Draft Code of Manufacturing Practice Guidelines

Natural Health Products

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# Risk

## Introduction

Risk is a measure of the probability of an event happening, and the magnitude of adverse consequence if that event happens. Thus, an event of low probability but great consequence would be regarded as being a higher risk than a similar event with little adverse consequence. At the other end of the scale, an event of high probability but minor consequence would be regarded as low risk.

A number of factors affect the level of risk at a manufacturing facility, including:

* sources of ingredients (which in turn affects such things as the complexity of the formulation and what combination of ingredients are in it)
* dose form
* the way the product is intended to be taken and used (its route of administration),
* any manufacturing issues, such as:
* the experience of the manufacturer
* the types and range of products they make
* the scale of operations
* scale of distribution
* whether the manufacturer is making other products in addition to natural health products (NHPs).

Figure 1: Risk assessment factors



The risk-based Code of Manufacturing Practice (the Code) is based on the Act’s principle of proportionality: in other words, the controls on the manufacture of NHPs should be proportionate to the risks of their use. The requirements that all manufacturers must achieve are stipulated as outcomes, that is ‘what must be achieved’, and are highlighted in text boxes in the Code. Sections of the Code provide guidance on best practice for ‘how the outcome can be achieved’. Whether a particular best practice applies is dependent on the individual manufacturing circumstances and the nature of the NHP. The Code allows for appropriate standards to be applied to different manufacturing operations, proportionate to the risks to be managed.

## Risk assessment matrix

To provide guidance in applying the Code, a risk assessment matrix has been constructed (see Table 1 below).

The matrix is intended to provide product notifiers and manufacturers with an idea of the types of risks their manufacturing operations present, and to provide the Authority with guidance on what types of operations (and risks) may necessitate an audit of facilities.

The matrix lists a number of key risks identified as being associated with NHPs. The risks are split into broad risk factor groupings, dependent on the risks associated with the ingredients, dose form, route of administration, and production/manufacturing issues.

Table 1: Risk assessment matrix

| **A Ingredients** |
| --- |
| **Attribute** | **Level 1 (low risk)** | **Level 2 (medium risk)** | **Level 3 (higher risk)** |
| Ingredient suppliers | Locally sourced ingredients. Either grown or made by the NZ-based manufacturer (excludes animal material).Low risk of contamination, substitution or adulteration. | Sourced overseas.Can supply evidence of GMP certification from another regulator.Suppliers are well-established international manufacturers with known internal QA systems, and ingredients are consistently supplied with good documentation. | Sourced from overseas, less known about suppliers, but ingredients are still supplied with good documentation. |
| Identification*\* Particularly relevant to plant materials* | Easily distinguished ingredients, and no effectiveness or toxicity issues exist between similar ingredients. | Some ingredients may be difficult to identify from other similar ingredients.Mistaken identity may present effectiveness or toxicity issues. | Difficult to distinguish between similar ingredients with differing effectiveness or toxicity profiles. |
| Toxicity | Non-toxic, at highest daily or individual doses. | Potential toxicity if highest daily or individual doses exceeded. | Toxic at higher concentrations or if scheduled as a medicine at higher concentrations (eg, vitamin D) |
| Pharmacological activity | Has an identified low level of pharmacological activity.Dose variability will not lead to clinical issues. | *\* Determine risk at this level based on different factors* | Has known dose-related pharmacological activity. |
| Allergenic potential | No ingredients with known allergenic potential. | Uses allergenic ingredients, but segregation practices not required (eg, all products contain the same ingredients). | Contains an allergen or sensitising ingredient in some products, and strict segregation practices are required (for instance, bee and honey products, those derived from milk, egg, fish or nut products). |
| Interaction | Ingredient not known to interact with other ingredients. | *\* Determine risk at this level based on different factors* | Ingredient known to interact with other ingredients or manufacturing equipment (eg, St John’s wort, echinacea, or are corrosive, oxidative or reductive).Manufacturing process will need to account for interactions. |
| Microbial risk | Processed material with low bioburden. | Mineral, or partially processed ingredients with low to medium levels of bioburden. | Unprocessed biological materials with high bioburden (eg, plant or animal material). |
| Source | Chemical or mineral material. | Plant material. | Animal, bacterial or fungal material. |

