caramel - Caustic sulfite caramel | Caramel II | - | 150b |
| Caramel - Plain | CI Natural Brown 10 Caramel IBurnt sugar | - | 150a |
| Caramel - Sulfite ammonia caramel | Caramel IV | - | 150d |
| Carmoisine | Ext. D&C Red No. 10 CI Food Red 3 Azorubine | 14720 | 122 |
| Carotenes | CI Food Orange 5Mixed carotenesCarotenes (Algae)Carotenes (Vegetable) | 75130 | 160a(i) |
| Chlorophyllins | CI Natural Green 5 Sodium chlorophyllinPotassium chlorophyllin | 75815 | 140(ii) |
| Chlorophylls  | CI Natural Green 3 Magnesium chlorophyllMagnesium phaeophytin | 75810 | 140(i) |
| Cochineal  | CI Natural Red 4 Carminic acid Carmines | 75470 | 120 |
| Copper Complexes of Chlorophyllins (name currently used in NZ)Chlorophyllins - Copper Complexes of Sodium and Potassium salts (name currently used in Australia) | CI Natural Green 5 Sodium Copper Chlorophyllin Potassium Copper Chlorophyllin  | 75815 (CI number in NZ)75810 (CI number in Australia) | 141(ii) |
| Copper Complexes of Chlorophylls (name currently used in NZ)Chlorophylls - Copper (name currently used in Australia) | CI Natural Green 3Copper ChlorophyllCopper Phaeophytin | 75815 (CI number in NZ)75810 (CI number in Australia) | 141(i) |
| Curcumin  | CI Natural Yellow 3 Turmeric Yellow Diferoyl Methane | 75300 | 100 |
| D&C Red No. 27 (name currently used in NZ)Red 27 (name currently used in Australia) | Phloxine B acid form | 45410:1 | - |
| Erythrosine | CI Food Red 14 FD&C Red No. 3 | 45430 | 127 |
| Fast Green FCF | CI Food Green 3 FD&C Green No. 3 | 42053 | 143 |
| Green S | CI Food Blue 4 Brilliant Green BS | 44090 | 142 |
| Indigo Carmine | CI Food Blue 1FD&C Blue No. 2 Indigotine | 73015 | 132 |
| Iron Oxide Black | CI Pigment Black 11Iron oxides and iron hydroxides | 77499 | 172(i) |
| Iron Oxide Red | CI Pigment Red 101 and 102Iron oxides and iron hydroxides | 77491 | 172(ii) |
| Iron Oxide Yellow | CI Pigment Yellow 42 and 43Iron oxides and iron hydroxides | 77492 | 172(iii) |
| Lutein | Mixed Carotenoids (comprising Xanthophylls and Zeaxanthin) | - | 161b |
| Patent Blue V  | CI Food Blue 5 | 42051 | 131 |
| Phloxine B | D&C Red No. 28 Acid Red 92 Eosin 10B Red 28 Phloxine B sodium salt | 45410 | - |
| Ponceau 4R (name currently used in NZ)Brilliant Scarlet 4R (name currently used in Australia) | CI Food Red 7 New Coccine Cochineal Red A | 16255 | 124 |
| Quinoline Yellow | CI Food Yellow 13 D&C Yellow No. 10 Yellow 10 | 47005 | 104 |
| Riboflavin | Lactoflavin Vitamin B2 | - | 101(i) |
| Riboflavin -5- phosphate  | Vitamin B2 phosphate | - | 101(ii) |
| Saffron | CI Natural Yellow 6CrocetinCrocin | 75100 | 164 |
| Sunset Yellow FCF | CI Food Yellow 3Orange Yellow SFCF Orange YellowFD&C Yellow No. 6 | 15985 | 110 |
| Tartrazine1 | CI Food Yellow 4FD&C Yellow No. 5 | 19140 | 102 |
| Titanium dioxide | CI Pigment White 6 | 77891 | 171 |
| Vegetable carbon (name currently used in NZ)Carbon Black (name currently used in Australia) | Vegetable blackD&C Black No. 2 | 77266 | 153 |

1. The presence of tartrazine must be declared on the label.
	* 1. *Use of colours not on these lists*

Where a sponsor wishes to use a colouring agent not included in these lists in a psychoactive product, the sponsor should provide a justification for its use.

A data package for that colouring agent should be submitted together with the NPPA.

1. Quality data should be consistent with the Common Technical Document (CTD) requirements for Module 3 and should include:
	* requirements as outlined in 2.2.2 of the EU Guideline - Excipients in the Dossier for Application for Marketing Authorisation of a Medical Product ([3AQ9a)](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003428.pdf).
2. Non-clinical data should be consistent with the CTD requirements for Module 4 (except that animal studies cannot be used) and should include:
	* reports of all toxicology studies that are relevant to the assessment of the chemical
3. Clinical data should be consistent with the CTD requirements for Module 5 and should include reports of all human studies (if any).
	1. **Manufacture of Finished Product**

The manufacturing processes, packaging processes, equipment used, and batch sizes must be described in detail, fit for purpose and justified. Any overages or ranges of quantities for the active ingredient(s) or any excipients must be appropriate and adequately justified.

Any overfill of the container(s) must be justified. Any solvents or gases used in the manufacturing process must be of adequate quality. If alternative processes are intended at some steps in the manufacture, these must have been justified and shown to yield finished product of equivalent quality.

The in-process controls (including temperatures, mixing times and speeds, filter integrity), test methods and acceptance limits at each step in the manufacturing, sterilisation (if any) and packaging processes must be defined, appropriate and adequate to assure batch quality and unit-to-unit consistency.

If relevant, any processing (eg, neutralising, cleaning, washing) of the containers before filling must be adequately controlled.

All critical steps in the manufacturing process (including any cleaning steps) must have been adequately developed and validated at each manufacturing site at either production scale or at pilot scale (≥10% of full scale or 100,000 solid dose units, whichever is the greater unless otherwise justified) using production scale equipment.

If only pilot scale validation has been completed, confirmation that full scale validation is scheduled for when commercial scale production commences must be provided.

* + 1. *Active ingredient controls applied by the finished product manufacturer*

The finished product manufacturer must test the active ingredient before use to ensure that the active ingredient has remained within specification.

The active ingredient specifications applied by the finished product manufacturer in testing bulk active substance before use in manufacture of the finished product must be in accordance with a recognised pharmacopoeia (eg, Ph. Eur., BP, USP), where a relevant monograph exists.

If there is no relevant monograph, non-pharmacopoeial specifications may be applied, which must cover all of the relevant identity, organoleptic, physical (including crystalline form and particle size distribution, if applicable), chemical, stereochemical and microbiological quality parameters.

A manufacturer may choose to use non-pharmacopoeial specifications where a pharmacopoeial monograph exists but the non-pharmacopoeial specifications must be shown to be equivalent or superior to the pharmacopoeial monograph.

Justification must be given for the selection of any non-pharmacopoeial tests, test procedures, requirements and limits. If certain tests are not carried out routinely, adequate justification must be provided. Physical, chemical and microbiological test procedures (whether pharmacopoeial or not) must be self-validating or have been validated in accordance with pharmacopoeial standards or ICH guidelines in the testing laboratory(ies) used by the finished product manufacturer for routine quality control of the bulk active(s).

All assay and related product/degradation product and residual solvent impurity level tests must have been validated (as appropriate) for specificity/selectivity, limit of detection, limit of quantitation, accuracy, precision, repeatability, linearity, stability of solutions, and robustness/

ruggedness.

Satisfactory representative batch analytical data generated by the finished product manufacturer(s) must have been supplied for at least three typical batches of bulk active substance from each supplier.

Any certificates of analysis submitted must have been signed. If a “house” reference standard is used in the assays, characterisation and analytical data

confirming its suitability for use must be provided.

* + 1. *Quality Control of Excipient(s)*

The identity and quality of all excipients (including capsule shells and their constituents) must be controlled by either pharmacopoeial or appropriate in house specifications.

Any non-pharmacopoeial specifications must be appropriate to control the identity and the physical, chemical and microbiological quality of the material adequately.

Adequate measures must be taken to ensure that any ingredients of animal origin (eg, gelatin, magnesium or calcium stearate, stearic acid) used in the product are free from TSE contamination in accordance with European Commission (EC) and US guidelines.

Satisfactory representative batch analytical data must be provided for any excipients controlled by non-pharmacopoeial specifications. Any certificates of analysis submitted must have been signed.

