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Psychoactive Substances

Code of Manufacturing Practice

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Foreword

New Zealand is a world leader in the regulation of psychoactive substances. The importation, manufacture and supply of these substances are regulated through the Psychoactive Substances Act 2013.

The Act establishes the Psychoactive Substances Regulatory Authority with the aim to ensure that products meet adequate safety requirements before they can be distributed in New Zealand. Risk assessments focus on approving only those substances that pose no more than a low risk of harm to users.

The Psychoactive Substances Code of Manufacturing Practice (the Code) focuses on making sure all psychoactive products on the market in New Zealand are made to a consistently high standard in clean, controlled environments, and details the quality control requirements for manufacturers of psychoactive substances. The Introduction to the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods: Part 1: Manufacture of pharmaceutical products should be read in conjunction with the Code, as it provides valuable guidance that will assist with meeting the GMP requirements for psychoactive substances and products.

This is the second version of the Code and reflects the full regulatory requirements for manufacturing following the passage of the Psychoactive Substances Amendment Act 2014 on 8 May 2014 and commencement of the Psychoactive Substances Regulations 2014 on 3 November 2014.

The first version of the Code (17 January 2014) was structured into two documents: the technical requirements of the Code, as outlined in this document, and an Implementation Plan. The Implementation Plan was designed to manage the interim regime. It gave manufacturers with an interim licence sufficient time to develop the documentation that would allow them to move to a fully compliant Good Manufacturing Practice environment, as well as providing an assurance around the process used to manufacture those psychoactive products that were being sold on the local market during the interim transition period.

Under this second version of the Code, a manufacturing facility in which a psychoactive product is manufactured will need to demonstrate full compliance with the Code before a licence to manufacture is granted and a product can be approved.

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acting as the Psychoactive Substances Regulatory Authority under a delegated authority from the Director-General of Health

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1.1 Overview of the Psychoactive Substances Act

1.1.1 Purpose of the Act

The Psychoactive Substances Act 2013 (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.[1]

The Act establishes the Psychoactive Substances Regulatory Authority (the Authority) with the aim to ensure that products meet adequate safety requirements before they can be distributed in New Zealand. The Authority approves products and licenses importers, researchers, manufacturers, wholesalers and retailers. The Office of the Psychoactive Substances Regulatory Authority (the OPSRA) is responsible for administration of the Act and its associated regulations.

1.1.2 Psychoactive substances regulations and guidelines

The Psychoactive Substances Regulations 2014 (the Regulations) further define the full regulatory requirements for psychoactive substances.

Additional supporting detail relating to implementation of the regulatory scheme is set out in the Psychoactive Substances Regulatory Guidelines - Products (the Guidelines). Anyone seeking to have a product approved will be required to demonstrate that the product poses no more than a low risk of harm to individual consumers. Before the Authority can approve a psychoactive product, the degree of harm will be assessed on the basis of the evidence supplied and the advice of the Psychoactive Substances Regulatory Authority Expert Advisory Committee.

The Guidelines can be found at the Psychoactive Substances Regulatory Authority website: www.psychoactives.health.govt.nz

1.1.3 The Code of Manufacturing Practice

The Act defines the manufacture of psychoactive substances or products as the means to make up, prepare, produce, or process the substance or product for the purpose of sale. It also includes packaging the substance or product for the purpose of sale.

Section 29 of the Act specifies the requirement for the Authority to develop and maintain a code of manufacturing practice relating to the manufacture of psychoactive substances and products. The Code of Manufacturing Practice (the Code) covers the quality and consistency of the manufacturing process.

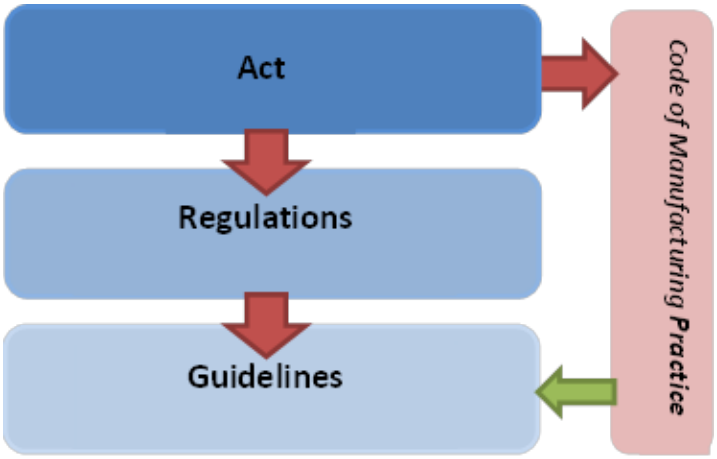
[1] A psychoactive substance is anything that can be used for a psychoactive effect in humans. A psychoactive product is a product containing a psychoactive substance that is intended for retail sale.

The Code sets out the OPSRA's expectations to manufacturers to ensure that they consistently produce psychoactive substances to an accepted quality. The Code details the quality requirements necessary for manufacturers to demonstrate that they are able to produce psychoactive substances and products that:

- are manufactured in Good Manufacturing Practice (GMP) licensed facilities
- are manufactured to defined quality standards
- use ingredients that comply with internationally established standards
- comply with a set of specifications agreed by the OPSRA as part of the product approval.

Under section 17 of the Act, it is a compulsory condition of any licence to manufacture that the licence holder complies with the Code at all times.

Figure 1: Psychoactive Substances Regulatory Scheme



The Code forms an integral part of the quality control of psychoactive substances, and together with the regulations and other guidelines, will ensure psychoactive substances and products comply to safety standards that consumers and the Authority can rely on.