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| **B Dose form** |
| **Attribute** | **Level 1** | **Level 2** | **Level 3** |
| Dose form – type | Topical – for use on unbroken skin.Aromatherapy products. | Topical – use on broken skin, topical (with a potential for systemic absorption).Suppositories and pessaries. | InhaledAural (ear)NasalOral – liquidOral – solid dose |
| Microbial risk | Topical – unbroken skin. | Oral – liquidOral – solid dose | AuralInhaled  |
| Complexity of dose form | Simple mixture of less than 2 or 3 materials in a single phase – eg, powders, granules, capsules, tablets, solutions, sprays/aerosols/vapours, pastes, plant or animal parts or extracts, creams, liniments, ointments, balms. | Multi-component or multi-phase formulations.Multi-active ingredient (4 or more) formulation or mixture in a single phase – eg, powders, granules, capsules, tablets, solutions, sprays/aerosols, pastes, creams, liniments, ointments, balm.Multi-phase formulation – eg, multi-layer or multiple compression tablets, buccal or sublingual tablets, gels, lotions, suspensions, dispersions, topical jellies. | Controlled release – time / location – dependentComplex dose forms – eg, microspheres, transdermal and other patch systems, metered or microdose delivery systems, controlled or modified release dose forms with high risk of performance failure if not manufactured correctly. |
| Dose accuracy / repeatability | Dose accuracy and/or repeatability not important. | Dose accuracy and/or repeatability important. | Micro-dose manufacture. |
| Route of administration | Topical – for use on unbroken skin. | Topical – for use on broken skin, topical (with a potential for systemic absorption).Suppositories and pessaries. | InhaledAural (ear)Oral |

|  |
| --- |
| **C Route of administration** |
| **Attribute** | **Level 1** | **Level 2** | **Level 3** |
| Route of administration | Topical – for use on unbroken skin. | Topical – use on broken skin, topical (with a potential for systemic absorption).Suppositories and pessaries. | InhaledAural (ear)Oral |

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| --- |
| **D Manufacture** |
| **Attribute** | **Level 1** | **Level 2** | **Level 3** |
| Manufacturing complexity | Simple mixing and filling process (1 to 3 steps involved).A mostly manual process with ability to perform mostly visual in-process checks. | Single step or limited number of steps (1 to 5 steps) process. Complex equipment that may involve some semi-automated steps.In-process checks more complex. | Multi-step process (over 5 steps), using complex and automated equipment.In-process checks more complex, and include some automation (eg, in-line filling). |
| Manufacturing volume | Small scale of manufacture (eg, < 3,000 units, and between 10 and 20 batches produced per year). | Medium scale of manufacture (eg, 3,000 to 10,000 units, and over 20 batches produced per year). | High volume of manufacture (eg, > 10,000 units, and over 20 batches per year). |
| Manufacturing range | Low number or single product and/or dose form.Facility dedicated to NHP products. | ‘Medium’ range of similar products and/or dose forms.Multi-purpose facility (NHP and non-NHP, and may include a range of dose forms). Segregation practices in place. | High range of different types of products and dose forms, including products that need strict segregation practices in place.Multi-purpose facility (NHP and non-NHP, and may include a range of dose forms). |

## Identifying risk level

The approximate risk level of a manufacturing facility can be determined using the risk assessment matrix, plus any other factors and attributes applicable to the particular product or manufacturing facility (see Figure 2).

If the assessment of risk results in some attributes being at a different level to others (for example, most level 1 but some level 2 or 3), then the higher risk assessment will predominate (so the overall risk will be level 3) unless the product notifier or manufacturer can develop policies or procedures that would safely mitigate the risk identified. The justification would need to be detailed in depth within the documentation held by the manufacturer, and be supported by qualified processes and procedures. A manufacturer would review their facilities against the risk assessment matrix, and confirm their assessment with the Natural Health Products Regulatory Authority (the Authority) when seeking a licence.

Once an overall risk level determination has been made, this should be used as the basis for determining t what best practice measures are necessary to achieve the required outcomes of the Code. It may be helpful to manufacturers to formally document the risk assessment decision as part of the compliance documentation developed, and keep risk registers and risk management plans as part of their risk management processes.

Figure 2: Identification of risk level based on use of the risk assessment matrix



Product notifiers and manufacturers should undertake a risk assessment exercise using the risk assessment matrix as a guide to some of the commonly identified risks associated with NHPs. Once manufacturers understand where their product fits into the risk assessment matrix, they can develop documentation to meet the requirements of the Code (as outlined in section 3).

## Application of the risk assessment matrix

### Lower risk example

A manufacturer makes a small range of products for use on unbroken skin for a general health benefit. The product contains herbal ingredients, regarded as non-toxic, which are grown by the manufacturer in New Zealand. The formulations are not complex, are easily manufactured, and sales volumes are low.

In this example the risk analysis results in the following.

* Control of suppliers can be less rigorous than if the herbs were supplied by another grower, or if the suppliers were located overseas.
* Manufacturing documentation need not be complicated.
* Testing of the finished product is likely to be simple (eg, not requiring analytical testing).