* + 1. *Quality Control of the Container (Immediate Packaging)*

The Psychoactive Substances Regulations 2014 define the container as any bottle, jar, box, packet, or other receptacle that contains or is to contain the approved product (see regulation 3). This does not include a capsule or cachet as these form part of the product itself or another receptacle in which the container is to be contained (such as the carton in which blisters are packaged)

The container materials used (polymers, types of glass, etc), seals, closures and any delivery device(s) supplied with the product must be clearly defined, suitable for pharmaceutical use, and adequately controlled for identity, dimensions, physical and chemical properties, manufacturing defects, as applicable.

Any plastic or rubber packaging/closure materials in contact with the product must be free from any leachable toxic impurities and must comply with Ph. Eur. and USP requirements for polymeric materials used in packaging of medicines.

Satisfactory representative batch analytical data must be provided for any primary packaging materials, containers and closures that come into contact with the product. Any certificates of analysis submitted must have been signed.

* + 1. *Quality Control of Delivery Device(s)*

Any delivery device(s) supplied with the product must be clearly defined, suitable for pharmaceutical use and adequately controlled for identity, dimensions, physical and chemical properties, manufacturing defects, and dose delivery, as applicable.

Where a novel delivery device is proposed, eg, an electronic vaporiser, the application must contain information supporting the use of the device including information validating the testing system used to demonstrate the effectiveness and safety of the delivery device.

* + 1. *Quality Control of Intermediate Products*

An intermediate product is any isolatable partly processed material that is formed during the manufacturing process, but which must undergo further manufacturing steps before it becomes a finished product. For example, during the manufacturing process, ingredients A, B and C are mixed together and form the stable compound D which can be stored for further processing at a later date, or directly converted to the final product, compound E. In this instance, compound D is considered to be an intermediate product. The definition of an intermediate product includes bulk product.

If there is an intermediate product, it must controlled by separate, appropriate specifications that adequately control all relevant parameters. Satisfactory representative batch analytical data must be provided.

Any certificates of analysis submitted must have been signed.

* + 1. *Quality Control of the Finished Product*

The complete identity and quality of the finished product must be adequately

controlled at release and throughout its shelf-life by appropriate pharmacopoeial or in house specifications that cover all of the necessary organoleptic, physical, dissolution, chemical, microbiological and dose delivery parameters relevant to the dose form.

It must be clear which requirements apply at release and which apply throughout the shelf-life. If applicable, any non-pharmacopoeial test procedures used as replacements for, or in addition to, the procedures in a pharmacopoeial monograph must be appropriate and have been justified.

If all specified tests are not carried out routinely, justification must be provided. The test procedures used must be self-validating or have been adequately validated in accordance with pharmacopoeial requirements or ICH guidelines at each of the testing sites intended for routine quality control of the product.

All assay and related product/degradation product and residual solvent impurity level tests must have been validated (as appropriate) at each testing

laboratory involved in the quality control of the product for specificity/selectivity, limit of detection, limit of quantitation, accuracy, precision, linearity, repeatability, stability of solutions, and robustness/ ruggedness.

Satisfactory recent (preferably generated within the last three years) analytical reports must be provided for at least three batches of the final market formulation(s) of the product manufactured at least at pilot scale at each of the proposed manufacturing sites. The manufacturing sites must have held GMP or AMP at the time the batches were manufactured. Results must be included for each specified test and all of the reported test results must comply with the specifications. If not, an adequate explanation or justification must be provided.

Any certificates of analysis submitted must be signed and evidence that the facility is accredited by an OPSRA recognised agency (ie, ILAC or APLAC) as meeting International Accreditation New Zealand (IANZ) or Joint Accreditation System of Australia and New Zealand (JAS-ANZ) standards must be provided.

* + 1. *Stability of the Active Ingredient(s)*

The stability data submitted must have been produced in accordance with ICH guidelines and adequately establish that the bulk active substance packaged in the intended storage container and stored under the prescribed storage conditions will remain within specifications for the whole of the claimed shelf-life or retest period.

* + 1. *Stability of the finished product*

The stability of the market formulations of the finished product (or formulations that may reasonably be expected to have the same stability) packaged as

intended for marketing must have been tested in accordance with ICH guidelines (including the ICH requirements for the number and sizes of batches used) unless otherwise justified. Preferably, more than one batch of active substance should have been used in the manufacture of the stability batches.

The stability trial protocol, packaging, packaging orientation (if relevant), storage conditions and test procedures must be described in detail. All of the stability-indicating organoleptic, physical, chemical and microbiological quality parameters relevant to the dose form and type of packaging must have been included in the testing schedule and have been monitored using appropriate, clearly defined, validated (in the testing laboratory used for the stability samples), stability-indicating test procedures.

Any changes in test procedures during the stability trials must be justified and results correlated. At least 12 months data for storage under the recommended storage conditions must be available and be submitted with the application (unless otherwise justified). The most up to date stability data should be submitted. Wherever relevant, results should be expressed quantitatively rather than as “complies” or “passes test”. Any lack of mass balance between assays and degradation products must be explained or discussed. If relevant, preservative levels or effectiveness must be monitored.

The results (and allowing for extrapolation within reasonable limits) must adequately support the proposed shelf-life under the recommended storage conditions (otherwise a shorter shelf-life may be granted until adequate stability data can be provided to support the proposed shelf-life).

If relevant, the stability of the product after first opening must have been investigated and shown to be adequate for the intended use of the product. This does not apply to product packaged in single use containers such as blisters containing a single dose of the product.

If relevant, adequate storage instructions and time-limits for use of the product after first opening must be stated on the draft product label, and in any package insert.

### Individual Patient Data

Normally individual patient data from clinical trials need not be included in an application dossier. However, tabulated individual patient data may be included in clinical trial documentation if the applicant considers it appropriate.

Before an application is lodged, applicants should ensure that individual patient data (case report forms) are available, and indicate in the application that these data are available. Individual patient data not already supplied may be requested during the evaluation period.

Where not already presented in the Clinical Expert Report, overall numbers of clinical trial patients and treatment subgroups should be tabulated and submitted with Module 1 of the application.

1. **Submitting an Application or Notification**

### 12.1 Covering Letter

All NPPAs and NSPPAs should be accompanied by a covering letter (a copy of the template cover letter can be found on www.psychoactives.health.govt.nz) which includes a brief background on the product details and the information included in the application.

### Submitting an Application or Notification

All data, including supplementary data, must be submitted on A4 sized paper and should be bound in sturdy ring-binders (or other types of binders from which pages can be removed and replaced) that do not spill their contents when opened. Each part of the application should contain a detailed Table of Contents.

One hardcopy of all applications and supporting data should be submitted. Eight copies of all applications and supporting data should be submitted on CD to allow each member of the Psychoactive Substances Expert Advisory Committee (PSEAC) to review the data.

Send completed applications (with supporting data) to the Manager:

Postal Address: The Office of the Psychoactive Substances Regulatory Authority

 The Ministry of Health

PO Box 5013

Wellington

Street/Courier Address: **For delivery prior to 2 December 2014**:

The Office of the Psychoactive Substances Regulatory Authority

The Ministry of Health

Level 6

Deloitte House

10 Brandon Street

Wellington

**For delivery after 2 December 2014**:

The Office of the Psychoactive Substances Regulatory Authority

The Ministry of Health

Freyberg Building

20 Aitken Street

Wellington

Payment **should not** be enclosed in one of the cartons of data. The OPSRA will invoice the applicant when they are notified that the application has been accepted.

When sending dossiers please ensure that:

* all dossiers that are delivered in boxes are labelled clearly on at least two sides that are visible when the box is stacked
* the box label includes:
	+ the box number and the total number of boxes associated with the application (eg, Box 1 of 5)
	+ the name of the product
	+ the contents of each box by module and volume number
* modules 1 & 2 are included in Box 1 (if more than one box), together with the cover letter. If possible, the label of box 1 should be identifiable by colour
* each box only contains documentation relating to one NPPA or NSPPA
* boxes containing volumes of data must be sturdy enough to provide adequate protection to their contents
* each box weighs less than 10 Kg.

Applicants should contact the OPSRA at psychoactives@moh.govt.nz prior to submission of their dossier if they have any questions.

### Updating the Data package

While a product is being evaluated, applicants should notify the OPSRA of:

* any rejections or withdrawals of applications in other countries
* any serious adverse effects observed for the first time, or at a frequency which has become a concern.

Applicants can do so by emailing the OPSRA at psychoactives@moh.govt.nz and referencing the product name and OPSRA file number, if known.