1.2 The quality risk management approach to the manufacture of psychoactive substances and products

Risk management principles are used in many areas of business and government, including finance, insurance, occupational safety, public health and pharmacovigilance, and by agencies regulating these industries. The importance of *quality systems* is recognised in these industries, and quality risk management is a valuable part of any effective quality system. In approaching the risk management of psychoactive substances, the OPSRA has drawn extensively on risk management experience in the pharmaceutical and chemical manufacturing sectors.

The manufacture and use of a psychoactive product involves a degree of risk. The quality of the product is just one component of the overall risk, and needs to be managed by developing appropriate quality risk management systems. In order to comply with the Code, manufacturers of psychoactive substances and products will need to develop and use quality risk management processes to assess, control, communicate and review the risks to the quality of their products, and reduce the potential harm due to its manufacture to an acceptably low level.

The Code details the outputs (in terms of the quality control of psychoactive products) that a systematic approach to quality risk management will deliver and sets out a framework for the risk management of psychoactive product manufacturing. It is a foundation document that is independent of, yet supports, international guidelines and codes (such as the International Committee on Harmonisation guidelines). It also complements existing quality practices, requirements, standards and guidelines used within the pharmaceutical industry and other regulatory environments.

The Code provides specific 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 the OPSRA and by the psychoactive substances industry, regarding the quality of psychoactive substances and the facilities they are manufactured in. The information required as part of compliance with the Code provides assurance that a particular manufacturer can produce psychoactive substances or products in an environment that incorporates appropriate risk management systems.

As a result, the Code has been developed with a 'product' focused approach to quality risk management, with manufacturers required to provide product-based documentation to the OPSRA that demonstrate that they have the appropriate 'quality systems' in place in the manufacturing facility (ie, demonstration that a product is manufactured to a high quality necessitates the pre-development of quality systems, and supporting documentation).

The effectiveness of risk management systems for specific products will be assessed by the OPSRA through a review of both the facility and the product data generated by the manufacturer. The specific details of what data and information must be produced are detailed in section 2.

1.3 Overview of the Code

1.3.1 General approach to the information required

The Code describes the specific information required to demonstrate that a manufacturer can consistently produce quality psychoactive products by using:

- a controlled process
- ingredients that comply with internationally established standards
- detailed specifications
- defined quality standards.

1.3.2 Overview of specific requirements

For each psychoactive substance or product manufactured in the facility

The OPSRA requires:

- information on the source, quantity and quality of the psychoactive substance in any psychoactive product, presented as certificates of analysis[2]
- information to demonstrate the full characterisation of the psychoactive substance, including full details of the chemistry, the manufacture and the controls placed on manufacture, and information on the stability of the psychoactive substance

[2] A certificate of analysis refers to an authenticated document that is generally issued by Quality Assurance that ascertains that a psychoactive substance or product has met its stated specifications.

- agreed specifications (quality tests) that any psychoactive substance and product manufactured must meet before it is released to be sold
- the quantitative formulation of the psychoactive product
- the dose form of the psychoactive product (eg, tablet, suspension, capsule)
- information on how the psychoactive product is made, and proof that the process consistently produces a high-quality product
- proof that the manufacturing facility can test the quality of the psychoactive product accurately
- validation of the test methods used for the psychoactive substances used and the psychoactive products manufactured at the facility
- an outline of stability trials that will be conducted to show the psychoactive product does not degrade
- information to support the ongoing stability of the psychoactive product
- information on the controls on the quality of the excipients, packaging materials, delivery devices and intermediate products used.

For the manufacturing facility

The OPSRA also requires evidence of GMP compliance for all psychoactive substance and product manufacturing sites, with appropriate certification.

1.4 What the Code is based on

The Code is based on internationally established standards and criteria published by the International Conference on Harmonisation (ICH). Additional guidance on GMP, Ingredients of human or animal origin and TSE risk management, Colouring agents and DMFs and CEPs published by pharmaceutical regulators such as Medsafe and the European Medicines Agency is included in Appendix 1. A brief summary of the key points of the ICH guidelines relevant to the Code is included in Appendix 11.

1.5 What is required for compliance with the Code?

All psychoactive substances and products, and their manufacturers, will be assessed to the same requirements. However, the OPSRA does not test every product itself. The assessment by the OPSRA of compliance with the Code is based on the information supplied by the manufacturer on the quality of the specific products they manufacture, as well as by the OPSRA conducting regular inspections on manufacturing facilities to ensure they have the required systems and documentation in place.

> **A note on terminology**
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> In this document, and the referenced guidance documents, the term ‘active ingredient’ or ‘drug substance’ is used to refer to the psychoactive substance in the final psychoactive product, which in turn is referred to as the ‘finished product’ or ‘drug product’. ‘Excipient’ refers to other ingredients that make up the psychoactive product but do not possess a psychoactive effect (eg, bulking or binding agents).

