Preparation of pharmaceutical and advanced therapeutic products

Summary NSW Health public health facilities must have appropriate infrastructure, staff capabilities and processes in place relevant to the type of pharmaceutical and advanced therapeutic products being prepared to ensure the safe and efficient product preparation in the public health facility.

Document type Policy Directive

Document number PD2023_021

Publication date 22 August 2023

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Replaces PD2015_007

Review date 22 August 2026

Policy manual Not applicable

File number DG22/1956

Status Active

Functional group Clinical/Patient Services - Human Tissue, Pathology, Pharmaceutical, Research
Corporate Administration - Governance
Personnel/Workforce - Occupational Health and Safety
Population Health - Pharmaceutical

Applies to Ministry of Health, Local Health Districts, Board Governed Statutory Health Corporations, Chief Executive Governed Statutory Health Corporations, Specialty Network Governed Statutory Health Corporations, Affiliated Health Organisations, NSW Health Pathology, Public Health System Support Division, Cancer Institute, Public Hospitals

Distributed to Ministry of Health, Public Health System

Audience Pharmacy; Nursing Staff; Clinical Trials; Clinical Research; Medical Research

Secretary, NSW Health

NSW Health

POLICY DIRECTIVE

Preparation of pharmaceutical and advanced therapeutic products

POLICY STATEMENT

NSW Health facilities must have appropriate infrastructure, staff capabilities and processes in place relevant to the type of pharmaceutical and advanced therapeutic products being prepared to ensure the safe product preparation in the facility.

SUMMARY OF POLICY REQUIREMENTS

This Policy Directive includes the preparation, procurement, storage, transportation, waste disposal and guidance for outsourcing the preparation of pharmaceuticals, clinical trial investigational medicinal products (IMPs), genetically modified organism medicinal products, chimeric antigen receptor (CAR) T-cell products, antigen specific cell and bacteriophage products for human use.

The Chief Executive is responsible for the risk assessment of the current facilities and are to provide a plan to the NSW Ministry of Health's Chief Pharmacist Unit, of works and procedures necessary to meet the minimum facility standards for the compounding or preparation of pharmaceutical and advanced therapeutic products relevant to the scope of practice of the local health district, specialty health network or affiliated health organisation.

The Director of Pharmacy is responsible for the compounding or preparation of pharmaceutical and advanced therapeutic products, including investigational medicinal products (IMPs), at the pharmacy service in accordance with NSW Health Policy Directive *Medication Handling* (PD2022_032). Upon supply of the prepared product to the patient care area the nurse unit manager or delegate is responsible for the storage, handling and administration of the prepared product.

NSW Health facilities undertaking aseptic compounding or preparation of pharmaceuticals and advanced therapeutic products must be compliant with the infrastructure, personnel, documentation, processes, and quality control standards described in the Pharmaceutical Inspection Co-Operation Scheme (PIC/S) G*uide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010).

A pharmacist in a public hospital can compound a pharmaceutical product in anticipation of a medication order, under the *Therapeutic Goods Regulation 1990* (Cth), when the pharmaceutical medicine is required urgently and a delay in treatment is detrimental to the outcome for the patient. Compounding in anticipation of an order must be approved by the Drug and Therapeutics Committee and for aseptically compounded or prepared products, sterility testing of each batch must be performed.

It is the responsibility of the Director of Pharmacy to ensure a risk assessment is completed prior to the compounding or preparation of each pharmaceutical or advanced therapeutic product by the pharmacy service, in accordance with the Pharmacy Board of Australia's

Guidelines on Compounding of Medicines. The risk assessment must identify the containment requirements for all non-aseptically and aseptically prepared products according to the occupational exposure risk for staff handling hazardous products as per the National Institute for Occupational Safety and Health *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016*.

The preparation in a pharmacy of non-aseptically compounded oral products must be undertaken within a high efficiency particulate air (HEPA) filtered powder containment cabinet or equivalent.

The preparation of non-aseptically compounded hazardous drugs must be undertaken in a negative pressure HEPA filtered powder containment cabinet in a negative or neutral pressure room.

The reconstitution of a hazardous drug oral suspension, as per the manufacturer's product information, must at a minimum be undertaken in a segregated area away from the main dispensary and the use of a negative pressure HEPA filtered powder containment cabinet or equivalent should be considered.

The application of an extended beyond use date (BUD) beyond 24-hours for aseptically prepared pharmaceutical products must be supported by a consistently high level of microbial quality control and assurance within PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) acceptable colony forming unit limits for the duration of the BUD to be assigned. Under this Policy Directive a BUD must not exceed 7-days for aseptically prepared products.

The Director of Pharmacy is responsible for the approval of any NSW Health employee or contractor to enter a pharmacy clean room environment. They must be satisfied that any NSW Health employee entering the clean room have a thorough understanding of clean environments including; Good Manufacturing Practice (GMP), PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010), local standard operating procedures, occupational exposure, and microbiology. All external contractors entering the clean room environment must be supervised and accompanied by the senior production pharmacist or senior production pharmacy technician.

Continuous temperature logging is required for all stages of storage and transportation of prepared refrigerated or frozen pharmaceuticals and IMPs within the same public health facility and when transporting all prepared pharmaceutical and IMPs, including room temperature products, to another facility, including courier transportation.

To prepare doses of medium-risk occupational exposure therapeutic medicinal products, including monoclonal antibodies, in the patient care area, nurses and midwifes are required to have received additional training like local chemotherapy handling accreditation.

Where a pharmaceutical product is initiated in a public health facility that does not have the facilities to prepare onsite, this can be sourced from a third-party supplier. Non-aseptically prepared compounded products can be sourced from a community compounding pharmacy on prescription for an individual patient.

Aseptically prepared products intended to be sterile must only be sourced from a Therapeutic Goods Administration manufacturing licenced facility.

Clinical trial investigational products

A Drug and Therapeutics Committee (DTC) is responsible for the governance and approval of all clinical trials involving medicines and bacteriophage. The DTC is responsible for the oversight of clinical trials involving gene therapies according to the organisations accreditation under the *Gene Technology Act 2000* (Cth) and for the oversight of CAR T-cell and antigen specific cell therapies.

Where the investigator at the principal trial site facility is the holder of the Clinical Trial Approval (CTA) or Clinical Trial Notification (CTN) and the approval applies to multiple satellite clinical trial sites, the pharmacy service at the principal trial site facility may prepare Schedule 2, 3 or 4 IMPs and unapproved IMPs, other than biologicals, for supply to the multiple NSW Health facilities within NSW stipulated in that approval.

REVISION HISTORY

Version	Approved By	Amendment Notes
PD2023_021 August-2023	Deputy Secretary, People, Culture and Governance	New policy directive to update NSW Health Policy Directive *Pharmaceuticals - Preparation in NSW Public Health Facility Pharmacy Services* (PD2015_007) to include clinical trials and advanced therapeutics.
PD2015_007 February-2015	Secretary, NSW Health	Updates and replaces PD2005_590 and PD2005_200
PD2005_590 June-2005	Director-General	Re-issue of Circular No. 95/86 as a Policy Directive
PD2005_200 January-2005	Director-General	Re-Issue of Circular No. 2001/48 as a Policy Directive (Replaced Circular Nos. 81/282, 83/65 and 91/10)

CONTENTS

1. BACKGROUND

Preparation of pharmaceutical products covers a range of activities and products from non-aseptically prepared extemporaneous compounding through to aseptically prepared compounding of products in specialised cleanroom environments. Preparation of pharmaceutical and advanced therapeutic products must meet relevant legislation and standards to ensure a quality product and the safe use of medicines.

Manufacturing of a pharmaceutical medicine or biological requires a manufacturing licence from the Therapeutic Goods Administration (TGA) who assess that all manufacturing processes meet the Good Manufacturing Practice (GMP) standards.

A TGA manufacturing licence is needed regardless of whether the medicine or biological is included on the Australian Register of Therapeutic Goods (ARTG). Overseas manufacturers cannot apply for a TGA manufacturing licence, but can obtain GMP certification following a successful on-site inspection by the TGA, refer to the TGA *Australian manufacturing licences and overseas GMP certification*.

Pharmacists working in a NSW Health facility may be exempt from a TGA manufacturing licence to compound pharmaceuticals, (see Section 3 Pharmaceutical Products). A pharmacist working in a Health facility must not compound a pharmaceutical product when a similar medicine is available registered or listed on the ARTG. For more detail refer to the Pharmacy Board of Australia (PBA) *Guidelines on compounding of medicines*.

Advanced therapeutic products, for example genetically modified organism (GMO) medicinal products, are rapidly becoming registered medicines in Australia. To meet the unique health care demand for advanced therapeutics the number and complexity of products required to be prepared by pharmacists will see a substantial increase.

1.1. About this document

This Policy Directive applies to all public health facilities, including hospitals, clinical services, outpatient clinics, community health centres, day centres, day procedure centres, community-based/ outreach nursing services and Hospital in the Home within the NSW Health system's jurisdiction.

This Policy Directive provides guidance to all Directors of Pharmacy, Directors of Nursing and Midwifery, Bone Marrow Transplant and Cellular Therapy (BMT/CT) Laboratory Medical Directors, Directors of Clinical Governance, NSW Health Pathology and all relevant staff on preparing aseptically prepared and extemporaneously compounded pharmaceutical products and advanced therapeutic products to standards that are of a high quality, are safe. They are to be made in compliance with the *Therapeutic Goods Act 1989* (Cth), *Poisons and Therapeutics Goods Act 1966* (NSW), *National Health and Medical Research Council Act 1992* (Cth), *Gene Technology Act 2000* (Cth), comply with professional practice and other standards, and are likely to produce the therapeutically intended and expected effect.