Applicants should consider withdrawing an application if, during the evaluation period, significant new data become available that are contrary to the use of the product.

Once an application has been submitted, the OPSRA will not accept any updates to the data package, other than those specified above, unless the data has specifically been requested by the OPSRA.

### Sponsors’ Responsibility to Retain Copies of All Documents

Sponsors are expected to retain a copy of all documentation submitted to the OPSRA and all correspondence relating to NPPAs, NSPPAs, and package inserts. They are also expected to retain copies of product specifications and certificates of analysis for each batch of their products distributed in New Zealand.

In the event of a company merger or takeover, regulatory files should be transferred to the new sponsor and an NSPPA should be submitted to the OPSRA to notify of the change.

### Proprietary Names

The proposed proprietary name for a new psychoactive product must not

* be similar to, or likely to be confused in any way with another approved product currently registered in New Zealand.
* be likely to be confused with any non-psychoactive product available in New Zealand
* be misleading in any way with regard to the nature, composition, purpose, uses or effects of the product.

### Labelling

* + 1. *Legislation*

This guideline includes guidance on best labelling practices. Sponsors are strongly recommended to apply best practice concepts when designing labels. Although best practice labelling is not mandatory, any deviations should be suitably justified on the basis of user safety.

The following legislation governs the labelling of psychoactive products in New Zealand:

* [section 58 of the Psychoactive Substances Act](http://www.legislation.govt.nz/act/public/2013/0053/latest/DLM5042921.html?src=qs) 2013 - Restrictions and requirements relating to labelling of approved products
* [regulation 9 of the Psychoactive Substances Regulations](http://www.legislation.govt.nz/regulation/public/2014/0243/latest/DLM6203143.html?src=qs) 2014 – Labelling of approved products
	+ 1. *Mandatory labelling requirements for Psychoactive Products*

All containers of psychoactive products must comply with mandatory labelling requirements.

Product sponsors must ensure labels include all of the required information and that the appearance and layout of the label are designed to maximise the safe use of the product. A label must not be designed in a way that is likely to appeal to minors

Consent from the Authority to distribute a new psychoactive product is not to be construed as an endorsement of the product. No reference may be made to this consent in any label or advertising, promotional or other published material about the product.

* + 1. *Content*

The quantity must be printed on the label

* + 1. *Storage conditions*

The storage conditions statement should be selected or compounded using elements from the following list (or words of similar meanings):

|  |  |
| --- | --- |
| protect from lightprotect from moisturebelow -20°C (Deep freeze)below -5°C (Freeze)at 2° to 8°C (Refrigerate, do not freeze)  | at 8° to 15°C (Cool)at 15° to 25°C (Controlled room temperature)at or below 25°Cbelow 30°CUse immediately |

[Note that in New Zealand “below 25°C” means room temperature, whereas in Australia “below 25°C” refers to air-conditioned facilities and “below 30°C” refers to room temperature].

* + 1. *CAS registry numbers*

CAS registry numbers (CAS numbers) are unique numerical identifiers assigned by the Chemical Abstracts Service to every chemical substance described in the open scientific literature. Where a CAS number is assigned to a substance, the CAS number must be included on the label to help in the clear identification of substances.

*12.6.6 New Zealand Universal list of Medicines*

It is important to have consistent and standardised names of active ingredients where possible. This facilitates the recording of safety information and adverse reaction monitoring.

The New Zealand Universal List of Medicines (NZULM) is a dictionary of standardised information about medicines covering medicines approved for supply in New Zealand. The NZULM can also provide standardised information for psychoactive substances. The application form for product approvals requires the applicant to apply to the NZULM for the psychoactive substance in the product.

It is free to use and can be accessed through this website www.nzulm.org.nz

* + 1. *Health and safety warnings*

The following statements **must be** **prominently** **displayed** on the label unless the applicant can adequately justify their omission:

* This product is restricted to individuals 18 years or older (or words to that effect - R18 is sufficient).
* Psychoactive product.

The following statements **must be displayed** on the label unless the applicant can adequately justify their omission, but do not need to be displayed prominently:

* Do not use with alcohol, drugs or medication
* Do not drive a motor vehicle or operate any heavy machinery during or after use
* Not suitable for use by pregnant women, breast-feeding mothers or anyone with a mental illness
* Any other labelling requirement imposed as a condition during product evaluation
	+ 1. *Label format requirements for psychoactive products*

Labels for all psychoactive products must be:

* printed in in English
* be clearly visible, legible and durable
* securely placed in a prominent position on the approved product so that it is not able to be damaged, defaced, destroyed or removed when the container is opened
* designed to maximise safe use of the product.

Each layer of packaging should meet the legislative requirements. Where it is not practically possible to fit all of the required information on the container label, reduced labelling requirements may be approved on a case by case basis provided the following criteria are both met:

* a pack insert containing the additional required information is included in the container
* the Authority is satisfied that the safe use of the product would not be compromised.

A diagrammatic and summarised representation of the labelling requirements for psychoactive products is provided in Figure B below.

* The numbered dark blue boxes[[1]](#footnote-1) show the information that is required to appear on the label
* The pink boxes[[2]](#footnote-2) provide additional guidance on meeting the labelling requirements.

The figures are intended as a ready reference for those designing labels or assessing labels for compliance with the regulations. Because the information in the diagrams is in summarised form, the Act and the regulations should be consulted for further detail on the requirements for the labelling of psychoactive products.

**Figure B: Requirements for psychoactive product labels**

10. Name and address of the importer, manufacturer, wholesaler or retailer

or distributor

A NZ street/postal address if manufactured in NZ, or the name and overseas address if the product is wholly manufactured and packed outside NZ**.** In the latter case, the name and street/postal address of a responsible entity in NZ is also strongly encouraged.

9. Directions for use

Dose and frequency of dose

Detail of the purpose, dose and dose frequency to be included

Based on stability data, but in no case can it be later than 5 years from the date of manufacture.

The expiry date and batch number may be printed or embossed conspicuously on the container.

3. Dose form or presentation

**2.** Name and strength of each active ingredient

**1. Trade name**

The New Zealand Approved Name (NZAN) should be used. Go to section 9.11.5 for further information on NZANs.

Strengths must be expressed in milligrams or micrograms.

* **R18**
* **Psychoactive product**
* do not use with any medication
* do not drive a motor vehicle or operate any heavy machinery during or after use
* not suitable for use by breast-feeding mothers or anyone with a mental illness
* the CAS number
* content (net weight or volume or number of the contents of the container)
* storage conditions
* any other labelling requirement imposed as a condition during product evaluation

The name should be presented prominently.

Refer to 3.11.13 below for more information on the GS1 standard

4. Batch number

“Batch number”, “Lot number”, “Batch”, “Lot”, or “B” followed by the number

5. Expiry date

“Use by”, “Use before” or words of similar meaning, followed by the expiry date

8. Statements required as conditions of approval

6. The National Poisons Centre phone number

0800 764 766

1. Bar code

That meets the GS1 standard

**Reduced labelling requirements:**

Where it is not practically possible to fit all of the required information on the container label, reduced labelling requirements may be approved on a case by case basis provided the following criteria are both met:

* a pack insert containing the additional required information is included in the container
* the Authority is satisfied that the safe use of the product would not be compromised.
	+ 1. *Use of package inserts for psychoactive products*

The legislation allows the use of a separate information sheet to provide information that is required by the legislation but which is not included on the label that is attached to the container. This separate information sheet is known as a package insert.

The use of a package insert is only permitted provided the Authority is satisfied that the safe use of an approved product would not be compromised. and would only be considered by the Authority where it is impractical to put all the required information on the label Package inserts require the consent of the Authority and must be included in the approved container.

The package insert must comply with any applicable labelling requirements . In addition, the insert may not

* convey that the product is safe
* be particularly appealing to minors
* reference incentives to encourage persons to buy an approved product, such as competitions, rewards
	+ 1. *Use of over-labelling to achieve compliance with labelling requirements*

Attaching a label over the original label to make the container label compliant with New Zealand legislation is permitted. New Zealand and overseas sites where labelling (including over-labeling) is carried out must comply with Acceptable or Good Manufacturing Practice requirements (AMP and GMP, respectively) and the sites must be registered as part of the product application. All labelling activities carried out in New Zealand must occur at a site that has been issued with a licence to manufacture psychoactive products.

* + 1. *Brand names using umbrella segments*

An umbrella segment is a section of a brand name that is used in the name of more than one psychoactive product to create a brand for a range of products. For example, if a range of products were to be called “Mr Blog’s Alpaca”, “Mr Blog’s Bonobo” and “Mr Blog’s Chinchilla”, the term “Mr Blog’s” would be regarded as an umbrella segment.