### Medium risk example

A manufacturer makes a range of skin creams and decides to also manufacture a tablet. The creams contain herbal ingredients, regarded as non-toxic, which are grown by the manufacturer in New Zealand. The formulations are not complex, are easily manufactured, and sales volumes are low. The tablet contains herbal ingredients grown by the manufacturer and vitamins purchased from overseas via a local agent. Sales volumes for the tablet are projected to be low initially.

In this example the risk analysis results in the following.

* Control of the herbal materials can be less rigorous than if the herbs were supplied by another grower, or if the suppliers were located overseas.
* Particular attention is required with respect to overseas supplier validation and approval, and testing of ingredients used in the manufacture of the tablet.
* Manufacturing documentation need not be complicated for the creams, but should be appropriately comprehensive for the tablet dose form.
* Segregation of materials, production and storage areas would be required.
* Testing of the finished products is likely to be simple for the creams and require more extensive analytical testing for the tablet.

### Higher risk example

A manufacturer makes a product for application to the ear. The ingredients are imported herbal ingredients that can be easily confused with other (toxic) materials. The dose accuracy is important to avoid adverse effects or to ensure intended action. Complex manufacturing process and controls are required to preserve the active ingredient and it is made on a multi-product site where allergenic and sensitising substances are also handled.

In this example the risk analysis results in the following.

* Particular attention is required with respect to supplier approval and testing of ingredients.
* Possible microbial contamination issues need to be addressed with respect to ingredients and the process.
* Manufacturing arrangements must be described in detail and closely controlled.
* Cross-contamination potential must be addressed.

# Case studies

## Introduction

Included below are five case study examples to assist with application of the Code. Each case study describes a scenario and its key product and manufacturing attributes, and a summary of some of the key considerations of application of the Code. In essence, the higher the risk level of the product or manufacturing process, the greater the extent of detail required in compliance with the Code.

## Case study 1

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| --- |
| A Nelson lavender farmer grows lavender and produces her own hand cream to sell locally at the weekend farmers’ market. The hand cream is the only item produced and all of the lavender used in the cream is grown by the farmer. Approximately 15 units of the cream are sold each week. |
| **Risk level 1**All attributes indicate the lowest risk on the spectrum – topical cream for unbroken skin, low quantities produced, is the only product produced, and certainty of source ingredient. As the manufacturer is very small and is producing a low-risk, low-volume product, the systems required of a larger manufacturer would not generally be applicable. |
| **Key examples of Code interpretation** |
| **Personnel*** **Key personnel –** With only a single person involved in manufacture, full separation of roles for quality and production is not possible, as would normally be expected for a larger or higher risk NHP manufacturer. Based on the low volumes produced and relatively low risk of the product, the situation may be able to be accepted by the auditor. Acceptance could be based on evidence that the manufacturer has taken particular care to protect herself from conflicts of interest that may arise if production/sales priorities conflict with quality responsibilities. This could include having clearly defined responsibilities for quality activities in the documentation system with records of the actions taken, coupled with periodic audits of the operation to confirm the quality responsibilities were being properly executed.
* **Personal hygiene –**Although the product is relatively low risk, a basic clothing change would be required to minimise the potential for the cream to be contaminated by the general farm environment. For example, using specific overalls or lab coats in the manufacturing area, change of footwear, wearing gloves when handling the product.
* **Training –** A formal training system would not be required for a single person operation; however, the farmer would still be expected to demonstrate she had appropriate experience and knowledge relevant to the manufacture of the NHP, including knowledge of the Code. The farmer should keep records of any training she has done.
 |
| **Premises and equipment*** **Premises** – The premises may be very small for the scale of the operation. The manufacturing area may potentially be used for other purposes when creams are not being manufactured. Procedures and records of the steps taken to clear the area of equipment or materials not related to the NHP and to ensure it was clean prior to starting manufacture should be available.
* **Equipment –** This should be dedicated to manufacture of the cream to minimise the potential for contamination with other materials used on the farm. As the equipment would likely be small scale and manual, there would only need to be limited qualification of it based on an assessment of risks to the product. Equipment qualification would likely be focused on ensuring the equipment is constructed to an appropriate ‘sanitary’ standard to enable easy cleaning, and ensuring any measuring instruments are appropriately calibrated.
* **Cleaning** – As only one simple product is manufactured with dedicated equipment, the risks of cross-contamination with other products would be low. Cleaning procedures would be focused on ensuring equipment is visually clean. Basic disinfection and ensuring equipment is dry after use would be expected to minimise the potential for microbial contamination of the cream.
 |
| **Production*** As the key starting material is produced by the farmer, who would be expected to have full control and knowledge of the material, supplier approval processes would not be applicable. Other ingredients in the cream should be obtained from reputable suppliers, with evidence they meet relevant specifications. Some sampling and testing may be warranted depending on the farmer’s risk assessment of the potential for poor quality ingredients affecting the final cream.
* Water used to prepare the cream should not be a source of microbial contamination (may be an issue if drawn from a bore).
* Control of status (approved/quarantine) could be very basic. It may be possible for the farmer to justify a system where status is managed by time rather than by labelling or segregation, so all the lavender for a batch of hand cream is brought into the facility, checked, released and then used (or discarded) so that at no time would there be a mix of quarantined and approved materials present.
* Validation of the process would likely be restricted to confirming appropriate mixing of ingredients occurred to ensure the final product is homogenous.
* A system to assign unique identifiers (batch numbers) would be needed for traceability.
 |
| **Quality control*** The lavender starting material is grown by the farmer and is unlikely to be mixed up with other plants or be contaminated by pesticides. Therefore very basic quality checks of the lavender would be required to ensure it has an appropriate appearance and does not carry any gross contamination through the harvesting and drying processes.
* Finished product testing requirements would be minimised. These would likely include organoleptic checks that the appearance and odour of the product are acceptable.
* If the product is subject to microbial spoilage, a microbiological test should be undertaken.
* Use of experience and/or stability information on similar products may be possible in lieu of formal stability studies for this low-risk, low-volume product.
 |
| **Documentation*** Detailed procedures would not be expected for a single person operation. A basic quality manual that outlines the approach for addressing key elements of the Code and/or checklists that combine instructions with records of completed activities may be alternatives.
* A site master file and annual product quality reviews would not be expected.
* Ensuring good records of the manufacturing process are made and retained would remain important to provide traceability of the manufacturing activities.
 |