This Policy Directive can be used as the basis for public health facilities to develop detailed protocols and procedures specific to the local situation and circumstances.

The Director of Pharmacy is responsible for the storage, handling, dispensing and preparation of all scheduled medicines, including compounded and investigational medicinal products (IMPs) under NSW Health Policy Directive *Medication Handling* (PD2022_032). The

Director of Pharmacy may delegate tasks to the responsible pharmacist, clinical trials pharmacist or specialist senior pharmacist; however, the final responsibility remains with the Director of Pharmacy. Upon supply of the prepared product to the patient care area the nurse unit manager (NUM) or equivalent is responsible for the storage, handling and administration of the prepared product.

The dispensing of compounded, aseptically prepared pharmaceutical products or advanced therapeutic products within public health facilities must not occur unless the Director of Pharmacy or Chief Executive of the public health facility has confirmed there are appropriate standards of training, skill, facilities, and preparative and quality assurance procedures in place to provide a high level of confidence that the preparations are of a consistently high-quality standard.

The requirements for electronic prescribing and medication orders described in the NSW Health Policy Directive *Medication Handling* (PD2022_032) apply to all medicines prepared and compounded in public health facilities, including advanced therapeutic products and IMPs.

Novel units of measure may be required to be added to electronic prescribing software for example, vector genomes/mL. In circumstances where electronic prescribing is not available, a paper National Standard Medication Chart (NSMC) can be used in accordance with guidelines published by the Australian Commission on Safety and Quality in Health Care (ACSQHC).

1.2. Scope of Policy Directive

The scope of this Policy Directive includes the preparation, procurement, storage, transportation, and potential for outsourcing preparation of the following pharmaceutical and advanced therapeutic products for human use:

- Non-aseptic extemporaneous preparation of pharmaceutical products
- Reconstitution of hazardous pharmaceutical suspensions, for example:
    - mycophenolate has a black box warning for embryo foetal toxicity, malignancy and serious infections with reconstitution of the oral suspension
    - valganciclovir suspension is cytotoxic and carcinogenic, and
    - oral antibiotic suspensions have a risk of hypersensitivity reactions
- Aseptically prepared pharmaceuticals, for example intravenous preparations, total parenteral nutrition, ocular and inhalation preparations
- Aseptically prepared hazardous pharmaceuticals, for example cytotoxic products
- Clinical trial investigational medicinal products (IMPs)
- Biological medicines, for example monoclonal antibodies
- Biologicals, for example chimeric antigen receptor (CAR) T-cells and antigen specific T-cell therapy
- Bacteriophage therapy.

The scope of this Policy Directive does not include:

- Radiopharmaceutical products
- Dose preparation by a health practitioner, outside of pharmacy, that is ready for administration as per the manufacturer's instructions or *Australian Injectable Drugs Handbook* (AIDH) in a patient care area immediately before use, for example injectable antibiotics and vaccines (refer to Section 6.6 Principles for safe medication administration in NSW Health Policy Directive *Medication Handling* (PD2022_032).

1.3. Key definitions

Active pharmaceutical ingredient (API)	The active component in a pharmaceutical product that produces the intended effects.
Advanced therapeutic product	For this Policy, genetically modified organism, human cell, or bacteriophage product.
Antigen specific T-cell therapy	An advanced therapeutic product. Human T-cell immunotherapy that recognises tumour antigens to treat virus associated diseases and malignancies.
Approved product information	Written information by the sponsor pharmaceutical company for a medicine included on the Australian Register of Therapeutic Goods (ARTG) and approved by the Therapeutic Goods Administration (TGA). Provides objective information about the quality, safety, preparation and effectiveness of the medicine as demonstrated in the data provided to the TGA by the pharmaceutical company.
Aseptically prepared	A pharmaceutical, advanced therapeutic or investigational medicinal product (IMP) compounded or prepared for use under specialised conditions with the intention to be sterile. This is achieved through aseptic manipulation, reconstitution, and dilution from terminally sterilised components in a high-efficiency particulate air (HEPA) filtered cabinet or primary engineering control (PEC) within a HEPA filtered clean room or secondary engineering control (SEC), using aseptic techniques designed to prevent microbial contamination. Examples include injectables, total parenteral nutrition, and ocular products, prepared both from sterile ingredients and from non-sterile to sterile manipulation (such as sterilisation by filtration).
Aseptic technique	Using practices and procedures during preparation of products to prevent contamination from pathogens in sufficient quantity to cause infection.

Australian Register of Therapeutic Goods (ARTG)	The public database of therapeutic goods that can be legally supplied in Australia. Therapeutic goods entered on the register are either: • Registered – higher risk therapeutic goods must be registered on the ARTG which involves individually evaluating the quality, safety and effectiveness of the product, for example prescription medicines • Listed – lower risk therapeutic goods that can be purchased off the shelf from pharmacies, health food shops and supermarkets The ARTG includes information on the product name, formulation details and sponsor or manufacturer details.
Bacteriophage therapy	Bacteriophage (or 'bacteria eater') are viruses that infect and replicate within bacteria by injecting nucleic acid into a bacteria cell and are used to treat bacterial infections. Bacteriophage are found wherever bacteria are found. They attack bacteria, constituting an unlimited resource to explore the development of biomedical therapies. Bacteriophage are replicated using a host bacteria and bacteriophage propagation for example, sewage is a rich source of bacteriophages that infect enteric bacteria such as *E. coli*. Bacteriophages are an unapproved therapeutic good, accessed through the TGA Special Access Scheme (SAS).
Biological medicine	Prescription biological medicines regulated by the TGA as a therapeutic good under the *Therapeutic Goods Act 1989* (Cth), but not as a biological. For example: • Vaccines • Plasma derivatives • Recombinant products (monoclonal antibodies).
Biologicals	The following products are regulated by the TGA as a biological: • Tissue-based products, for example skin, bone, ocular, cardiovascular, amnion • Cell-based products, for example genetically modified organisms, in vitro cell expansion or depletion, for example chimeric antigen receptor (CAR) T-cell therapy • Immunotherapy products containing human cells • Combination products, for example cell therapy and medical device

	• Products that comprise or contain live animal cells, tissues, or organs, for example pancreatic islet cells isolated from pigs • Autologous human cells and tissue products, including stem cells • Faecal microbiota transplant products containing or derived from human stool.
Biological safety cabinet (BSC)	A ventilated cabinet with unidirectional HEPA-filtered airflow to provide a sterile environment to protect the product from particles and provides protection to the worker.
Beyond use date (BUD)	Date and time after which a compounded preparation shall not be stored, transported, or used. Application of a BUD must consider the intended commencement time of administration of a medicine to the patient and is determined from the date and time the preparation of the product begins, for example the time a vial of an injectable medicine is first accessed.
Bone Marrow Transplant + Cellular Therapy (BMT+CT)	The transplantation of human cells to replace or repair damaged tissue and/or cells. They are regulated as a biological.
Chimeric antigen receptor (CAR) T-cell therapy	Immunotherapy that uses specially altered T-cells to target cancer cells directly and precisely. A type of cell therapy regulated as a biological.
Chem Alert	A web-based chemical information database accepted by NSW Health as a repository of safety data sheets (SDSs) for chemicals.
Clean room environment	An engineered space, which by HEPA filtration maintains an extremely low concentration of airborne particulate, where pollutants like dust, airborne microbes, and aerosol particles are filtered out. Also referred to as SEC.
Closed system transfer device	Prevents vapor escape, plunger contamination and accidental pulling-out of the plunger. A Food and Drug Administration (FDA) approved or TGA registered closed-system transfer device (CSTD) may prevent microbial contamination of preservative-free vials after being accessed. Seek supporting studies before use.
Colony forming unit (cfu)	A unit of measurement used to determine the number of bacterial cells in a settle or contact plate environmental monitoring sample.

Cytotoxic drug safety cabinet (CDSC)	Negative pressure primary engineering cabinet that provides protection to staff from exposure to aerosols and vapours which may be generated in the preparation of cytotoxic drugs.
Clinical Trial Approval (CTA)	A scheme where the clinical trial sponsor requires approval from the TGA and the relevant Human Research and Ethics Committee (HREC) to import/ supply an 'unapproved' therapeutic good for high risk or novel treatments, such as gene therapy, where there is no or limited knowledge of safety.
Clinical Trial Notification (CTN)	A scheme where the Australian clinical trial sponsor must notify the TGA of the clinical trial before they begin using the 'unapproved' therapeutic good in the trial.
Clinical trial research agreement (CTRA)	The sponsor of a trial must enter into a clinical trial research agreement with each site documenting the obligations of each party with respect to the conduct of the trial.
Compounding	A preparation of a product by a pharmacist in a pharmacy service from raw ingredients, the manipulation of a medicine registered or listed on the ARTG or investigational medicinal product (IMP) ready for administration to an individual patient. The preparation of compounded products requires specialised pharmacy facilities, specialist trained staff, and reputable formulas or published stability study data.
Cryopreserved	Preservation of cells or tissues by cooling them below the freezing point of water.
Dealings involving intentional release (DIR)	The handling or administration of a genetically modified organism (GMO) medicinal product which is subsequently expected to be released into the environment. The GMO medicinal product is not fully contained within the person and may shed to the environment/ excreted for example, intranasal administration.
Dealings not involving intentional release (DNIR)	The handling or administration of a GMO medicinal product which is not expected to be released into the environment. The GMO medicinal product is contained within the person and not intentionally released into the environment.
Dispensing label	It is a legal requirement that all dispensed medicines have a dispensing label applied before providing to the consumer. Mandated minimum requirements include the consumer's name; medicine name, strength and dose form; date of dispensing; and the name and address of the dispensing pharmacy.