To avoid confusion in adverse reaction reporting, the Authority is unlikely to approve umbrella branding in any instance except where the only difference is in the flavourings or when the name of the psychoactive substance forms part of the trade name.

* + 1. *Obtaining approval for new psychoactive product labels*

All labels for new psychoactive products (including container and package labels) are required to be submitted with the application for the new product and are assessed during the evaluation of the NPPA. Applicants should NOT provide a sample of the product along with the label.

An NPPA is required whenever a change:

* is made to the actual information appearing on the label relating to the name, strength of active ingredient, dosage instructions or warning statements.
* This does not apply if the change is only to the colour or print style used for this information.

**However, a full dossier and full fee will not be required for such a label change. Contact the OPSRA to discuss this process.**

An NPPA must include the following:

* Colour artworks of labels and packaging material. Artwork does not need to be actual size, but must be legible, drawn to scale and include a statement of the label dimensions. If the same label (apart from the contents statement) is to be used for several pack sizes of the same strength of a product, it is only necessary to submit exemplar artwork for one pack size and state that it applies across the pack size range.
	+ 1. *Best practice guideline on labelling of Psychoactive Products*

The Psychoactive Substances legislation sets out the mandatory requirements for the labelling of psychoactive products. These represent the minimum requirements to be met when designing labels. In general, these requirements relate to the information that needs to be included on the label, rather than to the way in which that information is presented.

Good label design plays a significant role in improving safe use of products by enhancing the ability of users to identify, select and use psychoactive products correctly.

Sponsors should, always utilise the available guidance on best practice for medicine labelling when designing and assessing the suitability of labels for psychoactive products supplied in New Zealand.

* + 1. *Recommended best practice guidance on the labelling of medicines*

The following resources provide useful guidance on best practice in medicines labelling:

* *Best practice guidance on labelling and packaging of medicines* (MHRA Guidance Note No.25 published June 2003)<http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/index.htm>
* *Best practice guideline on prescription medicine labelling* (published by the Australian Therapeutic Goods Administration November 2005)<http://www.tga.gov.au/industry/labelling-pm-best-practice.htm>
* *Guideline on the readability of the labelling and package leaflet of medicinal products for human use* (Revision 1 published by the European Commission 12 January 2009)
* [http://ec.europa.eu/health/files/eudralex/vol-2/c/2009\_01\_12\_readability\_guideline\_final\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf%20)
* *Design for Patient Safety* (A guide to the graphic design of medication packaging) (NHS National Patient Safety Agency 2nd Edition 2007) <http://www.hhc.rca.ac.uk/CMS/files/NPSA-Design-for-patient-safety-.pdf>
	+ 1. *Barcoding on psychoactive product labels*

Barcoding is mandatory for labels on psychoactive products supplied in New Zealand. Sponsors must place GS1 bar codes on original packs at the point of manufacture/packing.

The following links can be used to find information about barcode types and product identifiers (Global Trade Item Numbers (GTINs)):

* [http://www.gs1.org/barcodes/technical/bar\_code\_types](http://www.gs1.org/barcodes/technical/bar_code_types%20)
* <http://www.gs1.org/sites/default/files/docs/media_centre/gs1_pr_210110_healthcare_AIDC_Application_Standards.pdf>
* <http://www.gs1.org/docs/gsmp/healthcare/GS1_Healthcare_GTIN_Allocation_Rules.pdf>

### Requirement to demonstrate the absence of abuse potential

The Act requires the potential for any psychoactive product to create physical or psychological dependence (see Section 11(3)(d)), to be considered when determining if a product is able to be approved for use by individuals. Physical or psychological dependence is also known as abuse potential.

Applicants should refer to the FDA draft guidance document called [Guidance for Industry: Assessment of Abuse Potential of Drugs](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf) for guidance on how to demonstrate the absence of abuse potential. Applicants should ignore any reference to animal testing. The remainder of the document remains relevant to developing a new psychoactive product.

**The OPSRA is unaware of any *in-vitro* abuse potential tests which are a comprehensive and suitable alternative to animal testing for abuse potential and any human clinical trial investigating abuse potential would not be considered ethical.**

**See Appendix 3 for the PSEAC Position Statement on animal testing**

Applicants should be aware of these difficulties when deciding whether to develop a psychoactive product as fees refunds are unlikely to be granted once an application has been accepted.

### Guidance on the minimum acceptable level of evidence for determination of potential alcohol interactions

Section 4(c) of the Act requires a product application to include a report on the risks to, and impact on, public health and vulnerable or at-risk populations that may arise if the psychoactive product is approved, including:

* information about the interaction of the product with alcohol; and
* a plan to mage those risks.

The OPSRA is unaware of any suitable tests or guidelines that are capable of adequately demonstrating the absence of any interactions with alcohol, and which do not require animal trials.

The OPSRA is willing to consider any information that the applicant can compile on demonstrating the absence of any interactions with alcohol. A combination of *in vitro* pre-clinical testing and human clinical trials may be sufficient to demonstrate the absence of interactions with alcohol. Human clinical trials, however, must be performed in an ethical manner, which may be difficult to demonstrate without pre-clinical animal trials. The OPSRA will not consider the results of any human clinical trial that does not have suitable ethics committee approval.

**See Appendix 3 for the PSEAC Position Statement on animal testing**

Applicants should be aware of these difficulties when deciding whether to develop a psychoactive product as refunds are unlikely to be granted once an application has been accepted.

# Post-approval requirements

### Post-market safety assessment

The sponsor’s responsibility for the safety of a product does not end following approval of the product.

As part of the product approval process the applicant must provide:

* a plan to manage the risks to vulnerable or at-risk populations that may arise if the psychoactive product is approved, including information about the interaction of the product with alcohol
* a detailed plan of how the risk of harm posed by the psychoactive product will continue to be monitored and managed by the applicant if the product is approved, including how the applicant would comply with a recall order issued under [section 88](http://www.legislation.govt.nz/regulation/public/2014/0243/latest/link.aspx?id=DLM5278451) of the Act.

Furthermore, the Act requires that all specified persons must notify the OPSRA of any adverse reaction arising from the use of a psychoactive substance or an approved product, whether it occurred within New Zealand or overseas, as soon as the person becomes aware of it (see section 98).

The term *specified person* includes all persons who hold a licence in respect of a psychoactive substance and the person who applied for approval of a product.

In order to fulfil this requirement to report adverse events, sponsors and manufacturers must monitor and report on the safety of its products over the entire life-cycle of that product. This encompasses the development stage until after the company decides to stop marketing the product and no further product is available on the market.

The range and extent of post-market safety monitoring will be determined by the OPSRA. It will make its decision on a case-by-case basis and additional testing and research can be required at any time after the product is approved eg, should a safety signal emerge from adverse event reporting or through other literature.

### Revocation of approval

New data may emerge in the post-market period which gives the OPSRA reasonable grounds to consider that the product poses more than a low risk of harm. If this happens the OPSRA can temporarily halt the distribution of the product, recall the product from the market and, if required, revoke the product approval. Sponsors of products are required by the Psychoactive Substances Regulations 2014 (see regulation 4(d)) to develop and maintain systems to manage recalls of the products they hold approvals for.

# Product approval fees

The fees and levies associated with the product approval process are described in detail in the Psychoactive Substances (Fees and Levies) Regulations 2014 and are summarised in table 2.

**Table 2: Product approval fees and levies**

|  |  |
| --- | --- |
| Charge type | NZD (includes GST) |
| New Psychoactive Product Application Fee | 175,000 |
| New Subsidiary Psychoactive Product Application Fee | 10,000 |
| Annual levy (per NPPA and NSPPA) | 88,000 |

Note that minor changes to products may not require a full dossier or the full fee. Contact the OPSRA at psychoactives@moh.govt.nz to discuss this process.

The annual levy is to be paid on a pro rata basis by the 20th of the month following approval of the product, and by the 20th of July for each subsequent year. Product sponsors will be issued with a tax invoice prior to the due date.

Applicants may apply for a waiver or refund of a fee or levy (see regulation 6). It is advised that applicants wishing to apply for a fee waiver contact the OPSRA at psychoactives@moh.govt.nz to discuss this process.

# Appendix 1: International Conference on Harmonisation (ICH) Standards

The ICH has developed a collection of guidelines which are the minimum acceptable standards for the approval of medicines. These guidelines also form the minimum requirements for the approval of psychoactive products in New Zealand. As such, where ever drug substance and drug product are referenced in regards to the ICH guidelines, the terms psychoactive substance and psychoactive product should be substituted instead.