2 The Code of Manufacturing Practice

2.1 Quality control of psychoactive substances

2.1.1 Controls applied by the manufacturer of a bulk psychoactive substance

a. Details of each psychoactive substance manufacturing site must be provided, including the postal and physical addresses, as well as any distinction about the particular sub-site details (eg, building number).

b. A satisfactory drug master file (DMF), or a certificate of suitability to the monographs of the European Pharmacopeia (CEP), issued by the European Directorate for the Quality of Medicines, must be submitted from each supplier of bulk psychoactive. Additional information on DMFs and CEPs is provided in Appendix 1. The essential information that the DMF must cover includes the following:

- A copy of the psychoactive substance specifications, including tests and specified limits applied by the manufacturer of the bulk psychoactive substance, must be provided. The specifications must cover all the relevant identity, organoleptic, physical (including crystalline form and particle size distribution, if applicable), chemical, stereochemical and microbiological quality parameters.
- A justification for the selection of any non-pharmacopoeial tests, test procedures, requirements and limits must be provided. 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.
- 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 laboratories used by the psychoactive product manufacturer for routine quality control of the bulk active(s).
- Satisfactory representative batch analytical data for two typical batches of bulk active substance in the form of certificates of analysis. The certificates of analysis must demonstrate that the results for tests performed on the psychoactive substance are within the limits specified on the psychoactive substance specification. Certificates of analysis must be signed, and for tests where the limits are numerically defined, the certificates of analysis should state the numerical result. (Note: just stating ‘conforms’ will not be accepted.) If an ‘in-house’ reference standard is used in the assays, characterisation and analytical data confirming its suitability for use must be provided.
- Reports demonstrating the validation of all tests must be provided. All non-pharmacopoeial tests must be shown to have been suitably developed and validated at an accredited laboratory (see section 3.2 for further information on laboratory accreditation).

- Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process, or through use of an analytical procedure transfer process.
- All assay and related substance/degradation product and residual solvent impurity-level tests on the psychoactive substance 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 psychoactive substance produced using the intended manufacturing process.
- Reference standards should be described, and if an 'in-house' reference standard is used in the test methods, characterisation and analytical data confirming its suitability for use must be provided.

c. Evidence of GMP (or at least evidence that a bulk active psychoactive substance is manufactured consistently and to acceptable quality standards) is required for all sites that manufacture bulk active psychoactive substance (see section below 2.10 for further information).

2.1.2 Controls applied by the psychoactive product manufacturer

a. A copy of the psychoactive substance specifications, including tests and specified limits, applied by the psychoactive product manufacturer in testing bulk active substance before use in manufacture of the psychoactive product must be provided. The specifications must cover all of the relevant identity, organoleptic, physical (including crystalline form and particle size distribution, if applicable), chemical, stereochemical and microbiological quality parameters.

b. A justification for the selection of any non-pharmacopoeial tests, test procedures, requirements and limits must be provided. If certain tests are not carried out routinely, adequate justification must be provided. Note: it is not acceptable for the psychoactive product manufacturer to take the results from the psychoactive substance manufacturer's certificates of analysis.

c. Certificates of analysis generated by the psychoactive product manufacturer must be supplied for at least two typical batches of bulk psychoactive substance, from each supplier. The testing must have been performed upon receipt. The certificates of analysis must demonstrate that the tests performed on the psychoactive substance are within the limits specified on the psychoactive substance specification. Certificates of analysis must be signed, and for tests where the limits are numerically defined, the certificates of analysis should state the numerical result (note: just stating 'conforms' will not be accepted).

d. Reports demonstrating the validation of all tests must be provided. All non-pharmacopoeial tests must be shown to have been suitably developed and validated at an accredited laboratory (see section 3.2 for further information on laboratory accreditation).

e. Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process, or through use of an analytical procedure transfer process.

f. 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.

g. 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 psychoactive substance produced using the intended manufacturing process.

h. The reference standards used for the analytical methods to test the psychoactive product should be described, and if 'in-house' reference standards are used, then these should be characterised and a certificate of analysis for the reference standard provided.

2.2 Quality control of excipient(s)

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

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

c. Adequate measures must be taken to ensure that any ingredients of animal origin (eg, gelatin, magnesium stearate, calcium stearate, stearic acid) used in the product are free from transmissible spongiform encephalopathy (TSE) contamination in accordance with European Community and United States guidelines (see additional guidance in Appendix 1).

d. 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.

e. Any colouring agents must comply with those accepted for use (see additional guidance in Appendix 1).

2.3 Quality control of packaging materials

a. The packaging materials used (polymers, types of glass, etc), containers, seals and closures supplied with the product must be clearly defined, shown to be suitable, and adequately controlled for identity, dimensions, physical and chemical properties, manufacturing defects and sterility, as applicable.

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

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

2.4 Quality control of delivery device(s)

a. Any delivery device(s) supplied with the psychoactive product must be clearly defined and have been shown to be suitable and adequately controlled for identity, dimensions, physical and chemical properties, manufacturing defects, sterility 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.

2.5 Quality control of intermediate products

a. If there is an intermediate product[3], it must be 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.

b. Reports demonstrating the validation of all tests must be provided. All non-pharmacopoeial tests must be shown to have been suitably developed and validated at an accredited laboratory (see section 3.2 for further information on laboratory accreditation).

c. Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process, or through use of an analytical procedure transfer process.

2.6 Manufacture of the psychoactive product

a. Details of each psychoactive product manufacturing site involved in the manufacture of the psychoactive product (including every packing, filling and sterilisation site) must be provided, including the postal and physical addresses, as well as any distinction about the particular sub-site details (eg, building number).

b. Full quantitative formulation details of the ingredients in the psychoactive product, including both the active and non-active constituents (excipients), must be provided.

c. The quantitative formulation should include details of the quality standards applied to the ingredients (both actives and excipients) (eg, pharmacopoeial or 'in-house' standards).

d. A detailed description of the manufacturing process, including a flow chart for each psychoactive product, must be provided. The information must detail, and justify, the manufacturing process, sterilisation (if any) and packaging processes; the equipment used; and the batch sizes (or range of batch sizes).

e. The in-process controls (including temperatures, mixing times and speeds, and 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.