Dose preparation	Dose preparation is the manipulation of a product by nursing, midwifery, or medical practitioners as per the approved product information to produce a product in a 'ready to administer' form, for example reconstitution of intravenous antibiotics using aseptic technique and further dilution in an intravenous fluid bag. This excludes preparation by the pharmacy service.
eviQ	An Australian Government, online resource of cancer treatment protocols developed by multidisciplinary teams of cancer specialists.
Ex vivo gene therapy	Harvesting of cells from a patient by apheresis, followed by genetic modification of these cells in a laboratory. The genetically modified cells are usually amplified in number, then the transduced cells, a GMO medicinal product, are administered back to the patient.
First-in-human use	First-in-human use of a substance in clinical trials or initial experimental studies in human volunteers will, but not always, be a phase 0 and phase I trial.
Gene therapy	A treatment that makes changes to genes in living cells or organisms using gene technology to help prevent or treat certain diseases.
Genetically modified organism (GMO)	An organism that: • has been modified by gene technology; or • has inherited traits from an initial organism that occurred because of gene technology.
GMO medicinal product	Any pharmaceutical or therapeutic product used to treat disease, which involves an organism modified using gene technology.
Good Manufacturing Practice (GMP) certification	Certification to manufacture therapeutic goods for import into Australia, may be issued by the TGA to overseas manufacturers following a successful on-site inspection by the TGA. GMP certification applications must be submitted by an Australian sponsor or an agent acting on the Australian sponsor's behalf.

Hazardous drug (HD)	The classification of a hazardous drug is when the hazard is to the health professional or technician preparing and handling the drug. A pharmaceutical that exhibits one or more of the following six characteristics in humans and/or animals: 1. Carcinogenicity 2. Genotoxicity 3. Teratogenicity 4. Reproductive toxicity or fertility impairment 5. Serious organ toxicity or adverse health effects at low doses, for example, hypersensitivity reactions 6. The structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the five previous criteria.
Haemopoietic progenitor cell (HPC)	Stem cells harvested by apheresis for use in bone marrow transplant therapy, used to treat cancer and autoimmune diseases.
Human leukocyte antigen (HLA)	Proteins located on the surface of white blood cells and other tissues in the body and are responsible for regulating the immune system. They are used to match patients and donors for blood or bone marrow transplants. If two people share the same HLA type, they are considered a match, meaning their tissues are immunologically compatible with each other.
Human Research and Ethics Committee (HREC)	Review research and monitor all clinical trials of unapproved therapeutic goods involving human participants to ensure that they are ethically acceptable and how they fit in the regulatory regimen.
Immune effector cell (IEC)	A cell that can create an immune response in the body. Immune effector cell therapy involves the body's own immune system to treat cancer.
In vivo gene therapy	A GMO medicinal product, usually DNA based, administered directly to the patient, to modify the genes of target cells, for example cancer cells, to achieve therapeutic goals.
Institutional Biosafety Committee (IBC)	Provide a quality assurance mechanism, providing advice to assist public health facilities with the identification and management of the risks associated with GMO medicinal product dealings, including containment of GMO medicinal products.

Investigational medicinal product (IMP)	Any pharmaceutical, advanced therapeutic product or placebo which is being tested or used as a reference in a clinical trial.
Investigator's brochure (IB)	A compilation of clinical and non-clinical data on the investigational product(s) used in clinical trials that are relevant to the study of the product(s) in human subjects.
Laminar airflow workstation (LAFW)	Laminar airflow workstations provide a sterile environment to protect products from particles. It is not a biological safety cabinet and does not provide any protection to the worker. Air potentially contaminated with infectious agents may be blown towards the worker.
May or may consider	Indicates a recommended action that should be followed unless there is a sound reason for taking a different course of action.
Manufacturing under licence	Industrial-scale preparation of pharmaceutical products by a TGA licenced manufacturing facility. Refer to the *Therapeutic Goods (Manufacturing Principles) Determination 2020* under Section 36 of the *Therapeutic Goods Act 1989* (Cth).
Must	Indicates a mandatory action requiring compliance by staff at NSW Health facilities, in accordance with a legislative requirement and/or an NSW Health policy or directive.
National Association of Testing Authorities (NATA)	Recognised national accreditation authority for laboratories, clean rooms, and associated HEPA filtered equipment to ensure facilities are compliant with the accreditation criteria, for example, air velocity, pressures, particles, and integrity of HEPA filters.
Non-aseptic compounding	For this Policy, compounding is undertaken by a pharmacist in a public health facility and is exempt from requiring a TGA manufacturing licence. Non-aseptically prepared products should be prepared in a powder containment hood or similar in an area that is clean, but not necessarily free of microorganisms. Non-aseptically prepared products are not intended to be sterile. Injections and ocular products must not be prepared under non-aseptic conditions.
Off-label use	A registered or listed good on the ARTG used in a manner other than in accordance with the approved product information.

Pharmaceutical products	For this Policy, a pharmaceutical product encompasses all compounded or prepared medicines by the public health facility. This will usually include ARTG registered or listed medicines or raw ingredients and excludes advanced therapeutic products.
Pharmaceutical isolator	A fully enclosed primary engineering cabinet to provide maximum protection to staff from aerosols and vapours which may be produced when preparing pharmaceutical products. Isolators may be negative or positive pressure.
Pharmacy service	A service administered by a Director of Pharmacy responsible for the procurement, distribution, preparation, and dispensing of pharmaceutical products as well as the delivery of clinical and other pharmacist practice services.
Prepared product	For this Policy, a prepared pharmaceutical, advanced therapeutic or IMP is a completed formulation by the pharmacy service, following a process of compounding or manipulation (as per the product information), ready for administration to the patient. Product preparation may require specialised facilities by the pharmacy service as described in this Policy.
Primary engineering control (PEC)	A cabinet used to reduce the number of airborne particles and microorganisms in the compounding environment by channelling filtered high-efficiency particulate air into the workstation which must be as contaminant free as possible, for example, biological safety cabinet (BSC).
Principal investigator (PI)	The person responsible, individually or as a leader of the research team at a site, for the conduct of a clinical trial at that site.
Professional practice guidelines	Provide recommendations for best practice.
Professional practice standards	Requires compliance for best practice.
Public health facility	A Public Health Organisation defined under the *Health Services Act 1997* (NSW), a local health district, specialty health network or affiliated health organisation.

Responsible pharmacist	The Director of Pharmacy maintains overall responsibility for pharmacy services but may delegate tasks to a specialist senior pharmacist. The responsible pharmacist must have extensive experience in production and formalised continuing professional development (CPD) accredited training in pharmaceutical preparation, including quality management systems.
Safety data sheet (SDS)	Important safety information about hazardous chemicals that can help keep workers safe.
Safe work practices (SWP)	A step-by-step set of instructions on how to perform a task safely.
Satellite site	Smaller ancillary site of a larger principal site.
Secondary engineering control (SEC)	A HEPA filtered cleanroom used to reduce the number of airborne particles and microorganisms in the compounding environment providing secondary protection to the PEC.
Section 19A	Under Section 19A of the *Therapeutic Goods Act 1989* (Cth), medicines not included on the ARTG may be approved by the TGA for import and supply in Australia when there is a shortage of an Australian registered medicine, and the medicine is needed in the interest of public health.
Schedule of medicines	The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) classifies medicines and chemicals into schedules: • Schedule 1 - (Not in use) • Schedule 2 - Pharmacy Medicine • Schedule 3 - Pharmacist Only Medicine • Schedule 4 - Prescription Only Medicine • Schedule 5 - Caution • Schedule 6 - Poison • Schedule 7 - Dangerous Poison • Schedule 8 - Controlled Drug • Schedule 9 - Prohibited Substance • Schedule 10 - Substances of such danger to health as to warrant prohibition of sale, supply, and use.

Special Access Scheme (SAS)	A process to prescribe unapproved products to individual patients, under the *Therapeutic Goods Act 1989* (Cth), if they meet the following criteria: • The patient is seriously ill (Category A) • The product can be requested for use by the application pathway (Category B) • The product is on the established history of use list (Category C).
Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)	The Poisons Standard is the legal title for the Standard for the Uniform Scheduling of Medicines and Poisons. The Poisons Standard consists of decisions regarding the classification of medicines and poisons into schedules and controls such as packaging and labelling. The NSW Poisons List adopts the schedules of the SUSMP as in force at any time.
Standard operating procedures (SOP)	A step-by-step set of instructions to help staff complete routine activities, making the process repeatable.
Therapeutic Goods Administration (TGA) manufacturing licence	A manufacturing licence issued by the TGA under the *Therapeutic Goods Act 1989* (Cth) to manufacture products and raw ingredients, on an industrial-scale, for individual patients and for wholesale supply in accordance with the *PIC/S Guide to GMP for medicinal products* (PE009). For this Policy, where a facility does not have a TGA manufacturing licence, product preparation may only be undertaken by a pharmacist under exemptions in the *Therapeutic Goods Regulations 1990* (Cth) which allow a pharmacist to compound medicines, not manufacture.
Unapproved therapeutic good	Any medicine, medical device or biological not included on the ARTG. When a pharmaceutical is included on the ARTG, the entry applies to a particular sponsor (such as the individual or company intending to supply the goods). If a same or similar pharmaceutical is imported by another company or individual it is considered 'unapproved.' Also referred to as an 'unregistered therapeutic good.'