Applicants should disregard all reference to animal testing. All other aspects of the following guidelines remain applicable to developing a new psychoactive product.

The Psychoactive Substances Act 2013 does not allow for the results of animal testing to be used to support the approval of a psychoactive product. Any reference to the use of animal testing in the following guidelines should be disregarded and alternatives sought.

**See Appendix 3 for the PSEAC Position Statement on animal testing**

The ICH guidelines recognise and support the use of non-animal tests which have been validated e.g. genotoxicity.

The OPSRA is willing to consider any information that the applicant can compile to demonstrate compliance with, or justify alternatives to, the following standards for each psychoactive product. Note that the OPSRA will not consider the results of any human clinical trial that does not have suitable ethics committee approval.

The lack of animal testing where required by these guidelines should be suitably justified in terms of safety of the user.

Applicants should be aware of the difficulties identified in the PSEAC Position Statement when deciding whether to develop a psychoactive product, as refunds are unlikely to be granted once an application has been accepted.

The ICH website ([www.ich.org](http://www.ich.org)) details the requirements for how the dossier of supporting quality, safety and efficacy data should be formatted. This format is called the common technical document (<http://www.ich.org/products/ctd.html>). Guidance on overall organisation of the information and on how to format and compile the quality, safety and efficacy data is also provided.

The ICH website also provides further detail on what is required to demonstrate the quality, safety and efficacy (including post-market monitoring) of a product (<http://www.ich.org/products/guidelines.html>). These quality standards are explained in further detail below and set out the OPSRAs expectations with respect to the development, manufacture, safety and post-market monitoring of psychoactive products.

Compliance with the standards applicable to the dose forms used for each psychoactive product, supported by evidence, or justification of why compliance with one of these standards is not demonstrated, is required if a product is to attain approval.

For the purpose of conducting a safety assessment, psychoactive products should be considered against the ICH guidelines for products intended for acute intermittent use.

The list of guidelines should be considered in their totality as the need to conduct one set of tests is often conditional on the results of another test.

The nonclinical safety assessment for marketing approval of a pharmaceutical usually includes pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Other nonclinical studies to assess phototoxicity, immunotoxicity, and abuse liability are conducted on a case-by-case basis.

# ICH Product Quality Standards

**ICH Q1A(R2) Stability testing of new drug substances and products**

This guideline defines the stability data package for a new drug substance or drug product.

The guideline seeks to exemplify the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH Q1C and Q5C, respectively.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

**ICH Q1B Stability testing: photostability testing of new drug substances and products**

This document is an annex to ICH Q1A(R2) and addresses the recommendations for photostability testing. ICH Q1A(R2) notes that light testing should be an integral part of stress testing.

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change.

Alternative approaches to those specified in this guideline may be used if they are scientifically sound and justification is provided.

The extent of drug product testing should be established by assessing whether or not acceptable change has occurred at the end of the light exposure testing as described in the Decision Flow Chart for Photostability Testing of Drug Products.

The formal labelling requirements for photo labile drug substances and drug products are established by national/regional requirements.

**ICH Q1C Guideline on Stability Testing of New Drug Substances**

This document is an annex to ICH Q1A(R2) and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.

A new dosage form is defined as a psychoactive product which is a different product type, but contains the same active substance as included in the existing psychoactive product approved by the pertinent regulatory authority. Such product types include products of new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet). For example, a tablet and a capsule that both contain kava would be different dosage forms of the same product.

Stability protocols for new dosage forms should follow the guidance in ICH Q1A(R2) in principle. However, a reduced stability database at submission time (e.g., 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases.

**ICH Q1D Bracketing and matrixing designs for stability testing of new drug substances and products**

This guideline is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in ICH Q1A(R2).

**ICH Q1E Evaluation of stability data**

This guideline is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in ICH Q1A(R2) to propose a retest period or shelf life in a registration application. This guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by “available data from the stability study under the long-term storage condition”.

This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. It also provides recommendations on establishing retest periods and shelf lives for drug substances and drug products intended for storage at or below “room temperature”.

ICH Q6A and Q6B should be consulted for recommendations on the setting and justification of acceptance criteria, and ICH Q1D should be referenced for recommendations on the use of full versus reduced-design studies.

**ICH Q2R1 Text on validation of analytical procedures**

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures. This text presentation serves as a collection of terms, and their definitions, and is not intended to provide direction on how to accomplish validation.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included.

**ICH Q3AR2 Impurities in new drug substances**

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state.

Impurities in new drug substances are addressed from two perspectives:

* chemistry aspects, which include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures; and
* safety aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

Impurities can be classified into the following categories:

• Organic impurities (process- and drug-related)

• Inorganic impurities

• Residual solvents

**ICH Q3BR2 Impurities in new drug products**

This document provides guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesised new drug substances not previously registered in a region or member state.

This guideline is complementary to the ICH Q3A(R2) which should be consulted for basic principles. ICH Q3C(R5) should also be consulted, if appropriate.

This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system.

Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline.

**ICH Q3CR5 Impurities: Guideline for residual solvents**

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products, and that are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

**ICH Q3D Impurities: Guideline for elemental impurities**

This guideline is intended to provide recommendations on how element impurity levels should be controlled within acceptable limits in the drug product. There are three components of this guideline: the evaluation of the toxicity data for potential elemental impurities, the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern, and development of controls designed to limit the inclusion of elemental impurities in drug products to levels at or below the PDE.

Developing a strategy to limit elemental impurities in the drug product is consistent with risk management processes identified in ICH Q9. The process is described in this guideline as a four step process to assess and control elemental impurities in the drug product: identify, analyse, evaluate, and control.

The PDEs in this guideline have been established based on acceptable safety limits of potentially toxic elemental impurities.

Please note that while this is a draft guideline, the OPSRA still considers it to be best practice to follow this guideline.

**ICH Q5AR1 Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin**

This document outlines the requirements for establishing and maintaining the safety of human or cell lines for production, and viral testing and inactivation.

**ICH Q5C Stability testing of biotechnological/biological products**

The guidance stated in ICH Q1A(R2) applies in general to biotechnological/biological products. However, biotechnological/biological products do have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. Biotechnological/biological products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. In order to ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary. The evaluation of stability may necessitate complex analytical methodologies.

With the above concerns in mind, the applicant should develop the proper supporting stability data for a biotechnological/biological product and consider many external conditions which can affect the product’s potency, purity and quality. Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications.

**ICH Q6A Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances**

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered.

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to GMP; eg, suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product. There is no requirement for psychoactive products to meet efficacy criteria.

**ICH Q6B Specifications: Test procedure and acceptance criteria for biotechnological/biological products**

This guidance document provides general principles on the setting and justification, to the extent possible, of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

**ICH Q7 Good manufacturing practice guide for active pharmaceutical ingredients**

This document is intended to provide guidance regarding GMP for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

The guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, or aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

**ICH Q8R2 Pharmaceutical development**

This guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 CTD format. The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.

**ICH Q9 Quality risk management**

The importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm.

The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company’s ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle.

Appropriate use of quality risk management can facilitate but does not obviate industry’s obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

**ICH Q10 Pharmaceutical quality system**

This document describes a comprehensive model for an effective pharmaceutical quality system that is based on ISO quality concepts, includes applicable GMP regulations and complements ICH Q8 and ICH Q9. ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 that is applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle.

**ICH Q11 Development and manufacture of drug substances**

This guideline describes approaches to developing and understanding the manufacturing process of the drug substance, and also provides guidance on what information should be provided in Module 3 of the Common Technical Document (CTD) Sections 3.2.S.2.2 – 3.2.S.2.6 (ICH M4Q). It addresses aspects of development and manufacture that pertain to drug substance, including the presence of steps designed to reduce impurities. In addition, ICH Q11 provides further clarification on the principles and concepts described in ICH Q8, Q9 and Q10 as they pertain to the development and manufacture of drug substance.

As discussed in ICH Q8 for drug product, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provided in the application for marketing authorisation.

# ICH Product Safety Standards

**ICH S1A Guideline on the need for carcinogenicity studies of pharmaceuticals**

The objectives of carcinogenicity studies are to identify the tumorigenicpotential. Any cause for concern derived from *in vitro* laboratory investigations and data in humans may lead to a need for carcinogenicity studies.

