Guidance for Industry: Premises Design for Manufacturers of Advanced Therapy Products

Version 1.1

Pharmacy and Poisons Board

Contents

A. Introduction

This document is intended to provide guidance on the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* with respect to requirements on premises design by manufacturers of advanced therapy products.

This guidance represents the Drug Office's current thinking on this topic and should be viewed only as recommendations. It does not establish legally enforceable responsibilities, create additional requirements, form the basis for GMP inspections, place any restraint on the development of new concepts or technologies, or operate to bind the Drug Office or the public. There may be other acceptable approaches that provide an equivalent level of quality assurance.

This guidance may be amended from time to time to include additional guidance arising from the development of the regulatory and industry environment.

B. Purpose

To provide guidance to manufacturers on how to design a premises for manufacturing advanced therapy products

C. Scope

This guidance relates to requirements on the design of production, storage, quality control and ancillary areas associated with the manufacture of advanced therapy products.

D. Background

Part 7 of the Pharmacy and Poisons Regulations, Cap. 138A, Laws of Hong Kong, relates to the licensing of pharmaceutical manufacturers. Accordingly, a person must not manufacture any pharmaceutical product on any premises unless he is the holder of a licence to manufacture pharmaceutical products on those premises. This is also applicable to premises where cell, tissue and gene therapy products falling within the definition of pharmaceutical products under section 2 of the Pharmacy and Poisons Ordinance, Cap. 138 are manufactured. These products are collectively referred to as advanced therapy products ("ATPs").

The licensing authority is the Pharmacy and Poisons (Manufacturers Licensing) Committee, an Executive Committee established under the Pharmacy and Poisons Board ("Board"). Compliance with the GMP Guide issued by the Board is one of the conditions of the licence.

The *Guide to Good Manufacturing Practice for Medicinal Products* published by the Pharmaceutical Inspection Co-operation Scheme ("the GMP Guide") and adopted by the Pharmacy and Poisons Board is available on the website of the Drug Office. Depending on the types of products and processes to be handled, requirements on premises design are laid down in various sections of the GMP Guide and its Annexes. These include but are not limited to those in *Chapter 3 Premises and Equipment of Part I*; *Section 4 Building and Facilities of Part II*; *Annex 1 Manufacture of Sterile Medicinal Products*; *Premises and Equipment section in Annex 2 Manufacture of Biological Medicinal Substances and Products for Human Use*; and *Annex 13 Manufacture of Investigational Medicinal Products* where applicable. Implications on premises design are also specified in other sections, for example, *Personnel* sections in *Annex 1* and *Annex 2*. Having regard to the unique and complex nature of ATPs, specific adaptations in premises design may be necessary without prejudice to the assurance on product quality.

According to the GMP Guide, premises and the equipment therein must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim at minimizing the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination or cross-contamination of materials or products. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Measures to prevent contamination and cross-contamination appropriate to the risks identified should be in place, which may include those on premises design, organizational and technical measures. Their effectiveness should be reviewed periodically.

The majority of ATPs cannot be terminally sterilized. In such cases, the manufacturing process should be conducted aseptically. It is acknowledged that establishing a premises in accordance with GMP requirements claims a considerable amount of effort. It is therefore important to avoid errors from initial design through to its operation and maintenance for the intended use. While this guidance does not intend to address all applicable requirements in the GMP Guide, focus is given to requirements that warrant attention of manufacturers at the early stage of premises design. Given the vast diversity and rapidly evolving science and technologies in the field of ATPs, it is understood that this Guidance may not be fully applicable to all products, processes and technologies handled by any single manufacturer of ATPs. Adaptions should also be made on the basis of compliance with other applicable Laws of Hong Kong.

It should be noted that, it is a requirement of GMP that manufacturers identify what qualification or validation work is needed to prove control of the critical aspects of their particular operations. Any planned changes to the premises which may affect the quality of the product should be formally documented and the impact on the validated status or control strategy assessed. A risk management approach should be used to determine the scope and extent of qualification or validation. The principles of premises qualification can be found in *Annex 15 Qualification and Validation* of the GMP Guide.