1.4. Drug and Therapeutics Committee

All public health facilities in NSW must have a formally constituted, multidisciplinary Drug and Therapeutics Committee (DTC) in place or have access to a NSW Health facility DTC as per NSW Health Policy Directive *Medication Handling* (PD2022_032).

Each DTC must report (directly or via a senior executive officer) to the Chief Executive of the public health facility who must ensure the committee is established with appropriate specialist expertise and terms of reference to provide governance of quality and safe medication management for the scope of medicines being handled and prepared, for example investigational medicinal product (IMPs) and specific advanced therapeutic products.

In accordance with NSW Health Policy Directive *Medication Handling* (PD2022_032), the DTC is responsible for:

- oversight of the use of all gene therapies according to the public health facility accreditation under the *Gene Technology Act 2000* (Cth)
- oversight of risks of clinical trials to the public health facility (other than the clinical considerations assessed by a Human Research and Ethics Committee (HREC)). The DTC must be notified of all clinical trials and provide approval for any involving medications or bacteriophage therapy occurring in the public health facility.

2. RISK ASSESSMENT

The Director of Pharmacy is responsible to meet the standards outlined in the *Work Health and Safety Act 2011* (NSW) and *Work Health and Safety Regulation 2017* (NSW) to provide a safe work environment and ensure the health and safety of all pharmacy staff. Safe work practices (SWP) must be available for all tasks covered by this Policy Directive.

It is the responsibility of the Director of Pharmacy to ensure a risk assessment is completed prior to the preparation of each pharmaceutical or advanced therapeutic product by the pharmacy service, as per the Pharmacy Board of Australia (PBA) *Guidelines on Compounding of Medicines*.

When compounding non-sterile products, pharmacists are referred to the risk assessment process for the preparation of extemporaneous preparations outlined in the section Extemporaneous dispensing in the current edition of the *Australian Pharmaceutical Formulary Handbook* (APF).

The principal investigator (PI) is responsible for completing the risk assessment for investigational medicinal products (IMPs) when the pharmacy service would not be required to prepare the product.

NSW Health Policy Directive *Work Health and Safety: Better Practice Procedures* (PD2018_013) and Safe Work Australia Model Code of Practice on *How to manage work health and safety risks* outline the risk assessment process.

The risk assessment must cover:

- occupational exposure risk to staff for all aspects of product handling from ordering, receipt and storage, to preparation, supply, transport, and disposal; and
- product risk including appropriate facilities, equipment and staff capabilities.

Staff not formally trained in a specific product preparation or who do not have access to reliable formula sources must not prepare the specific product. The Director of Pharmacy must document the reason(s) why a product cannot be prepared on the risk assessment.

The Safe Work Australia Model Code of Practice *Managing the risks of hazardous chemicals in the workplace* provides guidance on identifying hazardous medicines or chemicals and controlling handling and exposure risks.

2.1. Occupational exposure risk to staff

Occupational exposure must be assessed to ensure the safety of all staff handling pharmaceutical and advanced therapeutic products. The *Work Health and Safety Regulation 2017* (NSW) requires health monitoring of all staff that regularly handle hazardous drugs (HDs) in the workplace.

This Policy Directive has combined and adapted published resources from professional bodies on occupational health and safety risk to produce a risk assessment decision making tool for aseptically prepared pharmaceutical and advanced therapeutic products.

The risk assessment has been adapted from the *Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel* to include advanced therapeutics. Additional information to adapt the risk assessment was sourced from the Pharmaceutical Society of Australia (PSA) *Professional Practice Standards* Appendix 7 Compounding decision support and risk assessment tool, and NSW Health facility policies.

Safe Work Australia provide guidelines on *Health monitoring for persons conducting a business or undertaking guide* and *Health monitoring for cyclophosphamide*. The Pharmaceutical Inspection Co-Operation Scheme (PIC/S) *Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities* (PI 046) provides permitted daily exposure limits for staff handling HDs.

Compounding of non-sterile products must only be prepared by the pharmacy service. A risk assessment, outlined in Section 2 Risk Assessment, must be completed. The equipment requirements to provide protection to staff from occupational exposure to HDs are provided in Section 3.3.2 Non-aseptically prepared hazardous drug products.

Table 1 Occupational exposure risk for aseptic preparation of pharmaceuticals and advanced therapeutic products provides a quantifiable risk management score for occupational health and safety risk exposure for aseptic preparation of various products. A cumulative score of 1 to 2 is low risk; 3 to 4 is medium risk; and a score of ≥5 is high risk.

The risk score for each product can be applied to Figure 1 Occupational exposure risk flow chart for aseptic preparation of pharmaceuticals and advanced therapeutic products which provides guidance on controls to manage risk including level of staff experience and location for product preparation, for example ward level or pharmacy.

Figure 1 provides definitions of experienced staff and examples of simple and complex manipulations to assist in risk assessing staff competence and location of product preparation. For example:

- low risk products can be prepared in patient care areas by competent staff using aseptic technique or prepared by pharmacy services
- medium risk products can be prepared in patient care areas by experienced staff with additional training using aseptic technique or prepared by pharmacy services

- high risk products must be prepared by pharmacy services in specialist facilities, Therapeutic Goods Administration (TGA) manufacturing licenced or Good Manufacturing Practice (GMP) certified facilities (if sourcing from overseas). The Office of the Gene Technology Regulator (OGTR) must certify the public health facility prior to the preparation of any genetically modified organism (GMO) medicinal product.

Extra personal protective equipment (PPE) and precautions are required by nurses, midwives and medical practitioners reconstituting and diluting medium risk products ready for administration, due to the risk of prolonged repeated exposure. Nurses, midwives and medical practitioners preparing these products, including monoclonal antibodies, must have completed local chemotherapy handling accreditation. Further information for staff accreditation in handling chemotherapy can be found through the eviQ.

Note the patient bodily fluids component of the training is not applicable other than to cytotoxic products. An accreditation package for the reconstitution and dilution of non-chemotherapy HDs or advanced therapeutic products, where the occupational exposure risk is unknown, can include learning available, but not limited to:

- My Health Learning *Clinical management: Principles of safe handling and preparation* (Course Code 449310729)
- My Health Learning *Hazardous Drug Spills* (Course Code 219007052)
- eviQ Principles of safe handling and preparation of monoclonal antibodies.

For incident management following a needle stick injury during preparation, refer to Section 9.1 Recalls and incident reporting.

Table 1. Occupational exposure risk for aseptic preparation of pharmaceuticals and advanced therapeutic products

Risk factors	Description	Score
Monoclonal antibody origin	≥ 75% humanised Partially humanised Completely murine Other (for example phage display)	1 2 3 unknown
GMO	World Health Organisation (WHO) definition: Risk Group 1 Risk Group 2 – (including GMO bacteriophage) Risk Group 3 – Currently not prepared in public health facilities Risk Group 4 – Currently not prepared in public health facilities	 1 5 N/A N/A
Immunogenic or allergic toxicity	Low immunogenic or allergic risk of harm to the operator Theoretical risk of immunogenic or allergic adverse event Known serious immunogenic or allergic toxicity	1 2 3
Hazardous classification	Theoretical risk of haematological adverse effects Organ toxicity at low doses Known teratogenic or embryotic properties Cytotoxic or carcinogenic	2 3 4 5
Cell therapy	CAR T-cell - Currently not prepared in public health facilities	N/A

	Antigen receptor cell - Currently not prepared in public health facilities	N/A
Bacteriophage	Handled as WHO Risk Group 1	1

2.1.1. Monoclonal antibodies

The nomenclature for monoclonal antibodies was updated at the end of 2022, see Table 2 Monoclonal antibody nomenclature prior and post 2022.

The Clinical Oncology Society of Australia (COSA) position statement on *Safe handling of monoclonal antibodies in healthcare settings* recommends centralised preparation of monoclonal antibodies by pharmacy services where possible.