Results from genotoxicity studies, toxicokinetics, and mechanistic studies are routinely applied in preclinical safety assessment. These additional data are important not only in considering whether to perform carcinogenicity studies but for interpreting study outcomes with respect to relevance for human safety.

The objective of this guideline is to define the conditions under which carcinogenicity studies, should be conducted to avoid the unnecessary use of animals in testing, and to provide consistency in worldwide regulatory assessments of applications. The fundamental considerations in assessing the need for carcinogenicity studies are the maximum duration of patient treatment and any perceived cause for concern arising from other investigations. Other factors may also be considered such as prior assessment of carcinogenic potential, the extent of systemic exposure, the (dis)similarity to endogenous substances, the appropriate study design, or the timing of study performance relative to clinical development.

Any human clinical trial investigating the carcinogenicity of a psychoactive substance would not be considered ethical.

**ICH S1B Testing for carcinogenicity of pharmaceuticals**

This guideline outlines experimental approaches to the evaluation of carcinogenic potential that may obviate the necessity for the routine conduct of two long-term rodent carcinogenicity studies for those pharmaceuticals that need such evaluation.

**ICH S1CR2 Dose selection for carcinogenicity studies of pharmaceuticals**

This document aims to provide guidance on selecting the appropriate dosage for carcinogenicity studies in animals.

**ICH S2R1 Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use**

This document details the standard genetic toxicology battery for prediction of potential human risks, and provides guidance on interpretation of results, with the ultimate goal of improving risk characterization for carcinogenic effects that have their basis in changes in the genetic material. The revised guidance describes internationally agreed upon standards for follow-up testing and interpretation of positive results *in vitro* and *in vivo* in the standard genetic toxicology battery, including assessment of non-relevant findings.

Genotoxicity tests can be defined as *in vitro* and *in vivo* tests designed to detect compounds that induce genetic damage by various mechanisms. These tests enable hazard identification with respect to damage to DNA and its fixation. Fixation of damage to DNA in the form of gene mutations, larger scale chromosomal damage or recombination is generally considered to be essential for heritable effects and in the multi-step process of malignancy, a complex process in which genetic changes might possibly play only a part.

Numerical chromosome changes have also been associated with tumorigenesis and can indicate a potential for aneuploidy in germ cells. Compounds that are positive in tests that detect such kinds of damage have the potential to be human carcinogens and/or mutagens. Because the relationship between exposure to particular chemicals and carcinogenesis is established for humans, whilst a similar relationship has been difficult to prove for heritable diseases, genotoxicity tests have been used mainly for the prediction of carcinogenicity. Nevertheless, because germ line mutations are clearly associated with human disease, the suspicion that a compound might induce heritable effects is considered to be just as serious as the suspicion that a compound might induce cancer. In addition, the outcome of genotoxicity tests can be valuable for the interpretation of carcinogenicity studies.

Any human clinical trial investigating the genotoxicity of a psychoactive substance would not be considered ethical.

**ICH S3A Note for guidance on toxicokinetics: The assessment of systemic exposure in toxicity studies**

This document concerns toxicokinetics only with respect to the development of pharmaceutical products intended for use in human subjects.

In this context, toxicokinetics is defined as the generation of pharmacokinetic data, either as an integral component in the conduct of non-clinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure. These data may be used in the interpretation of toxicology findings and their relevance to clinical safety issues.

This document has been developed in order to provide an understanding of the meaning and application of toxicokinetics and to provide guidance on developing test strategies in toxicokinetics. The guidance highlights the need to integrate pharmacokinetics into toxicity testing, which should aid in the interpretation of the toxicology findings and promote rational study design development.

Any human clinical trial investigating the carcinogenicity of a psychoactive substance would not be considered ethical.

**ICH S3B Pharmacokinetics: Guidance for repeated dose tissue distribution studies**

A comprehensive knowledge of the absorption, distribution, metabolism and elimination of a compound is important for the interpretation of pharmacology and toxicology studies. Tissue distribution studies are essential in providing information on distribution and accumulation of the compound and/or metabolites, especially in relation to potential sites of action; this information may be useful for designing toxicology and pharmacology studies and for interpreting the results of these experiments.

Single dose tissue distribution studies are required as part of the non-clinical programme.

This paper provides guidance on circumstances when repeated dose tissue distribution studies should be considered and on the conduct of such studies.

The OPSRA is willing to consider any information that the applicant can compile on the tissue distribution of a psychoactive substance. A combination of *in vitro* pre-clinical testing and human clinical trials may be sufficient.

**ICH S5R2 Detection of toxicity to reproduction for medicinal products & toxicity to male fertility**

These systems cannot provide assurance of the absence of effect nor provide perspective in respect of risk/exposure. In short, there are no alternative test systems to whole animals currently available for reproduction toxicity testing.

The aim of reproduction toxicity studies is to reveal any effect of one or more active substance(s) on mammalian reproduction. For this purpose both the investigations and the interpretation of the results should be related to all other pharmacological and toxicological data available to determine whether potential reproductive risks to humans are greater, lesser or equal to those posed by other toxicological manifestations. Further, repeated dose toxicity studies can provide important information regarding potential effects on reproduction, particularly male fertility. To extrapolate the results to humans, data on likely human exposures, comparative kinetics, and mechanisms of reproductive toxicity may be helpful.

No guideline can provide sufficient information to cover all possible cases, all persons involved should be willing to discuss and consider variations in test strategy according to the state of the art and ethical standards in human and animal experimentation. Areas where more basic research would be useful for optimization of test designs are male fertility assessment, and kinetic and metabolism in pregnant/lactating animals.

Other test systems are considered to be any developing mammalian and non-mammalian cell systems, tissues, organs, or organism cultures developing independently *in vitro* or *in vivo*. Integrated with whole animal studies either for priority selection within homologous series or as secondary investigations to elucidate mechanisms of action, these systems can provide invaluable information and, indirectly, reduce the numbers of animals used in experimentation. However, they lack the complexity of the developmental processes and the dynamic interchange between the maternal and the developing organisms.

Any human clinical trial investigating the reproductive toxicity of a psychoactive substance would not be considered ethical.

**ICH S6R1 Preclinical safety evaluation of biotechnology-derived pharmaceuticals**

This guidance is intended primarily to recommend a basic framework for the preclinical safety evaluation of biotechnology-derived pharmaceuticals. It applies to products derived from characterised cells through the use of a variety of expression systems including bacteria, yeast, insect, plant, and mammalian cells.

Regulatory authorities have adopted a flexible, case-by-case, science-based approach to preclinical safety evaluation needed to support clinical development and marketing authorisation of biotechnology-derived pharmaceuticals.

Many of the minimum requirements, however, involve animal testing which is prohibited by the 2014 amendment to the Act. The OPSRA is unaware of any *in-vitro* tests which are a comprehensive and suitable alternative to animal testing. The OPSRA is willing to consider any information that the applicant can compile on the pre-clinical safety of biotechnology-derived psychoactive products. However, applicants should keep these difficulties in mind when choosing to develop or apply for approval of a biotechnology-derived psychoactive product.

**ICH S7A Safety pharmacology studies for human pharmaceuticals**

This guideline was developed to help protect clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals, while avoiding unnecessary use of animals and other resources.

The objectives of safety pharmacology studies are: 1) to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; 2) to evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies; and 3) to investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected. The investigational plan to meet these objectives should be clearly identified and delineated.

It is important to adopt a rational approach when selecting and conducting safety pharmacology studies. The specific studies that should be conducted and their design will vary based on the individual properties and intended uses of the pharmaceuticals. Scientifically valid methods should be used, and when there are internationally recognized methods that are applicable to pharmaceuticals, these are preferable. Moreover, the use of new technologies and methodologies in accordance with sound scientific principles is encouraged.

The OPSRA is willing to consider any information that the applicant can compile on the safety pharmacology of a psychoactive substance. A combination of *in vitro* pre-clinical testing and human clinical trials may be sufficient.

**ICH S7B The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals**

This guideline describes a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. This guideline includes information concerning non-clinical assays and integrated risk assessments.

The QT interval (time from the beginning of the QRS complex to the end of the T wave) of the electrocardiogram (ECG) is a measure of the duration of ventricular depolarization and repolarization. QT interval prolongation can be congenital or acquired (eg, pharmaceutical-induced). When ventricular repolarization is delayed and the QT interval is prolonged, there is an increased risk of ventricular tachyarrhythmia, including torsade de pointes, particularly when combined with other risk factors (eg, hypokalaemia, structural heart disease, and bradycardia). Thus, much emphasis has been placed on the potential proarrhythmic effects of pharmaceuticals that are associated with QT interval prolongation.