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[3] An intermediate product could be a psychoactive substance mixed with one or more excipients (often purchased as a proprietary blend). It could be the subsequent modification of the substance as an 'intermediate' in the manufacturing process. In both of these cases, the intermediate would not be considered the starting material and the OPSRA would need detailed information about both the initial substance and the intermediate.

f. A validation report for the manufacturing process from each manufacturing site demonstrating the consistent and reproducible production of the psychoactive product must be provided. The expectation is that this report will cover three batches of the psychoactive product, with two allowable at pilot scale (a minimum of 10 percent of the proposed full-scale manufacture) and one full-scale batch.

g. GMP certification, or other evidence of GMP compliance, must be provided for each psychoactive product manufacturing, testing and packing site (see section 2.10 below for further information).

2.7 Quality control of the psychoactive product

a. Details of each psychoactive product testing site must be provided, including the postal and physical addresses, as well as any distinction about the particular sub-site details (eg, building number).

b. Detailed specifications and testing requirements for each psychoactive product must be provided. These specifications (also called 'finished product specifications') are the criteria the psychoactive product must meet before it is released to be sold. Physical copies of the specifications for each psychoactive product must be supplied and must be specific for each product.

c. Documentation must be available to demonstrate that the identity and quality of the psychoactive product is adequately controlled at release by appropriate pharmacopoeial or 'in-house' psychoactive product specifications that cover all the necessary organoleptic, physical, chemical, stereochemical, microbiological and dose delivery parameters relevant to the dose form.

d. The documentation for two batches of the final market formulation(s) of the psychoactive product, manufactured at least at pilot scale (a minimum of 10 percent of proposed full-scale manufacture), at each of the proposed manufacturing sites must be provided. Results must be included for each specified test, and all the reported test results must comply with the specifications. If not, an adequate explanation or justification must be provided. Please note: the OPSRA would prefer the documentation to be in the form of certificates of analysis; however, analytical testing from an acceptably accredited laboratory will be accepted such as an IANZ-accredited laboratory or a comparable acceptable accreditation body (eg, an ILAC/APLAC recognised accreditation body) or a laboratory certified by a JAS-ANZ conformity assessment body (see section 3.2). Certificates of analysis submitted must be signed to be accepted.

e. A justification for the selection of any non-pharmacopoeial tests, test procedures, requirements and limits must be provided. 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.

f. Reports demonstrating the validation of all tests must be provided. All non-pharmacopoeial tests must be shown to have been suitably developed and validated at an accredited laboratory (see section 3.2 for further information on laboratory accreditation).

g. Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process or through use of an analytical procedure transfer process.

h. The reference standards used for the analytical methods to test the psychoactive product should be described, and if 'in-house' reference standards are used, then these should be characterised and a certificate of analysis for the reference standard provided.

2.8 Validation of analytical procedures

a. The OPSRA requires all manufacturers to demonstrate that all test methods used during manufacture or to test any psychoactive substances or products have been validated, or to provide an adequate justification for why this has not occurred.

b. The OPSRA expects all analytical procedures (pharmacopoeial and non-pharmacopoeial) to have been validated as suitable for use at each site where testing is to occur. Test method validation must have been performed prior to commercial marketing of the product.

c. The extent of validation required is determined by:

- whether the analytical procedure is in a recognised pharmacopoeia
- the type and complexity of the test method in question
- validation of the range of techniques, including: full validation in accordance with ICH guidance, analytical procedure transfer validation, or conformance with system suitability criteria.

d. All non-pharmacopoeial tests must be shown to have been suitably developed and validated at an accredited laboratory (see section 3.2 for further information on laboratory accreditation).

e. Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process, or through use of an analytical procedure transfer process.

2.9 Stability testing of the psychoactive product

a. Stability protocols, developed according to ICH guidelines that outline the stability trials to be undertaken to demonstrate the psychoactive product does not degrade over time must be provided. Please note that the protocol should outline all storage conditions, number of batches and parameters to be tested, and should cover at least a minimum of 24 months for all products manufactured.

b. The stability trial protocol must detail the packaging, packaging orientation (if relevant), storage conditions and test procedures used. All 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 stability protocol and have been monitored using appropriate, clearly defined, validated, stability-indicating test procedures.

c. At least 12 months' data under real-time storage conditions, and six months' data under accelerated storage conditions for two batches of all products manufactured must be initially provided. A commitment to provide all on going stability data as it becomes available, and to inform the OPSRA immediately of any issues with stability of the psychoactive product, must also be provided.

d. The data must support the stability of the market formulations of the psychoactive product (or formulations that may reasonably be expected to have the same stability), packaged as intended for marketing, and have been tested following protocols that are in accordance with ICH guidelines (including the ICH requirements for the number and sizes of batches used). Any deviations from this must be suitably justified.

e. Any trial deviations or changes in test procedure during the stability trials from that stated in the stability protocol must be justified and the results correlated.

f. The results (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).

g. If relevant, the stability of the psychoactive product after first opening, reconstitution or dilution (as applicable) must have been investigated and shown to be adequate for the intended use of the product.

2.10 Good manufacturing practice

Requirements of the Code

All sites involved in the manufacture of a psychoactive product must have GMP certification or other evidence of GMP compliance that is accepted by the OPSRA.

Valuable information about the general principles of GMP is found in the Introduction to the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods: Part 1: Manufacture of pharmaceutical products (see Appendix 1). It should be read in conjunction with the Code as it will assist with meeting the GMP requirements for psychoactive substances and products.