E. Guidance

1. General

	Consideration	Requirement	
1.1	Areas arrangement	1.1.1	In general, production, storage and quality control areas should not be used as a transit area by personnel who do not work in them, for example, access to production area should not pass through quality control area. Designated personnel entrance to and/or exit from each of the areas should be available. The same principle is applicable to the transfer of materials, products, equipment and other articles in and out of the areas.
		1.1.2	The layout of the premises should permit the separation of flows of non-sterile and used materials and equipment from those sterilized. Unidirectional material flow (e.g. segregated "clean corridor" and "waste corridor"; segregated "clean pass-through box" and "dirty pass-through box") may be considered. Where this is not possible, the handling of non-sterile and used materials/equipment should be separated in time and appropriate cleaning and/or decontamination measures should be applied.
		1.1.3	In general, personnel should not pass directly from areas where there

			is exposure to live microorganisms, genetically modified organisms (GMOs), toxins or animals to areas where other products, inactivated products or different organisms are handled. 1.1.4 In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents and disinfectants where used. 1.1.5 To reduce the accumulation of dust and to facilitate the cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Door should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors should preferably open to the high-pressure side and be provided with self-closers. 1.1.6 Air handling systems should be designed, constructed, and maintained to prevent the risk of cross-contamination between different areas in the manufacturing site and may need to be dedicated for an area. Depending on specific risks of the product, the use of dedicated or single pass air systems should be considered, taking into account of the biohazard classification and containment requirements of the relevant materials, product, process and equipment. 1.1.7 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps. 1.1.8 Labels applied to premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean …). 1.1.9 Where appropriate, contingency plans for breakdowns in critical services or equipment should be developed and regularly reviewed. For examples, in the event of power failure, where necessary there should be access to a power source to allow the maintenance of critical services and equipment to permit the safe conclusion of activities in progress.
1.2	Environmental conditions	1.2.1	Lighting, temperature, humidity and ventilation should be appropriate for the activities performed and should not adversely affect the ATPs or the functioning of equipment. Acceptance limits for illumination level, temperature, humidity and other necessary environmental conditions appropriate for the materials, products, equipment/instruments and operations handled in respective storage, production and quality control areas, should be defined.
1.3	Waste handling	1.3.1	Specific measures for waste handling (e.g. contaminated rinsing water, replacement of filters in exhaust air system, soiled gowning) commensurate with the biohazardous nature of the materials should be put in place. The following measures may be adopted as appropriate: 1.3.1.1 Drainage systems must be designed so that effluents can be effectively neutralized or decontaminated to minimize the risk of cross-contamination. Specific and validated decontamination systems should be considered for effluents when infectious and/or potentially infectious materials are

		used for production. 1.3.1.2 Where the filtration of exhaust air is necessary, the safe changing of filters should be ensured or bag-in-bag-out housings should be employed. Once removed, filters should be decontaminated and properly destroyed. 1.3.1.3 Clinical and/or biohazardous waste should be segregated from other waste, staged and handled in accordance with statutory requirements and/or recommendations issued by relevant authorities or statutory bodies (e.g. Environmental Protection Department, Occupational Safety & Health Council).

2. Production Area

	Consideration	Requirement	
2.1	General	2.1.1	Consideration should be given to designing facilities that permit observation of activities from outside the clean areas, e.g. through the provision of windows or remote camera access with a complete view of the area and processes to allow observation and supervision without entry.
		2.1.2	Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
		2.1.3	For material, product, equipment and other articles transfer in and out of the areas, the use of material airlocks, double-ended sterilizers or pass-through boxes sealed into a wall, as well as other effective procedures (e.g. H_2O_2 locks) should be considered where applicable.
		2.1.4	A critical clean area is an area where the product is exposed to environmental conditions and should be designed to ensure aseptic conditions. The air classification required for the background environment should also be controlled.
		2.1.5	In general, when the aseptically manufactured product is exposed to the environment (e.g. working under laminar air flow), a critical clean area of grade A with a background clean area of grade B is required for aseptic preparation and filling.
		2.1.6	Production in a closed system, in an isolator, or positive pressure isolators in a background clean area of grade D is acceptable.
		2.1.7	Clean areas of grade A and B should not have sinks or drains installed. In other areas, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.
		2.1.8	To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. It is fundamental for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. However, negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (e.g. pathogens), they should be surrounded by a positive pressure clean zone of appropriate grade. These pressure cascades should be clearly defined and continuously monitored with appropriate methods (e.g. alarm settings). Adjacent rooms of different grades should have a pressure differential of 10-15 Pa (guidance values).
		2.1.9	A warning system should be provided to indicate failure in the air

			supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.
		2.1.10	In all manufacturing steps that may lead to unwanted formation of aerosols (e.g. centrifugation, working under vacuum, homogenization, sonication), appropriate mitigation measures should be implemented to avoid cross-contamination. Special precautions should be taken when working with infectious materials.
		2.1.11	It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk. Airflow visualization (smoke test) should be conducted to verify airflow pattern.
		2.1.12	During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same areas by the same person.
		2.1.13	Clean/contained areas should be accessed through an airlock with interlocked doors or by appropriate procedural controls to ensure that both doors are not opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
		2.1.14	Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. Manufacturers may consider including a changing room for operators to remove personal clothing and shoes, and change into designated clothing and shoes of appropriate hygiene level, before they can change into protective clothing appropriate to the cleanroom grade.
		2.1.15	Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and to minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air.
		2.1.16	The final stage of the airlock should, in the at-rest state, be the same grade as the area into which it leads. This is also applicable in the case where the room for the final stage of changing is designed as the airlock.
		2.1.17	There should not be a change of more than one grade between airlocks or passages and changing rooms, i.e. a grade D passage can lead to a grade C airlock, which leads to a grade B changing room, which leads to a grade B cleanroom.
		2.1.18	Changing rooms should be of sufficient size to allow for ease of changing.
		2.1.19	Changing rooms should be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room.
		2.1.20	The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general, hand washing facilities should be provided only in the first stage of the changing rooms.
		2.1.21	For contained areas, protective clothing should be discarded before leaving the contained area. Sufficient space and appropriate container for collection of the discarded clothing should be available at the personnel exit of the contained area.
2.2	Multi-product facility	2.2.1	Manufacture of ATPs in a multi-product facility is acceptable when appropriate risk-mitigation measures commensurate with the risks are implemented to prevent mix-ups and cross-contamination.

		2.2.2 Separation in space 2.2.2.1 Concurrent production of two different ATPs/batches in the same area is not acceptable. However, closed and contained systems may be used to separate activities. 2.2.2.2 Segregated production areas should be used for the manufacturing of ATPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. 2.2.2.3 The use of more than one closed isolator (or other closed systems) in the same room at the same time is acceptable, provided that appropriate mitigation measures are taken to avoid cross-contamination or mix-ups of materials, including separated expulsion of the exhausted air from the isolators and regular integrity checks of the isolator. 2.2.2.4 When two isolators are used to process different viral vectors within the same room there should be 100% air exhaustion from the room and the facility (i.e. no recirculation). In other cases, air filtration may be acceptable. In addition, in case of concurrent production of viral vectors, it is necessary to provide for closed, separate and unidirectional waste handling. 2.2.2.5 The possibility of using more than one biosafety cabinet in the same room is only acceptable if effective technical and organizational measures are implemented to separate the activities (e.g. strict material and personal flows defined, no crossing lines in the use of equipment in the same room etc.). It is stressed that the simultaneous use of more than one biosafety cabinet entails additional risks and, therefore, it should be demonstrated that the measures implemented are effective to avoid risks to the quality of the product and mix-ups. 2.2.2.6 It is acceptable to conduct a manufacturing activity in a clean room which hosts an incubator which is used for a different batch/product if there is separated expulsion of exhausted air from the incubator. Particular attention should be paid to prevent mix-ups. 2.2.2.7 The simultaneous incubation/storage of different batches within the same incubator is only acceptable if they are physically separated (e.g. distinct cell cultures in closed vessels). When simultaneous incubation/storage of different batches takes place as described above, the manufacturer should evaluate the possible risks and implement appropriate measures to avoid mix-ups of materials. 2.2.3 Separation in time 2.2.3.1 Where there are no separate production suites, a thorough cleaning and decontamination procedure of validated effectiveness should take place before any subsequent manufacturing in the same area can occur. 2.2.3.2 The whole manufacturing facility or a self-contained production area may be dedicated to the manufacturing of a specific product on a campaign basis followed by a cleaning process of validated effectiveness.
2.3	Special considerations for ATPs	2.3.1 Special considerations must be applied to the segregation of materials obtained from infected donors. 2.3.2 Special precautions should be taken in the case of manufacturing