This guideline extends and complements ICH S7A. Conditions under which studies are not called for are described in ICH S7A.

Principles and recommendations described in ICH S7A also apply to the studies conducted in accordance with the present guideline.

**ICH S8 Immunotoxicity studies for human pharmaceuticals**

This guideline is focused on providing recommendations on nonclinical testing for immunotoxicity induced by human pharmaceuticals. It is restricted to unintended immunosuppression and immunoenhancement, excluding allergenicity or drug specific autoimmunity.

The objectives of this guideline are to provide (1) recommendations on nonclinical testing approaches to identify compounds which have the potential to be immunotoxic, and (2) guidance on a weight-of-evidence decision making approach for immunotoxicity testing.

Evaluation of potential adverse effects of human pharmaceuticals on the immune system should be incorporated into standard drug development. Toxicity to the immune system encompasses a variety of adverse effects. These include suppression or enhancement of the immune response.

Suppression of the immune response can lead to decreased host resistance to infectious agents or tumour cells. Enhancing the immune response can exaggerate autoimmune diseases or hypersensitivity. Drug or drug-protein adducts might also be recognized as foreign and stimulate an anti-drug response. Subsequent exposures to the drug can lead to hypersensitivity (allergic) reactions.

Existing guidance documents on sensitization or hypersensitivity remain in force and are not affected by this document. It is beyond the scope of this guideline to provide specific guidance on how each immunotoxicity study should be performed.

**ICH S9 Nonclinical evaluation for anticancer pharmaceuticals**

This guideline is not applicable to psychoactive products.

**ICH S10 Photosafety evaluation of pharmaceuticals**

The purpose of this document is to recommend international standards for photo safety assessment, and to harmonise such assessments supporting human clinical trials and marketing authorizations for pharmaceuticals. It includes factors for initiation of and triggers for additional photo safety assessment and should be read in conjunction with ICH M3(R2), Section 14 on Photosafety Testing.

# ICH Efficacy Guidelines

As psychoactive products do not have a therapeutic purpose, many of the ICH efficacy guidelines are not applicable. Guidelines that the OPSRA considers to be of particular importance to psychoactive products are discussed below although applicants should consider whether additional guidelines may also be useful.

**ICH E4 Dose-response information to support drug registration**

This document provides guidance on how to select the correct dose of a product.

Knowledge of the relationships among dose, drug-concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. Dose-concentration, concentration- and/or dose-response information is used to prepare dosage and administration instructions in product labelling. In addition, knowledge of dose-response may provide an economical approach to global drug development, by enabling multiple regulatory agencies to make approval decisions from a common database.

This guideline refers to effectiveness, which applicants should disregard. All other aspects of this guideline remain applicable to developing a new psychoactive product.

*Good clinical research practice*

The OPSRA expects all clinical trials involving humans to comply with the New Zealand Good Clinical Research Practice Guidelines found at Part 11 of the New Zealand Regulatory Guideline for Medicines ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)). For research in humans utilising psychoactive products covered by this legislation, the researcher is not required to seek the approval of the Authority before the study can proceed, however, the research licence holder is required to inform the OPSRA that the study is underway and has attained the relevant site and ethical approvals. Where a human clinical study is conducted outside New Zealand the OPSRA requires the study to comply with ICH E6R1 if it is to be acceptable.

**ICH E6R1 Guideline for good clinical practice**

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

*Post-market safety monitoring*

As indicated, the OPSRA may require the manufacturer to undertake specific post-market safety monitoring of their approved products. Details of this approach can be found in Part 8 of the New Zealand Regulatory Guideline for Medicines ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)), or in the relevant ICH Guidelines.

**ICH E2A Clinical safety data management**

This document is designed to provide guidance on the way to gather and if necessary, to take action on important clinical safety information arising during clinical development.

**ICH E2C Periodic benefit-risk evaluation report (PBRER)**

This document defines the recommended format and content of a PBRER and provides an outline of points to be considered in its preparation and submission.

When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomised trials. Patients in trials are closely monitored for evidence of adverse events. In clinical practice, however, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed (eg, severe liver injury). These factors underlie the need for continuing analysis of relevant safety, efficacy, and effectiveness information throughout the lifecycle of a medicinal product – promptly, as important findings occur – and periodically – to allow an overall assessment of the accumulating data. Although the majority of new information will be safety-related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug’s place in therapy may be pertinent to its benefit-risk assessment.

This guideline references the need to monitor efficacy and effectiveness, which applicant’s should disregard. All other aspects of this guideline remain applicable to developing a new psychoactive product.

**ICH E2D Post-approval safety data management: Definitions and standards for expedited reporting**

It is important to establish an internationally standardized procedure in order to improve the quality of post-approval safety information and to harmonise the way of gathering and reporting information. ICH E2A provides guidance on pre-approval safety data management. Although many stakeholders have applied ICH E2A concepts to the post-approval phase, there is a need to provide further guidance on definitions and standards for post-approval expedited reporting, as well as good case management practices. This guideline is based on the content of ICH E2A, with consideration as to how the terms and definitions can be applied in the post-approval phase of the product life cycle.

**ICH E2E Pharmacovigilance planning**

This guideline is intended to aid in planning pharmacovigilance activities, especially in preparation for the early postmarketing period of a new drug. The main focus of this guideline is on a Safety Specification and Pharmacovigilance Plan that might be submitted at the time of licence application. The guideline can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the Safety Specification and Pharmacovigilance Plan into the Common Technical Document (CTD).

This guideline describes a method for summarising the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval. It proposes a structure for a Pharmacovigilance Plan and sets out principles of good practice for the design and conduct of observational studies.

**ICH E8 General considerations for clinical trials**

This document provides a harmonised guideline on general consideration for clinical trials and the process of clinical development of pharmaceuticals for human use.

This document is intended to:

(a) describe internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategy for new medicinal products

(b) facilitate the evaluation and acceptance of foreign clinical trial data by promoting common understanding of general principles, general approaches and the definition of relevant terms

c) present an overview of the ICH clinical safety and efficacy documents and facilitate the user's access to guidance pertinent to clinical trials within these documents

(d) provide a separate glossary of terms used in the ICH clinical safety and efficacy related documents that pertain to clinical trials and indicate which documents contain them.

In order to protect human trial subjects, and before any clinical trial is carried out, results of non-clinical investigations or previous human studies should be sufficient to indicate that the drug is safe for investigation in humans, before any clinical trial is undertaken. This may be difficult to achieve without pre-clinical studies in animals. Applicants are reminded that the OPSRA will not consider the results of human clinical trials that are performed without suitable ethics approval.

# ICH Multidisciplinary Standards

The multidisciplinary guidelines that the OPSRA considers to be of particular importance to psychoactive products are discussed below although applicants should consider whether additional guidelines may also be useful.

**ICH M3R2 Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals**

The purpose of this document is to recommend international standards for, and promote harmonisation of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

The nonclinical safety assessment for marketing approval of a pharmaceutical usually includes pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential.

Other nonclinical studies to assess phototoxicity, immunotoxicity, juvenile animal toxicity and abuse liability should be conducted on a case-by-case basis. The need for nonclinical safety studies and their relation to the conduct of human clinical trials is delineated in this guidance.

The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information. The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. This information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterise potential adverse effects that might occur under the conditions of the clinical trial to be supported.

Human clinical trials are conducted to investigate the efficacy and safety of a

pharmaceutical, starting with a relatively low systemic exposure in a small number of subjects. This is followed by clinical trials in which exposure to the pharmaceutical usually increases by duration and/or size of the exposed patient population. Clinical trials should be extended based on the demonstration of adequate safety in the previous clinical trial(s), as well as on additional nonclinical safety information that becomes available as clinical development proceeds.

**ICH M4R3 Organisation including the granularity document that provides guidance on document location and paginations**

This guideline presents the accepted common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities. A common format for the technical documentation will significantly reduce the time and resources needed to compile and assess applications for registration of psychoactive products.

**ICH M4QR1 The common technical document for the registration of pharmaceuticals for human use**

*Module 2: Quality overall summary*

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

*Module 3: Quality*

This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products as defined in the scope of ICH Q6A and Q6B.

**ICH M4ER1 The common technical document for the registration of pharmaceuticals for human use**

*Clinical overview of module 2*

The Clinical Overview is intended to provide a critical analysis of the clinical data in the CTD. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarisation of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information.