## Case study 2

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| A small manufacturer employing 12 people makes capsules of echinacea powdered extract. The New Zealand manufacturer is using extract powder from an overseas supplier and encapsulating it, then packing and labelling the final product. The product is sold at health shops in the Waikato, and the company hopes to expand distribution throughout New Zealand. |
| **Risk level 2**The higher risk attributes for this product are the source of the raw materials and the identification of the raw materials. Overseas sources can present a higher risk as there may be little information available regarding how the raw materials are made or the quality standards of supplier. Identification of the powder as echinacea extract can be difficult as many powders have similar properties. |
| **Key examples of Code interpretation** |
| **Personnel*** **Key personnel** **–** There should be clear separation between the quality and production roles, and documentation, such as position descriptions, to define the key production and quality responsibilities. It may be possible for the quality assurance person to be part time in this small organisation.
* **Personal hygiene –** A basic clothing change would be required to minimise the potential for the product to become contaminated.
* **Training –** A formal training system would be required to demonstrate that the personnel are competent in the key critical steps such as approving and releasing raw materials.
 |
| **Production*** As the key raw material is sourced from another company, supplier approval is very important. It is not possible to test for all possible contaminants in the powder, so it is important that the manufacturer is confident that the standard of the powder supplied is suitable for their product. A thorough evaluation of the supplier is needed and should include consideration of the controls to ensure the echinacea powder is not contaminated with pesticides that may have been used during cultivation.
* The manufacturer should have detailed specifications for the raw materials. Sampling and testing of the raw materials should be completed and the results of the testing compared to the specifications. There should be procedures in place to reject raw materials that do not meet the specifications.
* Control and status would be important to segregate unapproved raw materials from approved raw materials in order to avoid mix-ups.
* The process is relatively simple so validation would not be extensive, for instance, ensuring the encapsulation process produces well-sealed capsules of correct weight.
 |
| **Quality control*** Raw material testing is very important. Testing should be completed using validated test methods.
* Finished product testing requirements could be simple, as the product only has a single raw material, and the focus is on testing the raw material on receipt.
 |

## Case study 3

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| --- |
| A manufacturer is producing and selling gripe water. Gripe water is produced for [infants](http://en.wikipedia.org/wiki/Infant) with [colic](http://en.wikipedia.org/wiki/Baby_colic), [gastrointestinal](http://en.wikipedia.org/wiki/Gastrointestinal) discomfort, [teething](http://en.wikipedia.org/wiki/Teething) pain, [reflux](http://en.wikipedia.org/wiki/Reflux) and other minor stomach ailments. It is ingested and generally contains herbs (such as dill and fennel) as well as bicarbonate of soda and water. |
| **Risk level 2**Gripe water can be a fairly straightforward and potentially a low-risk product, but is an oral product marketed for babies. |
| **Key examples of Code interpretation** |
| **Personnel*** A formal training system would be required with records to demonstrate that the personnel are competent in the key critical steps and understand the importance of hygienic production practices to prevent product contamination.
 |
| **Premises and equipment*** **Premises –** The standard of the premises must ensure that the integrity of the product is maintained. It is important that the production is protected from the outside environment and that there is a functional pest control system in place. Cleaning of the premises has to be sufficient to ensure the product is not at risk of contamination. There should be procedures in place to ensure that the areas are clean and free of materials from other processing activities before a batch of gripe water is made.
* **Equipment –** Equipment should be dedicated or adequate cleaning procedures should be in place to ensure it is suitable before use. The effectiveness of the cleaning procedure should be verified periodically by appropriate testing such as microbial swabbing.
 |
| **Production*** The manufacturer should have detailed specifications for the raw materials (including the water) used in the product. The raw materials should be sampled and tested, and the results of the testing compared to the specifications. There should be procedures in place to reject raw materials that do not meet specification.
* Control and status would be important to segregate unapproved raw materials from approved raw materials and to avoid mix-ups.
 |
| **Quality control*** Raw material testing should be completed to established specifications.
* Testing should confirm that the final product has been adequately formulated with the correct amount of bicarbonate of soda, is homogeneous, and is of a suitable microbiological quality for administration to infants.
 |