(i) GMP certification

a. All manufacturing sites must provide evidence of GMP certification.

- GMP certification, or other evidence of GMP compliance, must be provided for each psychoactive product manufacturing, testing and packing site. The certification must:
  - detail the manufacture of psychoactive substances and products within the scope of the certificate
  - have been issued by authorities recognised by the OPSRA
  - have not expired or be more than five years old at the time of submission.
- Evidence of GMP (or at least evidence that a bulk psychoactive substance is manufactured consistently and to acceptable quality standards) will be required for all sites that manufacture bulk psychoactive substances. Such evidence should be included with each application or notification that relates to a change of site.
- The name and address of the actual site of manufacture should be provided to ensure 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.

b. Any of the following are acceptable as evidence for manufacturers of bulk psychoactive substance:

- a GMP certificate or inspection report issued by a recognised authority (note that not all authorities issue certification for sites manufacturing bulk psychoactive substances)
- a DMF
- a *European Pharmacopoeia* certificate of suitability for a substance controlled according to the *European Pharmacopoeia*
- batch analytical data demonstrating consistent quality of the psychoactive substance produced, where product testing using a validated testing methodology has been conducted by a testing facility that is accredited by a recognised agency as meeting IANZ or a comparable acceptable accreditation body (eg, an ILAC/APLAC recognised accreditation body) or a laboratory certified by a JAS-ANZ conformity assessment body.

(ii) Recognised documentation

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 and a list of authorities whose competence to certify GMP compliance is recognised by the OPSRA (recognised authority) can be found in the Guidelines.

If the original documentation is 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.

GMP certification recognised by the OPSRA can be any document issued by a recognised authority which attests to GMP compliance. Legible photocopies of the documents are acceptable. Documents should contain the following information:

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

The following are examples of acceptable evidence of GMP certification:

- a 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 the name and address of the site are shown
- certification of pharmaceutical product issued under the WHO scheme by a recognised authority which certifies the quality of pharmaceuticals moving in international commerce
- Canadian Drug Plant Inspection Rating Report
- a letter or file note from a recognised authority which attests to GMP compliance – the most common example seen is an extract from Food and Drug Administration (FDA) files obtained by the manufacturer under the US Freedom of Information Act, which usually states that an audit occurred on the given date and gives the outcome of the audit
- a certificate issued by the Australian Therapeutic Goods Administration confirming that it has confirmed (eg, with the FDA) that GMP compliance at the particular site is satisfactory.

The following are *not* acceptable as evidence of GMP compliance:

- a licence to manufacture that has not been 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.

(iii) Recognised authorities

GMP certification issued by regulatory agencies listed in the Guidelines is recognised by the OPSRA. The authorities listed include the competent authorities in the European Community, member authorities of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (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 OPSRA has not assessed that authority's systems. It should not be construed in any way as an adverse reflection on the competence of the authority itself.

3 Further information

3.1 Auditing of manufacturing facilities

Under section 30 of the Act, the Authority has the ability to conduct an audit of a manufacturing facility at any time for the purpose of assessing compliance with any conditions of the licence to manufacture, and compliance with the Code.

For an application for a new licence to manufacture, the proposed manufacturing facility will be audited as part of the decision-making process. The OPSRA will also regularly audit a licenced manufacturing facility.

An Authorised person, appointed under section 31 of the Act, has the power to inspect a manufacturing facility, look at documents, open containers, take samples and remove documents, as required.

Following an audit the Authority may issue a compliance notice, under section 32 of the Act, that require the manufacturer to do, or refrain from doing, within a specified time, a particular thing which affects their compliance with the Code or any condition of the licence to manufacture.

In addition, it is proposed that manufacturers may be required to make periodic updates to the OPSRA on the routine manufacture of batches of psychoactive substances and products. Manufacturers will be informed of these requirements on a case-by-case basis.

3.2 Accredited testing facilities

As stated above, all psychoactive substance and product test procedures must be shown to have been appropriately validated, and evidence must be provided that the facility and the testing programme have been accredited by IANZ or a comparable acceptable accreditation body (eg, an ILAC/APLAC recognised accreditation body). Further information on accreditation of testing facilities can be found at the following websites: APLAC, (www.aplac.org/), IANZ (www.ianz.govt.nz), ILAC, (ilac.org/) and (JAS-ANZ (www.jas-anz.com.au).

Non-pharmacopoeial analytical procedures should be verified as suitable for use at all nominated sites of testing, either through a revalidation process, or through use of an analytical procedure transfer process.

3.3 Standards and pharmacopoeia

Where a product is required to conform (or is claimed to conform) to any particular 'standard' or pharmacopoeial monograph, it must comply with *all* of the requirements (including test methods, unless otherwise justified) of the *current version* of that standard or pharmacopoeial monograph.

Accepted pharmacopeia are:

- *British Pharmacopoeia*
- *European Pharmacopoeia*

- *Japanese Pharmacopeia*
- *United States Pharmacopoeia and National Formulary*.

3.4 Assistance preparing the documentation required

There are a number of consultants and companies who operate as regulatory consultants for the pharmaceutical sector and who may be able to provide some assistance. A list of such consultants and companies is available on the Medsafe website (www.medsafe.govt.nz).

Appendix 1: Additional guidance

Good Manufacturing Practice

GMP is a system that assures proper design, monitoring and control of manufacturing processes and facilities. Adherence to GMP principles assures the identity, strength, quality and purity of psychoactive substances and products from a manufacturing facility by requiring that manufacturers adequately control manufacturing operations.