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

*Clinical summary of module 2*

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the CTD. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the CTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

# Appendix 2: Recognised Authorities

GMP certification issued by the authorities listed below is recognised by the OPSRA. 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 the OPSRA has information that the GMP assessment systems are compatible with New Zealand expectations.

Omission of an authority from the list generally indicates that the authority’s systems have not been assessed for suitability, and should not be construed in any way as an adverse reflection on the competence of the authority itself. The inspectorates recognised by the OPSRA are listed below:

**Australia (TGA)**

Therapeutic Goods Administration, Commonwealth Department of Health and Family Services

**Austria (AGES)**

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

**Belgium (FAGG/AGMPS)**

Inspection general de la Pharmacie, Ministere de la Sante Publique et de la Famille

**Canada (Health Canada)**

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

**Czech Republic (SUKL)**

State Institute for Drug Control

**Denmark (DHMA)**

Medicines Division, Danish Medicines Agency (Sundhedsstyrelsen)

**Finland (fimea)**

Finnish Medicines Agency

**France (ansm)**

National Drug and Health Products Safety Agency (Agence nationale de sécurité du médicament et des produits de santé)

**Germany (ZLG)**

[Central Authority of the Laender for Health Protection regarding Medicinal Products and Medical Devices](http://www.zlg.de/cms.php?PHPSESSID=415ea7d2485723ec272d96cdd5fe3f16&mapid=1&lan=2) (Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten)

For immunologicals:

Paul-Ehrlich-Institut - Federal Institute for Vaccines and Biomedicines

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 (Stuttgart, Tübingen & Karlsruhe)

**Bayern (ZAB)**

Regierung von Oberbayern Zentrale Arzneimittelüberwachung (Munchen, Regensburg, Bayreuth, Ausburg & Ansbach)

**Berlin**

Landesamt für Gesundheit und Soziales (Berlin)

**Brandenburg**

Landesamt für Umwelt, Gesundheit und Verbraucherschutz (Zossen, Potsdam)

 **Bremen**

Die Senatorin für Arbeit, Frauen, Gesundheit, Jugend und Soziales der Freien Hansestadt (Bremen)

 **Hamburg**

Behörde für Gesundheit und Verbraucherschutz der Freien und Hansestadt (Hamburg)

**Hessen**

Regierungspräsidium (Darmstadt & Gießen)

**Mecklenburg-Vorpommern**

Landesamt für Gesundheit und Soziales Mecklenburg-Vorpommern (Schwerin)

**Niedersachsen**

Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit (Oldenburg)

Staatliches Gewerbeaufsichtsamt (Braunschweig, Hannover, Lüneburg, Oldenburg)

**Nordrhein-Westfalen**

Bezirksregierung (Arnsberg, Düsseldorf, Detmold, Köln & Münster)

Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen (Recklinghausen)

**Rheinland-Pfalz**

Landesamt für Soziales, Jugend und Versorgung Rheinland-Pfalz Beim Amt für soziale Angelegenheiten (Mainz & Landau)

Landesamt für Soziales, Jugend und Versorgung Rheinland-Pfalz (Koblenz)

**Saarland**

Ministerium für Gesundheit und Verbraucherschutz des Saarlandes (Saarbucken)

**Sachsen**

Landesdirektion (Dresden & Leipzig)

Landesverwaltungsamt Sachsen-Anhalt (Halle/ Salle)

**Schleswig-Holstein**

Landesamt für soziale Dienste Schleswig-Holstein (Kiel)

**Thüringen**

Thüringer Landesamt für Lebensmittelsicherheit und Verbraucherschutz (Bad Langensalza)

**Greece (EOF)**

National Organisation for Medicines (***Ε****θνικός* ***Ο****ργανισμός* ***Φ****αρμάκων*)

**Hungary (NIP)**

[National Institute for Quality- and Organizational Development in Healthcare and Medicines](http://www.ogyi.hu/main_page/). [National Institute of Pharmacy.](http://www.ogyi.hu)

**Iceland (IMA)**

Icelandic Medicines Agency

**Ireland (HPRA)**

Health Products Regulatory Authority

**Italy (AIFA)**

[Italian Medicines Agency](http://www.agenziafarmaco.it/en) (Agenzia Italiana del Farmaco)

**Japan**

Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

**Liechtenstein (AG)**

[Office of Healthcare](http://www.ag.llv.li/) (Amt für Gesundheit)

**Luxembourg**

Direction de la Santé Villa Louvigny Division de la Pharmacie et des Medicaments

**Malta (MAM)**

[Maltese Medicines Authority](http://www.medicinesauthority.gov.mt/)

**Netherlands (IGZ)**

[Inspectorate of Health Care](http://www.igz.nl/english/) (Inspectie voor de Gezondheidszorg)

**Norway (NOMA)**

Norwegian Medicines Agency

**Portugal (INFARMED)**

[National Authority of Medicines and Health Products, IP](http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH) (Autoridade Nacional do Medicamento e Produtos de Saúde IP)

**Romania**

National Agency for Medicines Devices (NAMMD)

**Singapore (HAS)**

Health Sciences Authority

**Slovak Republic (SIDC)**

State Institute for Drug Control

**Spain (AEMPS)**

[Agency of Drugs and Health Products](http://www.agemed.es/en/home.htm) (Agencia Española del Medicamento y Productos Sanitarios)

Subdirección General de Inspección y Controlo de Medicamentos
Division de Inspección y Control Farmaceútico

**Sweden (MPA)**

Medical Products Agency

**Switzerland (Swissmedic)**

Swiss Agency for Therapeutic Products

**United Kingdom (MHRA)**

Medicines and Healthcare Products Regulatory Agency

**USA (US FDA)**

Food and Drug Administration

# Appendix 3:



**Office of the Psychoactive Substances Regulatory Authority**

**Position Statement on**

**Alternatives to Animal testing**

**This position statement has been prepared by the Office of the Psychoactive Substances Regulator and is endorsed by the Psychoactive Substances Expert Advisory Committee.**

The Amendment to the Psychoactive Substances Act on 8 May 2014 removed the ability of the Psychoactive Substances Expert Advisory Committee (the Committee) to have regard to the results of animal testing when considering whether a psychoactive product should be approved for use by individuals.

The Committee has therefore considered whether suitable alternatives to animal testing are available for all aspects of the assessment that is needed to determine whether a product poses no more than a low risk of harm to the individual using it.

The Committee is required, under section 11(3) of the Psychoactive Substances Act 2013, to have regard to the following when evaluating psychoactive products to assess whether they should be approved for use by individuals:

* the specific effects of the product, including pharmacological, psychoactive, and toxicological effects; and
* the risks, if any, to public health; and
* the potential use of the product to cause death; and
* the potential for the product to create physical or psychological dependence; and
* the likelihood of misuse of the product; and
* the potential appeal of the product to vulnerable populations; and
* any other matters that the Authority considers relevant.

The “avoidance of doubt” provision in section 37(2) of the Act makes it clear that the Authority **must refuse** to approve a psychoactive **product if it is unable to satisfy itself** that the degree of harm that the product poses to individuals using the product is no more than a low risk of harm.

The Committee has considered the type of scientific evidence it would need to see in order to provide robust and evidence-based advice on whether a product posed no more than a low level of harm to the individuals who may use it. It has agreed to refer to technical guidance developed in the context of global harmonisation of requirements for the approval of pharmaceuticals. These guidance documents address the same elements that the Committee is required to consider for psychoactive substances and have been developed through a process of scientific consensus involving technical experts from a number of countries. They are known as the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines*.

After considering the ICH guidance and cognisant also of the consensus views of international toxicology experts in relation to risk assessments of chemicals in food[[3]](#footnote-3) the Committee has concluded that the tests required to address the following aspects of safety are currently only satisfactorily determined in animal models:

* Teratogenicity
* Toxicokinetics
* Immunotoxicity
* Carcinogenicity
* Addiction modelling

**The committee’s position is therefore that until suitable and internationally recognised non-animal study alternatives exist for assessing these aspects of product safety it may be unable to recommend approval of any psychoactive products.**

1. On black and white print-outs dark blue boxes can be identified by their single solid boundary line [↑](#footnote-ref-1)
2. On black and white print-outs pink boxes can be identified by their dotted boundary line [↑](#footnote-ref-2)
3. International Programme on Chemical Safety Environmental Health Criteria 240 “Principles and Methods for the Risk Assessment of Chemicals in Food”, WHO, 2009.

<http://www.inchem.org/documents/ehc/ehc/ehc240_chapter4.pdf> [↑](#footnote-ref-3)