Premises and equipment (Chapter 3, Part I - finished dosage form)

Technical guidance on the interpretation of the PIC/S Guide to GMP

Last updated

10 December 2019

Environmental controls

Environment for sampling non-sterile starting materials

Clause 3.9 describes the physical requirements for the area being used to sample non-sterile starting materials.

In order to protect the sampled material from contamination, this sampling would be expected to be carried out in a separate room, or appropriately qualified sampling hood, that supplies air of a quality and cleanliness equivalent to that used in the manufacturing area where the material is exposed. The sampling area would also be expected to be designed with dust extraction or equivalent controls to prevent contamination of adjacent areas.

Areas for the sampling of starting materials used in non-sterile products should be filtered using air filters of at least EU7 grade or equivalent. Areas used for the sampling of non-sterile starting materials used in the manufacture of sterile products should be designed and controlled in accordance with Annex 1 requirements.

Sampling hoods may be used provided there are adequate controls in place to ensure that materials are contained. Consideration should be given to the use of appropriate extraction/de-dusting facilities, the qualification of the hood, the possibility of contaminating the sampled material and adjacent storage area and whether materials sampled are hazardous.

Sampling primary packaging materials for non-sterile products

Clause 3.9 also describes the physical requirements for the area being used to sample primary packaging material for non-sterile products. As product-contact components, primary packaging materials should be sampled within an environment that adequately protects the packaging from contamination. However, sampling of primary packaging materials in an open warehouse would not be allowed.

Air quality for non-sterile medicine manufacture

The PIC/S Guide to GMP does not reference a specific standard for air quality for non-sterile manufacturing areas. There are also no Australian or ISO standards for air quality specific to non-sterile medicine manufacture.

In all cases, it is the manufacturer's responsibility to ensure that thorough qualification, validation and monitoring processes are in place to justify heating, ventilation and air-conditioning (HVAC) design and demonstrate that the air quality is sufficient for non-sterile manufacturing areas.

Manufacturers are required to demonstrate that the manufacturing environment for non-sterile products affords appropriate protection to the products, and prevents contamination. Use a risk-based approach to determine the required air quality and associated controls, based on a thorough understanding of:

- the manufacturing processes
- the nature of the product handled
- risks of contamination and cross-contamination
- risks to product quality

Minimum expectations

As a minimum expectation:

- air quality requirements (physical and microbiological) should be defined during system design and compliance demonstrated through qualification and on-going monitoring
- air filters used in manufacturing areas where product is exposed should be at least EU7 grade or equivalent
    - higher efficiency air filters may be required for products or processes that present a contamination risk
- pressure differentials and air flows must be defined and appropriate

Additional guidance

For additional guidance in relation to recommended levels of air filtration:

- World Health Organization: Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms- external site

Cleaning and sanitisation

The PIC/S Guide to GMP contains limited detail on requirements for cleaning and sanitisation. This is because the manufacturer is responsible for demonstrating that the applied cleaning and sanitisation procedures are suitable for its intended purpose. This can be demonstrated by qualification, validation and monitoring studies. The extent of these studies will depend on the nature and types of products manufactured and the associated risks of contamination.

Premises and equipment definitions

Campaign manufacture

Clause 5.19 defines campaign manufacture as being a separation in time of production. That is, manufacturing a series of batches of the same product in sequence in a given period of time and/or maximum number of batches followed by an appropriate (validated) cleaning procedure.

Campaign manufacturing operations may be performed where the manufacturer has undertaken an appropriate risk assessment of the proposed operations, considering all potential risks to product quality, and detailed instructions regarding the management of operations and associated control measures are in place.

Clause 3.6 – meaning of 'certain'

In clause 3.6 of the PIC/S Guide to GMP, the word 'certain' (as per certain additional products, certain antibiotics, certain hormones etc.) refers to materials known to cause specific (side) effects in low doses. For example:

- 'certain antibiotics' refers to antibiotics, usually of the beta lactam group, which are known to cause allergic reactions
- 'certain hormones' refers to hormones that can have pharmacological effects if trace amounts cross-contaminate other products e.g. oestrogens and some progesterone-like hormones

Manufacturers should evaluate materials that are processed and ensure that adequate control measures are in place.

Dedicated equipment may be required for potentially allergenic or sensitising products.

Dedicated facilities are normally required where the risk associated with the material cannot be adequately controlled by operational and technical measures, or the available scientific toxicological data does not support a controllable risk.

With respect to manufacture of medicinal cannabis products, dedicated premise/equipment would be preferable to ensure security and control of the operation. However, where adequate risk control is implemented and that all related operational and technical means are scientifically justified then non dedication may be acceptable.

Further guidance may be found in:

- EMA/CHMP/CVMP/SWP/246844/2018- Questions and answers on implementation of risk based prevention of cross contamination in production (pdf,148kb)- external site

Warehouses and distribution centres

By definition, 'manufacture' includes all steps in bringing the product to its final form and 'release for supply' is considered to be the last step in this process.

From a GMP point of view, warehousing and distribution after release for supply and after the product has left the manufacturer's control, is not currently regulated by the TGA. Hence, a facility that is used only for warehousing and distribution of **fully finished and released** products does not require a TGA manufacturing licence and is not required to comply with the PIC/S guide to GMP for medicinal products.

However, for an effective recall, cooperation from wholesalers and distributors is often essential. As a wholesaler, you should have a procedure for conducting a recall at a sponsor's request. For more information, refer to:

- Uniform recall procedure for therapeutic goods

There may be state or territory regulatory requirements that are applicable, which should be checked with the relevant state or territory authority.