This process includes establishing quality management systems, obtaining appropriate quality ingredients, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a manufacturing facility, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures and errors. This assures that psychoactive products reliably and consistently meet their quality standards.

The basic requirements of a GMP system are as follows.

- All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing psychoactive products of the required quality and complying with their specifications.
- Critical steps of manufacturing processes and significant changes to the process are validated.
- All necessary facilities for GMP are provided, including:
  - appropriately qualified and trained personnel
  - adequate premises and space
  - suitable equipment and services
  - correct materials, containers and labels
  - approved procedures and instructions
  - suitable storage and transport.
- Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided.
- Operators are trained to carry out procedures correctly.
- Records are kept, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product were as expected. Any significant deviations are fully recorded and investigated.
- Records of manufacture, including distribution, that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.
- The distribution of the products minimises any risk to their quality.
- A system is available to recall any batch of product from sale or supply.

- Complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent recurrence.

New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods

http://www.medsafe.govt.nz/regulatory/Guideline/code.asp

This guideline provides general information on the principles of GMP and detail on the New Zealand requirements for complying with pharmaceutical GMP.

Ingredients of human or animal origin and TSE risk management

If a product contains an ingredient (active or excipient) that is, or potentially is, of human or animal origin, or that comes into contact with material of human or animal origin during manufacture, the source of the material (or contact) must be declared. If it is of animal origin, evidence must be provided that the product is free from viruses, other micro-organisms and transmissible spongiform encephalopathy (TSE) agents.

The following guidelines should be followed in preparing the documentation to provide this evidence. These guidelines should be followed in preparing the documentation to show that ingredients of animal or human origin are suitable for use and are free from viruses, other micro-organisms and transmissible spongiform encephalopathy (TSE) agents.

ICH guidelines

- Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products:

  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6B/Step4/Q6B_Guideline.pdf
- Q5A(R1): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin:

  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5A_R1/Step4/Q5A_R1__Guideline.pdf
- Q5D: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological Products:

  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5D/Step4/Q5D_Guideline.pdf

Committee for Medicinal Products for Human Use (CHMP) guidelines

- Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 rev. 3).
- Position Paper on Production of Tallow Derivatives for Use in Pharmaceuticals (CPMP/1163/97).
- Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BW/269/95).
- Draft Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/385/99).

- Note for Guidance: Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses (CPMP/BWP/268/95).
- Note for Guidance on Plasma-Derived Medicinal Products (CMP/BWP/269/95 rev. 3); see Annexe V: CPMP/BWP/390/97.

Food and Drug Administration guidelines

- Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products.
- Guidance for Industry: Donor Screening for Antibodies to HTLV-II.
- Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use.
- Guidance for Industry: Revised Preventative Measures to Reduce the Possible Risk of Transmission of Creutzfeld–Jakob Disease (CJD) and Variant Creutzfeld–Jakob Disease (nvCJD) by Blood and Blood Products.

World Health Organization guidelines

- Guidelines for Assuring the Quality of Pharmaceutical Preparations Made by Recombinant DNA Technology (WHO/PHARM/89.542 BS/Rev.1).

New Zealand guidelines

- Minimum Standards for the Collection, Processing and Quality Assurance of Blood and Medicines Derived from Human Blood and Plasma (1998).

Note: a European Pharmacopoeial Commission certificate of suitability is acceptable as evidence of freedom from TSE agents (see www.edqm.eu/en/edqm-homepage-628.html).

Colouring agents

The list of colouring agents that are acceptable for use in psychoactive products in New Zealand can be found in the *New Zealand Regulatory Guidelines for Medicines* at: www.medsafe.govt.nz

DMFs and CEPs

Requirement for a DMF or CEP

Quality control of the bulk psychoactive substance is carried out by both the manufacturer of the substance and by the manufacturer of the psychoactive product. Where the psychoactive substance and product are manufactured by the same manufacturing facility, information on the production, quality control and stability of the psychoactive substance may be submitted as part of the information for the psychoactive product, rather than separately.

In cases where the substance is manufactured by a company other than the manufacturer of the psychoactive product, the manufacture, quality control and stability of the psychoactive substance should be described in a drug master file (DMF)[4] by the manufacturer of the

[4] A drug master file (DMF) is a confidential, detailed document submitted by the psychoactive substance manufacturer to a regulatory authority and details the chemistry, manufacturing and controls on the psychoactive substance.

psychoactive substance. The DMF may be submitted together with the information for the psychoactive product, but it is acceptable for the DMF to be submitted separately. This may be so that the psychoactive substance manufacturer can maintain confidentiality about the manufacture of the psychoactive substance. In order for the Authority to be able to refer to the DMF, a 'letter of access' from the psychoactive substance manufacturer, addressed to the Authority and clearly indicating the manufacturer and psychoactive product to which it applies, must be sent to the OPSRA by the psychoactive substance manufacturer, either with the DMF or separately.

If an active substance manufacturer has supplied (or been asked to supply) a DMF to the Authority 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. However, the psychoactive substance manufacturer needs to provide the OPSRA with a new letter of access, referring to the previously supplied DMF and the new applicant.

Psychoactive product manufacturers are responsible for the quality of their products and the raw materials used to manufacture them. Therefore, manufacturers should provide written assurance that there is a formal agreement between them and the psychoactive substance manufacturer, before any significant change is made to the method of manufacture or specifications of a psychoactive substance used in a psychoactive product distributed in New Zealand.