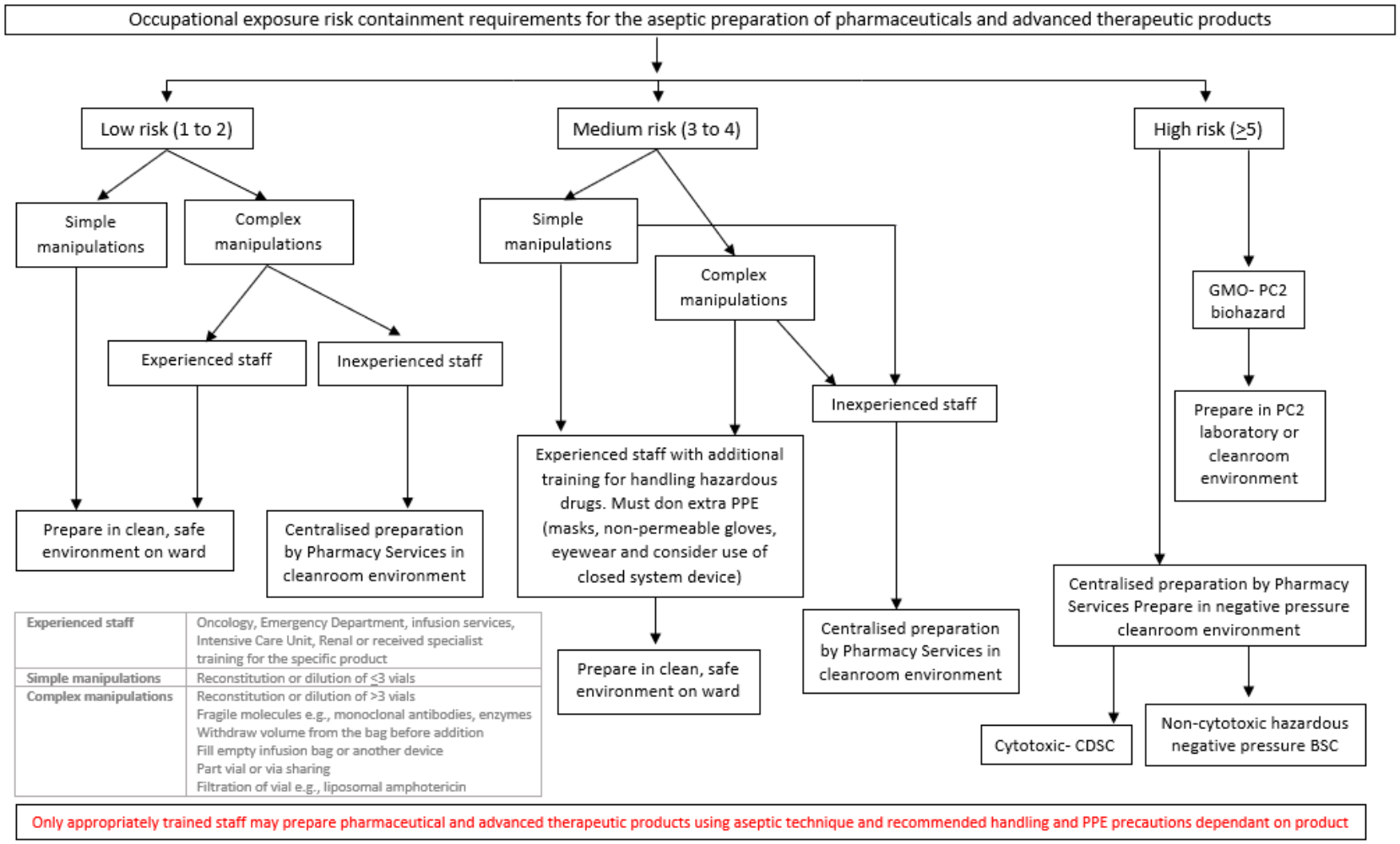
Monoclonal antibodies vary in occupational exposure risk. To help identify whether a monoclonal antibody can be prepared in the patient care area or should be prepared in the centralised pharmacy the occupational exposure risk must be assessed on an individual monoclonal antibody basis in accordance with Table 1 and Figure 1.

Where there is no classification or occupational exposure data available, a conservative approach to the risk assessment and preparation of the product must be taken to protect the health and safety of staff.

Table 2. Monoclonal antibody nomenclature prior and post 2022

Suffixes for monoclonal antibodies registered prior to 2022	**Origin**	
u" or "zu" mab	Humanised	Nomenclature provides a suffix to identify the origin
"xi" mab	Partially humanised or chimeric	
"o" mab	murine	
Suffixes for monoclonal antibodies registered from 2022 onward	**Origin**	
"tug" monospecific unmodified immunoglobulins	Refer to approved product information for origin	Nomenclature does not provide a suffix to identify the origin The occupational exposure risk score must be considered. This will include either humanised, chimeric, murine, or a combination, see Table 1.
"bart" monospecific artificial immunoglobulins with engineered constant regions or point mutations		
"mig" multi-specific or bi-specific immunoglobulins		
"ment" monospecific immunoglobulin with variable region fragments.		

Figure 1. Occupational exposure risk flow chart for aseptic preparation of pharmaceuticals and advanced therapeutic products



2.2. Product risk

Prior to preparation of pharmaceutical or advanced therapeutic products, the Director of Pharmacy, principal investigator (PI) or the Drug and Therapeutics Committee (DTC) must be sure that the public health facility has the appropriate facilities, equipment, and staff capabilities to prepare the product. NSW Health has developed two tools, to be completed simultaneously, to assist the Director of Pharmacy, PI or the DTC performing a product risk assessment:

- Checklist for production including approvals, standard operating procedures (SOPs), and processes to be in place prior to acceptance of product for preparation within the public health facility (see Appendix 1 Checklist of requirements prior to approving the preparation of a product in a public health facility)
- Production quality risk assessment of facility and staffing requirements prior to acceptance of product for preparation within the public health facility (see Appendix 2 Production Risk Assessment)

The Pharmaceutical Society of Australia (PSA) *Professional Practice Standards* Appendix 7 Compounding decision support and risk assessment tool, provides a risk assessment for non-aseptic compounding.

When various products are prepared in the same facility, the potential for cross-contamination is a concern, for example, where monoclonal antibodies are prepared in the same cabinet as cytotoxic products. A SOP for product separation between handling products must be in place, including appropriate cleaning and decontamination processes that must occur between preparations and the use of closed system devices may be considered for all cytotoxic products to minimise risk.

Some products require complex dosing calculations or complex reconstitution techniques. The risk of calculation errors can be reduced by a second independent check by a trained pharmacist prior to the preparation of the product.

Specialist aseptic technique training is needed when preparing monoclonal antibodies, for example, proteins are easily broken down with excessive shaking and may froth when reconstituted.

3. PHARMACEUTICAL PRODUCTS

The Director of Pharmacy is responsible for all pharmaceutical product preparation and the required quality assurance and quality control as described in the Pharmaceutical Inspection Co-Operation Scheme (PIC/S) *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010).

The Director of Pharmacy may delegate tasks allocated to them throughout this Policy Directive to the responsible pharmacist, for example product risk assessments, review safety data sheets and the establishment and maintenance of a quality management system. The Director of Pharmacy may also delegate tasks to the clinical trials pharmacist or other relevant senior pharmacists. However, the Director of Pharmacy maintains the overall responsibility to ensure compliance with this Policy Directive.

The Director of Pharmacy must confirm there are high quality procedures in place to support compliance with PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) before compounding or preparing pharmaceutical products. Compounding and preparation of medicines must be in accordance with the Pharmacy Board of Australia (PBA) *Guidelines on Compounding of Medicines*.

All NSW Health facilities must establish a high-risk medicines program in accordance with NSW Health Policy Directive *High-Risk Medicines Management* (PD2020_045). Specific strategies may be needed to mitigate the risk to the patient of causing injury or death from high-risk medicines if inadvertently misused or administered incorrectly. For example:

- preparing pre-mixed potassium chloride intravenous infusions in the pharmacy service, where possible, to reduce risk of toxicity
- warning labelling of vincristine preparations to reduce the risk of incorrect route of administration
- use of Tall Man Lettering to reduce the risk of product selection errors for look-alike sound-alike products; and
- second independent checks of calculations for cytotoxic products and investigational medicinal products (IMPs) when preparing products within the pharmacy service.

3.1. Legislative framework and practice standards

The *Therapeutic Goods Regulations 1990* (Cth) (TGR) exempts certain therapeutic goods (see Schedule 7 of the TGR) or certain persons (see Schedule 8 of the TGR) from the requirement to be licensed to manufacture therapeutic goods (other than medical devices).

The TGR also exempts certain therapeutic goods or classes of therapeutic goods, not including biologicals, from the requirement to be registered or listed on the Australian Register of Therapeutic Goods (ARTG) (see Schedules 5 and 5A of the TGR). The exemptions apply to, respectively, the obligations at Part 3-3, and Parts 3-2 and 3-2A, of the *Therapeutics Goods Act 1989* (Cth).

Schedule 5 of the TGR exempts pharmaceutical products from the requirement to be included on the ARTG where the product (excluding gene therapy or a medicinal cannabis product) is compounded by a pharmacist for a particular person for a therapeutic application to that person.

Schedule 8 of the TGR exempts a pharmacist from the requirement for a Therapeutic Goods Administration (TGA) manufacturing licence, when employed in a public hospital or public institution, manufacturing therapeutic goods (including compounding pharmaceutical products), other than biologicals, for supply in a public hospital or public institution in the same state. For further information on the manufacture and preparation of biologicals see Section 5 Genetically Modified Organism Medicinal Products.

While Schedule 8 of the TGR provides exemptions for medical practitioners and dentists to compound a pharmaceutical preparation, this Policy Directive does not allow medical practitioners or dentists to compound medicines in public health facilities.

Compounded pharmaceutical products can be prepared by a pharmacist in a public hospital in anticipation of a medication order when the pharmaceutical medicine is urgent and a delay

in treatment is detrimental to the outcome for the patient. A legal medication order must still be received prior to supply. Item 6A of Schedule 5 of the TGR provides an exemption for a TGA manufacturing licence for public hospitals to allow compounding or preparation of pharmaceutical products (other than medicines used for gene therapy or that are medicinal cannabis products) without a named patient where the medicine is:

- compounded by a pharmacist employed by a public hospital, engaged in the preparation of therapeutic goods (other than biologicals), and working out of that hospital
- compounded for the anticipated need of a patient of the hospital where the compounding is taking place, and
- considered by the hospital's Drug and Therapeutics Committee (DTC) (however described) to be appropriate for compounding in anticipation of need to treat a patient at the hospital.