## Case study 4

|  |
| --- |
| Production of probiotic capsules with an enteric coating. The manufacturer is completing all processing, from growing the cultures through to encapsulating. The manufacturer makes a range of similar probiotic products that are sold throughout New Zealand and is looking to enter the export market. |
| **Risk level 3**The higher risk attribute of this product is the multi-step processing using live micro-organisms. |
| **Key examples of Code interpretation** |
| **Personnel*** A formal training system would be required with records to demonstrate that the personnel are competent in the processing procedures.
* A high level of protective equipment would be expected due to the handling of microorganisms.
 |
| **Documentation*** The processing of this product is complex and there should be detailed procedures in place.
* Records should be kept of all processing steps and key decision points.
* Detailed specifications for raw materials, in process materials and final products would be expected.
 |
| **Premises and equipment*** The facilities used should be designed to prevent cross-contamination between the different micro-organisms used in the manufacture of different products. This could be achieved using dedicated facilities or by implementing validated cleaning procedures between campaigns of different products.
* Higher standards of air quality are likely to be required that would need air handling systems to be in place to provide filtered air to the facility.
 |
| **Production*** This more complex process would require in-process testing at critical stages to monitor the process.
* Validation of key processing equipment would be expected.
 |
| **Stability*** The expiry dates applied to products should be based on information gathered by stability studies.
 |
| **Quality control*** Comprehensive testing of the final product would be required. This testing would include:
* confirmation of the probiotic strain
* capsule disintegration
* identifying any contaminating organisms
* evidence to prove that specifications are met, for example ‘the capsule contains at least 2 billion probiotic organisms’.
 |

## Case study 5

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| Tablets manufactured using a complex mixture of various minerals and herbs as well as vitamin D. The tablet is produced by a large manufacturing company that produces a broad range of supplements and sports nutrition products, exported around the world. |
| **Risk level 3**Features of this case study place it at the high-risk end of the risk matrix. Raw materials are sourced from various suppliers. The potential toxicity of vitamin D at high volumes poses serious consequences if the wrong dosage is consumed. Other factors are the cross-contamination risk of multiple products manufactured and the high number of consumers due to the size of the manufacturer.  |
| **Key examples of Code interpretation** |
| **Personnel*** A formal training system would be required with records to demonstrate that the personnel are competent in the processing procedures.
 |
| **Documentation*** There should be established, detailed procedures for all activities; no dispensations are likely to be relevant.
 |
| **Production*** The key raw materials are imported via a series of brokers and traders. Supplier validation is thus very important so the source of the materials is understood by the manufacturer and to confirm that suppliers have robust systems in place to ensure raw materials are not contaminated during their cultivation and processing.
* The manufacturer should have detailed specifications for the raw materials. Sampling and testing of the raw materials should be completed and the results of the testing compared to the specifications.
* Manufacturing processes should be fully defined with detailed records and instructions on undertaking each process.
* There are multiple products made on this site, so there should be detailed cleaning procedures in place for the equipment. The effectiveness of these cleaning procedures should be verifiable.
* Validation of key processing steps such as product blending would be expected.
 |
| **Quality control*** Raw material testing is very important. Testing should be completed using validated test methods.
* This product has dosage claims, so the manufacturer should be able to demonstrate that the ingredients are present in the levels as listed on the label.
 |
| **Stability*** Stability studies should be conducted to demonstrate that the product remains within specification for the length of its shelf life.
 |
| **Recall*** The manufacturer should have systems in place to enable the recall of products from all of its markets. There should be a comprehensive recall procedure that is regularly tested through the use of mock recall.
 |

# Audit of manufacturing facility

## Introduction

Section 31 of the Act provides for the Authority 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. The Authority can also recognise an audit of the manufacturing facility conducted by another person under another enactment or for another purpose.