	containing or consisting of infectious materials /products		activities involving infectious viral vectors (e.g. oncolytic viruses): these activities should take place in a segregated area. 2.3.3 The simultaneous incubation/storage of infected material/products based on them with other materials/products is not acceptable.
2.4	Special considerations for ATPs containing or consisting of genetically-modified organisms (GMOs)	2.4.1 2.4.2 2.4.3 2.4.4 2.4.5	Concurrent manufacture of different viral gene therapy vectors in the same area is generally not acceptable. Please see section 2.2.2.4. Containment measures should be established according to the risk of the product that is handled, including measures regarding the design of the premises, organizational and technical measures, and measures regarding the treatment of residues. Where replication limited viral vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent recombinant vectors. The handling of viral vectors should take place in a segregated area in a biological safety cabinet or an isolator. Appropriate decontamination measures should be implemented when personnel or materials move from an area containing GMOs to an area not containing GMOs or between areas containing different GMOs. Unidirectional flows should be considered where possible. Emergency plans (adapted to the level of risk) should also be in place covering the actions to be taken in case of accidental release into the environment. The plan should foresee measures/procedures for containment, protection of personnel, cleaning, decontamination, waste management, as well as the notification to the local competent authorities, where appropriate, the emergency services.
2.5	Special considerations for ATPs containing or consisting of replication competent materials or products	2.5.1 2.5.2	Negative pressure in specific areas may be required for containment reasons (e.g. when replication competent vectors or pathogenic bacteria are used). In such cases, the negative pressure areas should be surrounded by a positive pressure clean area of appropriate grade. The simultaneous incubation/storage of replication competent vectors/products based on them with other materials/products is not acceptable.
2.6	Special considerations for Investigational ATPs	2.6.1	In the case of investigational ATPs in very early phase/proof of concept trials, it may be exceptionally possible to manufacture the product in an open system in a critical clean area of grade A with a background clean area of grade C if the following (cumulative) conditions are met: 2.6.1.1 A risk-assessment has been performed and demonstrated that the implemented control measures are adequate to ensure manufacture of the product of appropriate quality. In addition, the control strategy should be described in the investigational medicinal product dossier. 2.6.1.2 The product is intended to treat a life threatening condition where no therapeutic alternatives exist. 2.6.1.3 The relevant competent authorities agree (agreement of both the assessors of the clinical trial and the inspectors of the site).

3. Storage Area

	Consideration	Requirement
3.1	Storage for different categories of materials and products	3.1.1 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and raw materials, packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled. 3.1.2 All materials and products should be stored under appropriate conditions to ensure the quality and in an orderly fashion to permit batch segregation and stock rotation. 3.1.3 Storage areas should be clean and dry and maintained within acceptable temperature and/or humidity limits. Special storage conditions, if required, should be provided, checked and monitored. 3.1.4 Where quarantine status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security. 3.1.5 If dispatch areas are physically different locations from the storage areas, there should be provision for appropriate storage while awaiting transport. 3.1.6 Separated areas should be provided for the storage of recalled and returned materials/products, unless control of these materials/products is ensured through electronic means. 3.1.7 Rejected materials should be clearly marked as such and stored separately in restricted areas (e.g. locked). 3.1.8 Particular attention should be paid to implementing appropriate measures to prevent mix-up of autologous products and other dedicated products (*i.e.* products intended for specific patients).
3.2	Special considerations for ATPs containing or consisting of infectious materials /products	3.2.1 Special considerations must be applied to the segregation of materials obtained from infected donors. 3.2.2 The simultaneous incubation/storage of infected material/products based on them with other materials/products is not acceptable.
3.3	Special considerations for ATPs containing or consisting of genetically-modified organisms (GMOs)	3.3.1 Unidirectional personnel and material flows should be utilized where possible.