Products can be compounded in anticipation of an inpatient medication order for products approved by the DTC where:

- a delay in treatment is detrimental to the outcome for the patient, for example unable to compound the product on a weekend
- the quantity of a compounded product prepared in anticipation of an order is restricted to meet the urgent need of the patient, and not for convenience, with the reason documented on the risk assessment
- assigning a beyond use date (BUD) beyond 24-hours is supported by published stability studies. Where there is no published stability study to support a BUD beyond 24-hours the product cannot be compounded in anticipation of an order
- the facility and equipment for compounding the product within the public hospital is compliant with the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010), and
- for compounding for more than one patient in anticipation of multiple orders, sterility testing of each batch must be performed, for example a small aliquot is inoculated in a growth media and incubated, see Table 4 Comparison of PIC/S GMP PE 010 and USP <797>.

Nurses, including nurse practitioners, and midwives are not permitted to compound under the TGR. Registered nurses, midwives, and medical practitioners may prepare a dose of a product in a 'ready to administer' form when prepared in accordance with the approved product information or NSW Health facility procedures are followed, for example reconstitution of intravenous antibiotics and addition to an intravenous infusion fluid bag using aseptic technique.

Dose preparation of a product by nurses, midwives, or medical practitioners is for immediate use only and must not be assigned a BUD. Dose preparation in a patient care area must be labelled according to the Australian Commission on Safety and Quality in Healthcare *National Standard for User-applied Labelling of Injectable Medicines, Fluids and Lines*.

All non-aseptic extemporaneous compounding of pharmaceutical products must be in accordance with the:

- Pharmacy Board of Australia (PBA) *Guidelines on Compounding of Medicines*
- Pharmacy Council of NSW *Premises and Equipment Guidance for Non-Sterile Complex Compounding*
- compounding chapter in the *Australian Pharmaceutical Formulary Handbook* (APF), and
- reference to the United States Pharmacopeia (USP) General Chapter <795> *Pharmaceutical Compounding-Nonsterile Preparations.*

All aseptic compounding and preparation of pharmaceutical products in public health facilities must be compliant with the facility, personnel, documentation, process, and quality control standards described in the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010).

Australian specific guidance on staff training, equipment, documentation requirements, and preparation of pharmaceutical products at NSW public hospital pharmacy services is provided by the Society of Hospital Pharmacists of Australia (SHPA) *Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments* (2010).

Table 3. Legislation, practice standards and policy relevant to pharmaceutical preparation

Type of legislation	Title	Purpose
Commonwealth legislation	*Therapeutic Goods Act 1989*	Sets out the requirements for registration, listing or inclusion of therapeutic goods in the Australian Register of Therapeutic Goods (ARTG), the controls on the manufacture and advertising of therapeutic goods in Australia and scheduling of substances.
	Therapeutic Goods Regulation 1990	Schedule 5 provides the circumstances where an exemption to compound without the requirement for therapeutic goods to be listed on the ARTG. Schedule 8 provides the exemption to pharmacists in public hospitals to manufacture (such as compound) medicines for patients of hospitals or public institutions in that state or territory from the requirement to be a Therapeutic Goods Administration (TGA) licenced manufacturer.
	The Poisons Standard	The Poisons Standard consists of the Standard for the Uniform Scheduling of Medicines and Poisons.
NSW Legislation	*Poisons and Therapeutics Goods Act 1966*	Controls the supply, dispensing, prescribing, storage etc of scheduled medicines and some other therapeutic goods. Note: The *Medicines, Poisons and Therapeutic Goods Act 2022* (NSW) will be in effect in due course.
	Poisons and Therapeutic Goods Regulation 2008	Provides controls over for the supply, dispensing, prescribing, storage etc. of scheduled medicines and some other therapeutic goods. Note: The Medicines, Poisons and Therapeutic Regulation will be in effect in due course.

	Health Practitioner Regulation National Law No 86a of 2009	Controls and accredits health practitioners and students, to provide protection of the public by ensuring that only health practitioners who are suitably trained and qualified to practise in a competent and ethical manner are registered.
	Health Practitioner Regulation 2016	Provides control over the national registration and accreditation scheme for registered health practitioners.
	Work Health and Safety Act 2011	Outlines the legal obligations to ensure the health and safety of workers handling hazardous chemicals in the workplace, including hazardous drugs.
	Work Health and Safety Regulation 2017	Outlines the requirements for producing, handling, storing and transporting hazardous chemicals in the workplace, including hazardous drugs.
NSW Health Policy Directive	*High-Risk Medicines Management* (PD2020_045)	Outlines the requirements for the safe management and use of medicines which have a high risk of causing patient injury or death if inadvertently misused or administered incorrectly.
	Clinical and Related Waste Management for Health Services (PD2020_049)	Provides a minimum standard for waste management within health services to ensure handling and containment of specific clinical waste streams is in line with NSW legislation, licensing, and waste minimisation.
	Medication Handling (PD2022_032)	Consolidates procedures and standards on medication procurement, storage, prescribing, supplying, dispensing and administration at NSW public health facilities with the requirements of the *Poisons and Therapeutic Goods Act 1966* (NSW) and *Poisons and Therapeutic Regulation 2008* (NSW), and NSW Health policies relevant to medication handling.
	Approval Process for Medicines and Their Use (PD2022_056)	Outlines governance structures and standard procedures for medicines use and approval within NSW public health facilities. Approval processes to submit applications to amend the NSW Medicines Formulary and for individual patient use approvals.
Enforceable Standards under *Health Practitioner Regulation National Law No 86a of 2009* (NSW) and *Health Practitioner Regulation 2016* (NSW)	Pharmacy Board of Australia *Guidelines on Compounding of Medicines* (2015)	Under Section 39, instructs pharmacists who compound medicines to ensure medicine quality, safety, and efficacy.
	NSW Pharmacy Council of NSW *Fact Sheet: Raw materials used in compounding* (2018)	Support the decision-making process when procuring raw materials for compounded preparations.

Professional Practice Standards	Society of Hospital Pharmacists of Australia (SHPA) *Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments* (2010)	Guidance on practical process, facility and staffing requirements and system for managing quality in compounding and aseptic preparation in Australian hospital pharmacies. Note: A new standard of practice to replace the SHPA *Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments* (2010) is in development. The 2010 standard is available from the SHPA on request.
	The Society of Hospital Pharmacists of Australia (SHPA) *Safe Handling of Cytotoxic Drugs in Pharmacy Departments* (2005)	Guidance on practical processes of safe handling on cytotoxic drugs. Note: A new guideline to replace the SHPA *Standards of Practice for the Safe Handling of Cytotoxic Drugs in* Pharmacy *Departments* (2005) is in development. The 2005 standard is available from the SHPA on request.
	The Society of Hospital Pharmacists of Australia (SHPA) *Transportation of Cytotoxic Drugs from Pharmacy Departments* (2007)	Guidance on practical processes for the safe transportation of cytotoxic drugs within the public health facility. Note: A new guideline to replace the SHPA *Standards of Practice for the Transportation of Cytotoxic Drugs from Pharmacy Departments* (2007) is in development. The 2007 standard is available from the SHPA on request.
	Pharmaceutical Inspection Co-Operation Scheme (PIC/S) *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010)	Guidance on good manufacturing practice (GMP) for the preparation of medicinal products by healthcare establishments for direct supply to patients.
	United States Pharmacopeia (USP) Chapter <795> *Pharmaceutical Compounding - Nonsterile preparations*	Guidance on applying good compounding practices for the preparation of non-aseptic compounded formulations.
	Pharmaceutical Society of Australia (PSA) *Professional Practice Standard 5 - Compounding* (2016)	Competency framework for the minimum standard of pharmacist practice that must be achieved for compounding medicines.
	Pharmaceutical Society of Australia *Australian Pharmaceutical Formulary Handbook* (APF)	Provides essential reference information on simple compounding formulae and requirements for non-aseptically prepared extemporaneous products.
	Australian/New Zealand Standard 2252.4 *Biological safety Cabinets Classes I and II- Installation and use*	Guidance on the use of Class I and Class II Biological Safety Cabinets to provide protection against Risk Group 2 and 3 micro-organisms.

	Australian/New Zealand Standard 2252.2:2004 *Biological safety cabinets - Laminar flow biological safety cabinets (Class II) for personnel, environment, and medicine protection*	Specifies the basic requirements for Class II laminar flow biological safety cabinets (BSC) intended to provide protection for personnel and the environment from hazardous biological agents.
	Australian/New Zealand Standard 2252.5:2017 *Cytotoxic drug safety cabinets (CDSC) - Design, construction, installation, testing and use*	Specifies the basic requirements for cytotoxic drug safety cabinet (CDSC) design, construction, installation, testing and use, and the surrounding environment in which the CDSC is located.
	Australian/New Zealand Standard 2252.6:2011 *Clean workstations - Design, installation, and use*	Specifies design, construction, and performance requirements for clean workstations, together with requirements and guidance relating to their installation and use.
Professional Practice Guidelines	Pharmaceutical Inspection Co-Operation Scheme *(PIC/S) Guide to Good Manufacturing Practice for Medicinal Products Part I* (PE 009-15)	Guidance on Good Manufacturing Practice (GMP) for the industrial manufacturing of pharmaceutical medicines under an appropriate system for managing quality. The manufacture of products applies to Therapeutic Goods Administration (TGA) licenced facilities.
	Pharmaceutical Inspection Co-Operation Scheme (PIC/S) *Guide to Good Manufacturing Practice for Medicinal Products Part II* (PE 009-15)	Guidance on good manufacturing practice (GMP) for industrial TGA manufacturing of active pharmaceutical ingredients (APIs). The manufacture of APIs must not be undertaken in public health facilities.
	United States Pharmacopeia (USP) Chapter <797> *Pharmaceutical Compounding – Sterile Preparations*	Guidance on applying good compounding practices for the preparation of compounded sterile preparations for human use. For this policy, applies only to investigational medicinal products (IMPs).
	Occupational Safety and Health Administration (OSHA) *Controlling occupational exposure to hazardous drugs*	Guidance on the health and safety hazards faced by healthcare workers who handle Hazardous Drugs (HDs) and criteria to classify HDs.
	American Society for Parenteral and Enteral Nutrition (ASPEN) *Clinical guidelines: Parenteral nutrition ordering, order review, compounding, labelling, and dispensing*	Guidance for clinicians to minimise errors with parenteral nutrition prescribing, order review and verification, compounding, labelling, dispensing, and administration.