DMFs should be updated periodically to reflect any changes. The manufacturer 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. The changes made need to be described in sufficient detail to enable the Authority to determine if any material changes have been made to the characteristics, manufacture or quality control of the substance concerned and what those changes are. Where formal evaluation of the changes is required, the applicant will be required to submit these data to the Authority for approval.

Quality testing for psychoactive substances should be conducted using validated testing systems by laboratories accredited to IANZ, or a comparable acceptable accreditation body (eg, an ILAC/APLAC recognised accreditation body) or a laboratory certified by a JAS-ANZ conformity assessment body.

When is a DMF not required?

A DMF is *not* required for:

- any psychoactive substance that is controlled according to the relevant monograph in the *European Pharmacopoeia* and for which a valid (recently issued) European Pharmacopoeial Commission certificate of suitability (CEP) is provided
- common inorganic substances and simple organic compounds available commercially in high purity from chemical supply houses; for example, sodium chloride, magnesium hydroxide, naturally occurring organic acids and their salts (such as ascorbic acid and sodium citrate), sugars (such as dextrose, mannitol), amino acids (even though they may be synthesised rather than being extracted and refined)
- simple, unrefined extracts from plant materials.

Although a DMF is not required for these psychoactive substances, evidence needs to be submitted by the manufacturer that the substance is obtained from a reliable source and consistently complies with the applicable pharmacopoeial or non-pharmacopoeial specifications (in these cases the information listed as being required for a psychoactive substance (bullet

points under section 2.1.1(b)) must be provided). Any non-pharmacopoeial specifications need to be assessed to determine their appropriateness and adequacy to ensure the quality of the substance.

Format for a DMF

DMFs compiled using the European or US format are acceptable. If a DMF has already been assessed and approved by an overseas regulatory authority, and the evaluation report is available to the manufacturer, a copy of the full report should be forwarded with the DMF to the Authority.

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

Certificate of suitability

Where a psychoactive substance is described in the *European Pharmacopoeia*, the manufacturer may submit the DMF (or equivalent documentation) to the European Pharmacopoeial Commission for assessment and issue of a certificate of suitability. This certificate confirms that the purity of the substance, as produced by the manufacturer, is suitably controlled by the monograph in the *European Pharmacopoeia*. 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 at: www.pheur.org

Where a certificate of suitability is submitted in lieu of a DMF, the sponsor must also provide a written assurance that any conditions attached to the certificate of suitability 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 of psychoactive substance used in product intended for the New Zealand market.

The European Pharmacopoeial Commission also assesses and issues certificates of suitability for substances or excipients in pharmaceutical products confirming that they comply with European Pharmacopoeial requirements for minimising the risk of transmission of animal spongiform encephalopathies. The Authority accepts these.

Where a certificate of suitability is submitted in lieu of a DMF, the manufacturer must ensure that the certificate of suitability is submitted with the written permission of the manufacturer of the bulk psychoactive substance to be used in manufacture of the psychoactive product for the New Zealand market.

This agreement between the parties must be confirmed to the OPSRA by means of a formal 'letter of access' from the psychoactive substance manufacturer, addressed to the OPSRA and clearly indicating the psychoactive product manufacturer and the psychoactive products to which it applies. The letter of access should also confirm that the psychoactive substance manufacturer will, if requested, supply direct to the OPSRA data relating to the manufacture, quality control and stability of the psychoactive substance concerned.

Guidelines

The guidelines below should be referred to for more information on DMFs:

- EU Medicines Agency Committee of Human Medicinal Products: Guideline on Active Substance Master File Procedure.
- US Food and Drug Administration: Guideline for Drug Master Files (DMF).
- Australian Therapeutic Goods Administration: Guidance 11: Drug Master Files and Certificates of Suitability of a Monograph of the European Pharmacopoeia for Drug Substances.

Appendix 11: International guidelines

The following international guidelines are recommended references for developing the information that will be required for compliance with the Code. These should be viewed as quality standards that set out the Authority's expectations for the manufacture of psychoactive products. A summary of the key points of some of the more technical guidelines has been included. Further information and resources on the detail of the ICH guidelines referenced can be found on the ICH website (www.ich.org).

Establishing specifications and test procedures

ICH – Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf

Summary

This guideline aims to help establish a single set of global specifications for substances and products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for substances of synthetic chemical origin.

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 substances or products should conform to be considered acceptable for its intended use. 'Conformance to specifications' means that the substance and/or 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.

Specifications are one part of a total control strategy for the substance and product, and are designed to ensure product quality and consistency. Other parts of this control strategy include product characterisation during development, and it is on this development that specifications can be based, plus the adherence to good manufacturing practices (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 substance and product rather than to establish full characterisation, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the substance and product.

Validation of analytical procedures

ICH – Q2(R1): Validation of Analytical Procedures: Text and Methodology

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

Summary

This document discusses the characteristics to consider during the validation of analytical procedures. The objective of validating an analytical procedure is to show that it is suitable for its intended purpose.

Types of analytical procedures to be validated

The four most common types of analytical procedures requiring validation are:

- identification tests
- quantitative tests for the content of impurities
- limit tests for the control of impurities
- quantitative tests of the active moiety in samples of a substance
- the product or other selected component(s).

Impurities

ICH – Q3A(R2): Impurities in New Drug Substances

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf

Summary

This document aims to provide guidance on the identification and qualification of impurities in substances produced by chemical syntheses. Impurities in substances are addressed from two perspectives:

- chemistry, including the classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures
- safety, including specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a substance used in safety and clinical studies.

Classification of impurities

Impurities can be classified into the following categories:

- organic impurities (process- and drug-related)
- inorganic impurities
- residual solvents.