4. Quality Control Area

	Consideration	Requirement
4.1	General	4.1.1 Quality control laboratories should normally be separated from production areas. This is particularly important for laboratories for the control of biologicals and microbiologicals, which should also be separated from each other.

		4.1.2	Laboratory areas should be designed to suit the operations to be carried out in them.
		4.1.3	Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc. (e.g. analytical balance).
		4.1.4	For guidance on the laboratory design for sterility testing, please refer to guidance documents *Recommendation on Sterility Testing* (PI 012-3) and *Recommendation on Isolators Used for Aseptic Processing and Sterility Testing* (PI 014-3) published by the Pharmaceutical Inspection Co-operation Scheme.
		4.1.5	For guidance on the laboratory design for nucleic acid amplification, please refer to European Pharmacopoeia monograph *Nucleic Acid Amplification Techniques* (2.6.21).
		4.1.6	Sufficient space should be given to avoid mix-ups and cross-contamination during testing. There should be adequate suitable storage space for samples and records.
		4.1.7	Samples should normally be stored under the conditions foreseen in the product information.
4.2	Special considerations for ATPs containing or consisting of genetically-modified organisms (GMOs)	4.2.1	Unidirectional personnel and material flows should be utilized where possible.

5. Ancillary Area

	Consideration	Requirement	
5.1	General	5.1.1	Rest and refreshment rooms should be separate from production, storage and quality control areas. Toilets and washrooms should not directly communicate with production, storage and quality control areas.
		5.1.2	Separate janitor rooms should be available to support cleaning operations of cleanrooms and other areas where applicable.
		5.1.3	Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate. The types of records to be retained and their respective locations should be defined.
		5.1.4	Premises where laboratory animals are kept should be isolated from production, storage and quality control areas with separate entrance and air handling facilities.

F. Useful Reference Materials

1. European Commission. (2017). Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products.
2. Council of Europe. (2016). European Pharmacopoeia. Ninth Edition. Volume 1. [2.6.21] Nucleic Acid Amplification Techniques.
3. International Society for Pharmaceutical Engineering. (2011). ISPE Baseline® Guide. Volume 3 – Sterile Product Manufacturing Facilities. Second Edition.
4. International Society for Pharmaceutical Engineering. (2013). ISPE Baseline® Guide. Volume 6 – Biopharmaceutical Manufacturing Facilities. Second Edition.
5. International Society for Pharmaceutical Engineering. (2009). ISPE Good Practice Guide – Heating, Ventilation, and Air Conditioning (HVAC).
6. Pharmaceutical Inspection Co-operation Scheme. (2007). Recommendation on Sterility Testing (PI 012-3).
7. Pharmaceutical Inspection Co-operation Scheme. (2007). Recommendation on Isolators Used for Aseptic Processing and Sterility Testing (PI 014-3).
8. Therapeutic Goods Administration. (2013). Australian Code of Good Manufacturing Practice for Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products. Version 1.0.
9. United States Pharmacopoeial Convention, Inc. (2016). US Pharmacopoeia-National Formulary [USP 40 NF 35] Volume 1. [1046] Cellular and Tissue-Based Products.
10. United States Pharmacopoeial Convention, Inc. (2016). US Pharmacopoeia-National Formulary [USP 40 NF 35] Volume 1. [1047] Gene Therapy Products.
11. World Health Organization. (2016). WHO Good Manufacturing Practices for Biological Products. In: WHO Expert Committee on Biological Standardization: sixty-sixth report (Annex 2 WHO Technical Report Series, No. 996).
12. World Health Organization. (2011). WHO Good Manufacturing Practices for Sterile Pharmaceutical Products: (WHO Technical Report Series, No. 961).

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