	United States Pharmacopeia (USP) Chapter <800> *Hazardous drugs - Handling in Healthcare Settings*	Describes responsibilities of personnel handling hazardous drugs; facility and engineering controls; procedures for deactivating, decontaminating, and cleaning; spill control; and documentation.
	National Institute for Occupational Safety and Health (NIOSH) *List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* (2016)	A list of antineoplastic, non-antineoplastic and reproductive hazardous drugs. NIOSH consults a variety of resources including, but not limited to, safety data sheets, product labelling approved by the U.S. Food and Drug Administration and databases such as DailyMed and DrugBank.

3.1.1. PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (PE 010)

Pharmaceutical and advanced therapeutic preparations in NSW public health facilities must be prepared in accordance with the Society of Hospital Pharmacists of Australia *Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments* (2010) and comply with the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010).

Under Section 39 of the *Health Practitioner Regulation National Law 2009* (NSW), the Pharmaceutical Board of Australia (PBA) *Guidelines on Compounding of Medicines* states that the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) is the standard for all pharmacists, including those in public health facilities, aseptically preparing pharmaceutical and advanced therapeutic products.

The PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) provides a more conservative application of beyond use dates (BUDs), additional requirements for protection of the primary engineering control (PEC) and more extensive environmental monitoring systems to ensure safe quality products for our patients, when compared to the United States Pharmacopeia USP <797> *Pharmaceutical Compounding – Sterile Preparations*. Table 4 Comparison of PIC/S GMP PE 010 and USP <797> shows the differences between the USP <797> *Pharmaceutical Compounding – Sterile Preparations* and PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) standards.

Table 1. Comparison of PIC/S GMP PE 010 and USP <797>

	PIC/S GMP PE 010	USP <797>
Aseptically prepared preparations in cleanrooms	Endorsed by the Pharmacy Board of Australia	
	Referenced in the *Australian Pharmaceutical Formulary Handbook*	Referenced in the *Australian Pharmaceutical Formulary Handbook*
	Conservative standardised BUDs based on published studies and on-going stability testing:	Extensive and varied BUDs according to risk of preparation, based on extrapolation from literature sources:

	• All aseptic preparations are high risk and assigned a BUD of 24 hours Where a BUD greater than 24 hours is required, a stability study or stability data must be referenced and must be based on published studies using the unique combinations of active ingredient, diluents and packaging components. The justification for an extended BUD must be in the risk assessment.	• Category 1 aseptically prepared products in a primary engineering control (PEC) not in a cleanroom assigned a BUD of 12 hours at room temperature or 24 hours refrigerated • Category 2 aseptically prepared products in a cleanroom, using only sterile ingredients, assigned a BUD of 4 days at room temperature, 10 days refrigerated and 45 days in a freezer • Category 2 aseptically prepared products in cleanroom using non-sterile ingredients, assigned a BUD of 24 hours at room temperature, 4 days refrigerated and 45 days in a freezer. BUDs extended with sterility testing and terminal sterilisation. See *USP Compounding Standards and Beyond-Use Dates (BUDs).*
	Quality assurance media testing using settle plates, finger testing plates, and contact plates incubated for: • 48 hours at 30-35°C to assess for bacterial growth, and • an additional 5 days at 25°C to assess for moulds and fungi.	Quality assurance media testing using settle plates, finger testing plates, and contact plates using trypticase soy agar incubated for: • 48 hours at 30-35°C to assess for bacterial growth, and • an additional 5 days at 25°C to assess for moulds and fungi.
	BUD after opening (for example, needle puncturing) multi-dose vials is 24-hours.	BUD after opening (for example, needle puncturing) multi-dose vials is 28 days unless otherwise specified by the manufacturer.
	If a product is prepared for a single patient, it is assumed that no final product testing will be required. For compounding for more than one patient in anticipation of multiple orders, sterility testing is required. Refer to PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part 1 (PE 009).	Batch compounding is supported by the USP <797>. Sterility testing is required for high risk aseptically prepared products in batches of more than 25 identical containers.
HEPA classification for clean zones by number of particles/m^3 ISO 5 = Grade A and B ISO 7 = Grade C ISO 8 = Grade D	Four clean zones for aseptically preparing medicines: Grade A- PEC Grade B- buffer room Grade C- ante room, preparation of solutions to be filtered Grade D- support room	Three clean zones for aseptically preparing medicines: ISO 5- PEC ISO 7- buffer area ISO 8- ante room

The standards that apply to the preparation of investigational medicinal products (IMPs) are often determined by the sponsor company. To support sponsor led clinical trials in public health facilities, this Policy Directive permits compliance to the USP <797> *Pharmaceutical Compounding – Sterile Preparations* standards at the discretion of the sponsor. The application of the USP <797> *Pharmaceutical Compounding – Sterile Preparations*

standards allow for the handling and preparation of IMPs to meet the sponsor led requirements. The use of USP <797> *Pharmaceutical Compounding – Sterile Preparations* must be in the risk assessment.

Preparation of IMPs in public health facility led clinical trials must comply with PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010). Phase 2 and 3 clinical trials must be prepared in a Therapeutic Goods Administration (TGA) licenced manufacturing facility, see Section 4 Investigational medicinal products.

3.1.2. Staff capabilities and quality management

The Director of Pharmacy is responsible for maintaining appropriate staffing levels to conduct all tasks safely and effectively. Staff must be competent to conduct all tasks.

Pharmacists involved in aseptic preparation require an extensive understanding of good aseptic practices and a unique skillset. The Pharmacy Board of Australia *Guidelines on Compounding of Medicines* informs that to extend the scope of practice of a pharmacist beyond entry level competency, pharmacists must complete further training specific to the type of compounding, for example, compounding hormones, hazardous drugs (HDs) or aseptically prepared injectables and eye drops. This Policy Directive adopts the personnel and quality control components of the *Australian Pharmaceutical Formulary Handbook* (APF) compounding chapter for all non-aseptically prepared products.

The Director of Pharmacy, or delegate responsible pharmacist, must have relevant knowledge, current validation, appropriate training in microbiology and quality assurance, and theoretical experience in the preparation of relevant pharmaceutical and advanced therapeutic products.

The Director of Pharmacy, or delegate responsible pharmacist, may engage assistance in compounding tasks from suitably trained and experienced individuals working under their direct supervision, including pharmacy students, intern pharmacists, pharmacy assistants or technicians.

To have consistently safe aseptically prepared pharmaceutical or advanced therapeutic products, irrespective of scale and complexity, the Director of Pharmacy, or delegate responsible pharmacist, must implement a quality management system which incorporates the elements of PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) and the Society of Hospital Pharmacists of Australia *Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments* (2010).These elements include:

- a risk assessment performed for all persons entering a clean environment to assess for respiratory illness or conditions that may cause excessive skin shedding which may contaminate the clean environment

- a risk assessment performed for additional occupational exposure risk for staff who may be pregnant, trying to conceive or breastfeeding
- annual health monitoring, including full blood count, to identify changes to health status of staff due to workplace exposure to cytotoxic and other HDs. For more information refer to SafeWork NSW *Cytotoxic drugs and related waste - Risk management*
- all NSW Health employees entering a clean room environment must have a thorough understanding of clean environments including:
    - Good Manufacturing Practice (GMP)
    - PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010)
    - local standard operating procedures (SOPs)
    - occupational exposure, and
    - microbiology.

  As a minimum, GMP training and Pharmacy Technician Certificate IV unit of competency HLTPHA016 Conduct small-scale compounding and labelling of aseptically prepared pharmaceutical products should be completed or in progress. All external contractors entering the clean room environment must be supervised and accompanied by the senior production pharmacist or senior production pharmacy technician
- a risk assessment for any work that could affect the quality of products prepared, (for example maintenance work of air handling systems), key equipment (for example biological safety cabinet), and sterilisation of components. The risk assessment must include evidence that the contractor, either internal or external to the public health facility, complies with PIC/S standards and NATA requirements as required. A service level agreement is needed for any external contractor
- annual validation of pharmacy staff competence in aseptic technique must include a media fill process to replicate all techniques and equipment used. The validation must demonstrate competence to all SOPs and be under the direct supervision of a senior production pharmacist or senior production pharmacy technician validated in the processes being assessed
- documentation, including master formulation records to ensure reproducibility. All staff working in production roles must be educated on the potential consequence of any deviation from the validated SOPs, both to the integrity of the product and to the patient
- quality control and quality assurances, for example environmental monitoring, performance monitoring and continuous temperature logging. Final product quality checks and tests must be documented, including a product rejection procedure, for example contamination of product by a cored bung on a vial
- complaints and medicine recalls must be managed in accordance with Section 9.1 Recalls and incident reporting

- Self-audits, including auditing of contractors.