The nature and extent of auditing will depend on:

* the level of risk that a manufacturing facility presents
* compliance with requirements of the Code and manufacture licence conditions
* whether the product is the subject of any complaints.

## Frequency of audit

The Authority will use the risk assessment matrix to determine a frequency of audit according to their different levels of risk. A manufacturing facility that presents a very low level of risk may not require an audit, although the manufacturer will still have to meet the requirements of the Code. A low-risk manufacturer may need to be audited only once every five years, while, a higher-risk manufacturer might need a detailed audit every two years. Table 2 lists factors that have the potential to pose a ‘higher level of risk’. If the nature of manufacturing operations changes to shift the facility from low-risk to a medium or a higher level, the audit frequency may change accordingly.

Table 2: Potential factors that pose a higher level of risk that might require a more frequent rate of audit

| **Ingredients** | **Factors** |
| --- | --- |
| Ingredient suppliers | Sourced from overseasLess known about suppliers, but ingredients are still supplied with good documentation |
| Identification*(particularly relevant to plant materials)* | Difficult to distinguish between similar ingredients with differing efficacy or toxicity profiles. |
| Toxicity | Toxic at higher concentrations or if scheduled as a medicine at higher concentrations (such as vitamin D) |
| Pharmacological activity | Has known dose-related pharmacological activity |
| Allergenic or sensitising potential | Contains an allergen or sensitising ingredient in some products, and strict segregation practices are required (for instance, bee and honey products, those derived from milk, egg, fish or nut products) |
| Interaction | Ingredients known to interact with other ingredients or manufacturing equipment (such as St John’s wort, echinacea, or are corrosive, oxidative or reductive)Manufacturing process will need to account for interactions |
| Microbial risk | Unprocessed biological materials with high bio-burden (such as plant or animal material) |
| Source | Animal, bacterial or fungal material |
| **Dose form** |  |
| Dose form – type | InhaledAural (ear)NasalOral (liquid)Oral (solid dose) |
| Microbial risk | Aural (ear)Inhaled  |
|  | Complex dose forms, such as microspheres, transdermal and other patch systems, metered or micro-dose delivery systems  |
| Dose accuracy / repeatability | Micro-dose manufacturing (eg, vitamin D, selenium supplementation) |
| **Route of administration** |  |
| Route of administration | InhaledAural (ear)Oral |
| **Manufacture** |  |
| Manufacturing complexity | Multi-step process (over 5 steps), using complex and automated equipmentIn-process checks more complex, and include some automation (such as in-line filling) |
| Manufacturing volume | High volume of manufacture (eg, > 10,000 units, and over 20 batches per year) |
| Manufacturing range | High range of different types of products and dose forms, including products that need strict segregation practicesMulti-purpose facility (NHP and non-NHP, and may include a range of dose forms) |

## Exemption from audit

Small-scale manufacturers of very low-risk products can apply to be exempt from audit.

## Exemption from requirement to have a manufacturing licence

A manufacturing licence is not required if the manufacturer is making a product (or products) for a person to use for their own treatment after a consultation or on behalf of someone. This exemption is intended for natural health practitioners who may manufacture an NHP for a patient. It also applies if the practitioner uses another practitioner to manufacture the product for them.

In all other instances, including manufacturing by a natural health practitioner for commercial sale, a manufacturing licence is required.

## Licence granted by a recognised authority

A manufacturing facility in which NHPs are manufactured under a licence granted by a recognised authority is deemed to be compliant with the Code unless the Authority has reasonable grounds to believe otherwise. If there is evidence of any non-compliance with regulatory requirements, such as breaches of the Act, licence conditions or the Code, or the Authority has received complaints about a product, the Authority may require an audit of the manufacturing facility to determine the manufacturer’s level of compliance with the Code.

The Act provides for the Authority to declare a person or body to be a recognised authority if the Authority is satisfied that the person or body has the expertise to assess compliance with the Code or an equivalent code of manufacturing practice. The Authority will publish a list of recognised authorities for this purpose.

# Question and answer guidance

## Introduction

Included below are questions and answers (Q+A) to assist product notifiers and manufacturers to interpret the Code. The Q+A are intended to clarify areas of uncertainty and provide direction as to what manufacturers may need to consider, depending on the risk of their product or manufacture process. The Q+A are not intended to provide a detailed description of activities or list the requirements of the manufacturers under the Code.

Following consultation with relevant stakeholders, the Q+A will be updated and added to accordingly. It is anticipated that further areas for Q+A guidance development may result from the consultation.

## Personnel

### Do I need an organisation chart?

Not necessarily. If your operations are small and consist of one to perhaps three people, an organisation chart may not be necessary. However, if more than one person is involved, a chart listing functions and responsibilities would be useful.