Organic impurities can arise during the manufacturing process and/or storage of the substances. They can be identified or unidentified, volatile or non-volatile, and include:

- starting materials
- by-products
- intermediates
- degradation products
- reagents, ligands and catalysts.

Inorganic impurities can result from the manufacturing process. They are normally known and identified, and include:

- reagents, ligands and catalysts
- heavy metals or other residual metals
- inorganic salts
- other materials (eg, filter aids, charcoal).

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of substances. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH guideline Q3C(R5) for additional guidance).

Excluded from the guidance are:

- extraneous contaminants that should not occur in substances and are more appropriately addressed as GMP issues
- polymorphic forms
- enantiomeric impurities.

ICH – Q3B(R2): Impurities in New Drug Products

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf

Summary

This document provides guidance on the identification and qualification of impurities in products produced from chemically synthesised substances. The guideline complements the ICH guideline Q3A(R2), which should be consulted for basic principles. The ICH guideline Q3C(R5) should also be consulted, if appropriate.

The guideline addresses only those impurities in products that can be classified as either:

- degradation products of the substance, or
- the reaction products from interaction of the excipient and/or the container closure with the substance.

Generally, impurities present in the substance need not be monitored or specified in the product unless they are also degradation products (see ICH guideline Q6A for additional guidance).

Impurities arising from excipients present in the products or extracted or leached from the container closure system are not covered by this guideline. Excluded from this document are:

- extraneous contaminants that should not occur in products and are more appropriately addressed as GMP issues
- polymorphic forms
- enantiomeric impurities.

ICH – Q3C(R5): Impurities: Guideline for Residual Solvents

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Step4/Q3C_R5_Step4.pdf

Summary

This guideline recommends acceptable amounts for residual solvents. It also recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of substances or excipients, or in the preparation of products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a 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. Because there is no benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices or other quality-based requirements. Products should contain no higher levels of residual solvents than can be supported by safety data.

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.

Stability testing

ICH – Q1A(R2): Stability Testing of New Drug Substances and Products

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2__Guideline.pdf

The guideline addresses the information to be submitted to confirm the stability of substances. Stability testing aims to provide evidence of how the quality of a substance or 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 substance, or a shelf life for the product and recommended storage conditions. This guideline sets out the principles for designing stability trials, and the storage temperatures and other factors that should be considered in establishing the stability of psychoactive substances and products.

ICH – Q1B: Stability testing: Photostability Testing of New Drug Substances and Products

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1B/Step4/Q1B_Guideline.pdf

The guideline primarily addresses the generation of photostability information for determining shelf life and for stress testing substances and products. A systematic approach to photostability testing is recommended covering, as appropriate, studies such as:

- tests on the substance
- tests on the exposed product outside of the immediate pack~

and, if necessary:

- tests on the product in the immediate pack

and, if necessary:

- tests on the product in the marketing pack.

ICH – Q1C: Stability Testing for New Dosage Forms

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1C/Step4/Q1C_Guideline.pdf

This document is an annex to the other stability guidelines and addresses the recommendations on what should be submitted regarding the stability of new substances.

ICH – Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1D/Step4/Q1D_Guideline.pdf

This guideline is intended to address recommendations for the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH guideline Q1A(R2). The guideline notes that the use of matrixing and bracketing can be applied, if justified, to the testing of substances and products. The document provides guidance on bracketing and matrixing study designs, and specific principles are defined for those situations in which bracketing or matrixing can be applied.

ICH – Q1E: Evaluation for Stability Data

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1E/Step4/Q1E_Guideline.pdf

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

ICH – Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

Summary

This document is intended to provide GMP guidance for the manufacturing of substances under an appropriate system for managing quality. It is also intended to help ensure that substances meet the requirements for quality and purity that they claim or are represented to possess.

In this guideline, 'manufacturing' includes all operations involving the receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of substances and the related controls.

Other references

ICH – Q8(R2): Pharmaceutical Development

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

Summary

This guideline provides an interpretation of the application of scientific approaches and quality risk management (for a definition, see ICH guideline Q9) to the development of a product and its manufacturing process.

ICH – Q9: Quality Risk Management

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

Summary

This guideline offers a systematic approach to quality risk management. 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 regarding the quality of substances and products across the product lifecycle.

ICH – Q10: Pharmaceutical Quality System

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

Summary

This document describes a model for an effective *quality* management system, referred to as the 'Pharmaceutical Quality System'. The guideline describes a comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable GMP regulations, and it complements ICH guideline Q8 and ICH guideline Q9.

ICH guideline Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product life cycle, and is applicable to the manufacture of psychoactive substances and products. Much of the content of ICH guideline Q10 applicable to manufacturing sites is currently specified by regional GMP requirements.

ICH – Q11: Development and Manufacture of Drug Substances

www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11_Step_4.pdf

Summary

This guideline describes approaches to developing and understanding the manufacturing process of substances. It addresses aspects of development and manufacture, including the presence of steps designed to reduce impurities. In addition, ICH guideline Q11 provides further clarification of the principles and concepts described in ICH guidelines Q8, Q9 and Q10 as they pertain to the development and manufacture of substances.

A manufacturer can choose to follow different approaches in developing a substance. In this guideline, the terms 'traditional' and 'enhanced' are used to differentiate two possible approaches. In a traditional approach, set points and operating ranges for process parameters are defined, and the substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that have an impact on critical quality attributes, and to develop appropriate control strategies applicable over the life cycle of the substance, which may include the establishment of design space(s).