## Premises and equipment

### Do I need separate rooms to store quarantined, released, rejected, returned or recalled products?

Not necessarily. The Code requires ‘orderly storage’. Materials of different status stored in the same area should be clearly separated. Ways of achieving separation may include using partitions, cages, computer inventory systems or labelling. Smaller operations may consider using a simple system of storing products of different status on different shelves of the store room.

### Can I store raw materials in the same room I use to make products?

Generally, no. In very small facilities, it may be possible if raw material storage is physically segregated in a secure area of the room to prevent mix-ups, and raw material storage does not interfere with the effective cleaning of the production area. For crude herbal materials, separate storage areas with appropriate ventilation would be required to prevent the spread of any animals and micro-organisms brought in with the material and to prevent fermentation or mould growth.

### Can I store spare manufacturing equipment in the area used to store my raw materials?

If equipment is stored in these areas, it should be clean and dry, and protected and sealed to prevent contamination risk.

### Can materials used for other types of products that I also make (such as natural cleaning products, cosmetics or food) be stored with materials for NHPs?

This might be possible depending on the nature of the other materials and if measures are taken to reduce the risk of cross-contamination between materials. These include segregating materials into clearly designated areas, ensuring containers are thoroughly cleaned and properly sealed, and not using shared sampling equipment. Pesticides, herbicides and other similar poisonous materials should not be in the same premises as NHPs, however.

### My facility is very small, so do I need to have receiving and dispatch bays?

Not if you have other ways to ensure materials are sheltered from the weather while being unloaded or loaded and awaiting checking.

### How secure do storage areas need to be?

As a minimum, security measures should prevent non-company personnel accessing storage areas. This can be achieved using standard security precautions, such as making sure doors remain closed and locked when areas are unattended. Areas used to store higher-risk materials and printed packaging may require additional restrictions such as locked cages to ensure only authorised staff have access.

### What are acceptable temperature and humidity limits for storage?

This depends on the materials being stored. The storage conditions should ensure each material remains fit for its intended purpose throughout its shelf life. Each material should be assessed to ensure the storage conditions are suitable. This assessment may be as simple as referring to the labelled storage conditions for purchased materials. If humidity does not affect the materials, then humidity limits do not need to be established for them.

### Do I need to install air conditioning in storage areas?

Yes, if materials require storage at specific conditions that can’t be achieved without air conditioning. Generally, the New Zealand climate means that most materials will not require air conditioned storage areas. If it is not practicable or economic to install air conditioning, alternative approaches could be considered such as storing materials sensitive to temperature in cooler areas of the storage area (such as nearer the ground).

### Where should thermometers or temperature probes be located?

They should be located to monitor ‘worst case’ temperatures that materials are exposed to. These are usually those places with extremes of temperature. Care needs to be taken when choosing locations in large warehouses or in areas with windows that allow them to be heated by the sun.

### Do I need to keep a record of temperatures in storage areas? If so for how long?

Yes, the record of material storage conditions is important information relevant to your product and should be retained as for other documentation. Generally, documents should be retained for the shelf life of the material plus one year. Keeping only the electronic records is acceptable as long as the principles set out in Code are followed.

### How often should I check and record the temperature in storage areas?

Checks should be performed often enough to detect any significant deviations from the acceptable storage conditions. Devices able to record the minimum and maximum conditions may be useful. Relevant factors should be considered when determining how often readings should be taken, including the criticality of storage conditions and the ability of the storage area to reliably maintain the required conditions. Once some historical data is collated and there is confidence that storage temperatures are not likely to be breached, you could consider reducing the frequency of readings.

### Do I need a separate room to sample raw materials?

Not necessarily, but you must protect the material being sampled from contamination during the sampling process and take measures to prevent cross-contamination between materials. Manufacturers may consider using a sampling booth, or a production room that is dedicated for sampling on a campaign basis, ensuring that it is thoroughly cleaned before and after sampling events.

### Do sampling areas need to be supplied with filtered air?

The risks of contamination to the material being sampled should be assessed when determining the appropriate air quality for the sampling area. This may result in the need for at least a basic level of air filtration in the sampling area or the use of sampling hoods. The need for dust extraction should also be considered if sampling very dusty materials, to manage the risk of contamination to other areas. Conversely, manufacturers using very crude raw materials in very low-risk products may be able to justify that sampling is performed without a filtered air.

## Production

### What is small-scale production?

The Authority would consider production of less than 1000 product units (such as bottles) a year to be very small scale, and 1000 to 3000 product units to be small scale.

|  |  |  |
| --- | --- | --- |
| Small scale of manufacture (< 3,000 units, and between 10–20 batches produced per year). | Medium scale of manufacture (3,000 to 10,000 units, and over 20 batches produced per year). | High volume of manufacture (> 10,000 units, and over 20 batches per year). |

### When are my operations considered to have moved from small scale to medium or large scale?

The Authority would consider production of 60,000 to 200,000 product units (such as bottles) a year to be medium scale production, and greater than 200,000 product units to be large scale.

## Quality control

### Can the quality control testing be outsourced?

Yes, in which case appropriate technical agreements should be in place with contract laboratories.

### Do contract laboratories need to have any specific accreditation or certification?

Not necessarily, but you will have to be sure that quality systems used at the laboratory are appropriate for your product. If a laboratory does not hold accreditation, you may also need to audit the laboratory.

### Do test methods need to be validated?

The minimum expectation is for the test method to be scientifically sound. All test methods need to be repeatable and accurate to ensure the information they provide can be relied on, and the suitability of the method is demonstrated with an appropriate level of method validation. The need for an NHP manufacturer to perform extensive and often expensive validation of test methods can be reduced by using methods taken from pharmacopeia that have already been validated (for instance, methods set out in the British Pharmacopoeia).

If it is not possible to use an existing validated method, the amount of validation required will depend on the method and its intended purpose. For example, a test used to confirm identity will only need to be validated to ensure it is able to distinguish between the material in question and any other materials that may be present (specificity).

For complex products that may contain a mixture of vitamins and minerals, methods are likely to require more detailed validation to ensure the final product test will give an accurate measure of the product, and may require additional parameters to be validated (such as accuracy, precision, linearity).

Using a grouping approach for similar products using the same method may also reduce the need for validation.

For quality control tests that are based on physical inspection or organoleptic test methods, traditional method validation may not be appropriate or be possible. Instead, the knowledge, training and experience of personnel performing the tests will be critical in ensuring these tests are performed accurately.

## Complaints and recalls

### Do I need to record complaints?

For reputational reasons, complaints should be logged and followed up. All complaints should be investigated for their basis, as this may point to problems with the manufacturing process, for example, foreign matter in the product.

### Do I need to inform the Authority of complaints?

Not necessarily. Simple complaints that do not affect safety may be able to be resolved easily by the manufacturer, for example about damaged packaging. Complaints affecting safety and complaints about products in the high-risk category should be advised to the Authority.

### When do I need to recall my product?

Manufacturers should recall a product if a manufacturing problem or defect changes the risk profile of the product from low risk to high risk and affects safety, and it is likely that many people will be affected. The Authority will develop more guidance on this issue.

### Do I need to inform the Authority of recalls?

Recalls are complex events and the Authority has to be assured that the reach of the recall is appropriate to the risk that the product presents. This means that the Authority must be advised as soon as possible if a situation develops in which a recall may be necessary.

## Documentation

### There are a lot of different types of documents listed. Do I need to have all of them?

It is a basic principle of GMP that activities are defined and records kept. This helps ensure operations are conducted consistently and it is possible to trace important steps in the process if there is ever a problem discovered with the product. Some documents such as site master files may not be appropriate for very small operations, technical agreements may not be required if all steps of manufacture and analysis are performed in house, and training documents may not be applicable to some simple single person operations. However, it is important for all manufacturers to have documents such as specifications, procedures and records that cover the manufacturing activities.

### Can instructions be included in the same document as the records?

Yes. This is often very effective, as long as the instructions are easy to follow and all the important information is recorded. A combined document that includes the manufacturing formula, processing instructions and batch manufacturing record is an example of how this could be implemented.

### Do I have to have hard copy (paper) procedures and records?

No, the Code allows the use of electronic documents as an alternative. If using electronic documents, controls should be implemented to ensure documents are accurate, secure and able to be retrieved.

### Are there templates available for the procedures I need to have?

At the moment the Authority does not intend to publish templates to accompany the Code; however, industry organisations may be able to provide some guidance. Procedures should be developed to reflect the operations of the organisation. Larger organisations with complex operations will likely require more detailed procedures; smaller organisations with few employees are likely to require simpler procedures.

## Contract manufacture and analysis

### How is contract manufacturing and analysis defined?

Contract manufacturing and analysis is any step in the operations contracted by another company that could impact on the product, including receipt of material, production, packaging, labelling, relabelling, quality control, storage and distribution. It also includes any quality control testing that is completed by another company.

### What needs to be included in technical agreements?

Agreements should define how the responsibilities of the Code are shared between the two organisations. A matrix of responsibilities may help to simplify the agreement. Some important areas to define in agreements would include how changes to the manufacturing process, equipment or test methods are made, when deviations from agreed processes need to be notified to the other party, and the responsibilities for product release.

### As the contract giver do I have to know how the contract acceptor is performing the work?

Yes, you need to assess that the contracted facility’s methods are adequate for your products and assess that the contract acceptor is competent to perform the work.

### How long do contract manufacturers and laboratories need to keep records?

Batch-related records should be kept for the shelf life of the product plus one year.