3.1.3. Assignment of beyond use dates

The Director of Pharmacy is responsible for ensuring the shortest appropriate beyond use date (BUD) is assigned to all pharmaceutical and advanced therapeutic products prepared by the pharmacy service. This Policy Directive adopts the *Australian Pharmaceutical Formulary Handbook* (APF) application of BUDs for non-aseptically prepared products.

Consistent with the Pharmacy Board of Australia (PBA) *Guidelines on Compounding of Medicines* and PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) this Policy Directive adopts that without terminal sterilisation, the pharmacist should not assign a BUD of no more than 24-hours for aseptically prepared pharmaceutical products when stored under optimal storage conditions.

Where required, the application of an extended BUD beyond 24-hours for aseptically prepared pharmaceutical products must be supported by a consistently high level of microbial quality control and assurance within PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) acceptable colony forming unit (cfu) limits for the duration of the BUD to be assigned. For example, to apply a 72-hours BUD, there must be:

- supporting published stability data
- a demonstrated quality environmental monitoring system, including settle plates and finger dabs, to demonstrate microbial growth is consistently within acceptable cfu limits for testing periods of 72-hours in the primary engineering control (PEC) where products are prepared, and
- justification for assignment of an extended BUD. This must be documented in the risk assessment.

Under this Policy Directive a BUD must not exceed 7-days for aseptically prepared products. The assigned BUD must be adjusted/ reduced according to the circumstances that may affect the limits of stability and/or sterility of products, for example, level of microbial growth in the secondary engineering control (SEC) or PEC.

The use of a Food and Drug Administration (FDA) approved or Therapeutic Goods Administration (TGA) registered closed-system transfer device, for example Equashield®, may be used to extend the BUD after opening a multi-dose vial from 24-hours to a maximum of 7-days in accordance with FDA or TGA approval.

This Policy Directive adopts the USP <797> *Pharmaceutical Compounding – Sterile Preparations* on application of BUD for frozen prepared products. A BUD must not exceed 45-days at -30°C followed by a maximum of 72-hours at refrigerated temperature. The stability of the preparation must be supported by approved references and/or data.

Under extenuating circumstances where clinical benefit outweighs the microbial risk, the Drug and Therapeutics Committee (DTC) can review the quality management system data and stability references to assess the risk of applying an extended BUD and provide approval where appropriate, on an individual patient and product basis. The approval is not on-going and must be reviewed annually.

The Director of Pharmacy is responsible to implement procedures to ensure that:

- the compounded or prepared medicine is chemically and physically stable for the recommended BUD included on the label – inclusive of infusion time where appropriate, and
- appropriate storage facilities used to maintain the quality of the preparation over that period.

3.2. Procurement, receipt and storage

NSW Health Policy Directive *Medication Handling* (PD2022_032) outlines pharmaceutical ordering, receipt, storage requirements and management of cold chain breaches. Cold chain temperature must be monitored both at the pharmacy service, during transportation as necessary, and at the patient care area where the preparation is to be used.

Schedule 8 of the *Therapeutic Goods Regulations 1990* (Cth) exempts a pharmacist working in a public hospital pharmacy from the operation of Part 3-3 of the *Therapeutic Goods Act 1989* (Cth) and may therefore prepare therapeutic goods, other than biologicals, for supply in hospitals or public institutions in the same State or Territory.

It is the responsibility of the Director of Pharmacy to ensure that any products sourced from another health facility are prepared in compliance with PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010).

Where aseptically prepared products are used to treat a patient in their home, the pharmacist must, where possible, confirm that appropriate storage is available and that the patient is educated accordingly. The pharmacist may confirm storage conditions and patient education with the Hospital in the Home nurse or equivalent.

3.2.1. Importation

Pharmaceutical products imported into NSW by a public health facility for example, under the Special Access Scheme (SAS) with non-English product information must be risk assessed by the Director of Pharmacy at the public health facility to ensure there is adequate product information available in English to enable the completion of a risk assessment for the preparation, including confirmation of the correct active pharmaceutical ingredient and excipients.

3.2.2. Hazardous drugs

The Society of Hospital Pharmacists of Australia (SHPA) Guideline for *Safe Handling of Hazardous Medicines 2005* describes the procurement, receipt, and storage of hazardous drugs (HDs).

Staff must always don gloves that provide permeation resistance to the HD being handled. Drug packages, bins, shelves, and storage areas must display cautionary labels to identify special handling precautions, for example cytotoxic products. Safe Work Australia provides guidance on the *Global Harmonised System of Classification and Labelling of Chemicals*.

The Director of Pharmacy must evaluate HDs prior to ordering and must review the safety data sheet (SDS) from the supplier, the National Industrial Chemicals Notification and

Assessment Scheme (NICNAS) chemical assessment search, or Chem Alert, to establish if the facility has the capacity for suitable storage and handling processes for the product.

HDs listed on the current National Institute for Occupational Safety and Health *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016* or Victorian Therapeutics Advisory Group (VICTAG) *Handling of Hazardous Medicines* (2021) list must not be unpacked from the external shipping container in areas that are positive pressure relative to the surrounding areas, such as a positive pressure clean room environment. During receipt of HDs, visual examination of cartons for damage is important and policies and procedures must be in place for handling damaged cartons or containers of HDs.

HD spill kits must be available in any area where HD medicines are handled. The spill kit must contain complete personal protective equipment (PPE), including a generic N95 mask. This Policy Directive adopts the recommendation of the United States Department of Labor Occupational Safety and Health Administration *Controlling Occupational Exposure to Hazardous Drugs*, that all staff involved in the preparation of HDs must receive proper training and fit testing to don N95 masks. Surgical masks do not provide adequate protection from the harmful effects of repeated occupational exposure to HDs for staff involved in the preparation of these products.

3.2.3. Sourcing raw ingredients

The Director of Pharmacy is responsible for ensuring appropriate procedures are in place to evaluate all raw ingredients including active pharmaceutical ingredients (APIs) and inactive excipients, for example suspending agents, to ensure they are identifiable, comply with pharmacopeial standards and are produced by a Therapeutic Goods Administration (TGA) manufacturing licenced or Good Manufacturing Practice (GMP) certified manufacturers.

The Pharmacy Council of NSW *Fact Sheet Raw materials used in compounding* describes the obligations of the pharmacist with respect to assessing the authenticity of raw ingredients used in compounding. The *Australian Pharmaceutical Formulary Handbook* (APF) provides guidance for raw ingredients materials used for extemporaneous compounding.

Where ingredients are of biological or human origin, the Director of Pharmacy must confirm there is minimal risk of any disease transmission. The TGA regulates the use of material of animal or human origin in *Guidance 10: Adventitious agent safety of medicines* (2013) to ensure the safe inclusion of such materials in pharmaceutical preparations.

3.3. Facility and equipment requirements

The Director of Pharmacy is responsible for the provision of necessary facility and equipment requirements for each product prepared by the pharmacy service, for example:

- non-aseptically prepared products
- non-aseptically prepared hazardous drug (HD) products
- aseptically prepared products
- aseptically prepared HD products

The Australasian Health Facility Guidelines *Part B - Health Facility Briefing and Planning 0560 - Pharmacy Unit* outlines the specific requirements for pharmacy facilities and clean

room design. All facilities and equipment must be suitable for the intended use and protect the quality of the medicine.

All clean rooms and primary engineering controls (PECs), for example powder containment cabinets or biological safety cabinets (BSCs), must be accredited annually by the National Association of Testing Authorities (NATA). For more information on NATA accreditation refer to *How to become accredited*. All other equipment used in the preparation of pharmaceutical products must be calibrated annually.

Tap water is a source of microbial contamination for pharmacy cleanrooms. The two main threats from water are *Pseudomonas aeruginosa* and *Legionella* species. To help reduce the risk of water borne contamination sinks must not be adjacent to a Grade B cleanroom, refer to Table 4 Comparison of PIC/S GMP PE 010 and USP <797>. In addition, a plumbed shower and eye wash station are not required for a hospital pharmacy cleanroom, the provision of an emergency eyewash kit, located directly outside the cleanroom or laboratory, is acceptable and will reduce the risk of water borne threats.

Pharmacists must confirm that pharmaceutical preparations are compatible with the materials of the syringe, infusion bag, or other delivery device used to administer the medicine.

3.3.1. Non-aseptically prepared extemporaneous products

The *Australian Pharmaceutical Formulary Handbook* (APF) provides essential reference information on simple compounding formulae and requirements for non-aseptically prepared extemporaneous products.

The Director of Pharmacy is responsible for ensuring the appropriate facilities and equipment are provided before undertaking compounding of non-aseptically prepared products. The minimum facility and personal protective equipment (PPE) requirements include:

- eye protection, hair net, gloves and surgical mask
- a designated clean area must be away from the main pharmacy dispensary and parts of the pharmacy where there is a considerable amount of traffic (such as aisles, entrance and exit doors), to avoid contamination of the product with dust and dirt
- high efficiency particulate air (HEPA) filtered powder containment cabinets or laminar flow workstations should be considered.

Laminar flow clean workstations must be distinguished from biological safety cabinets, as any aerosol produced from work is discharged towards the operator and into the environment. They must not be used for handling hazardous drugs (HDs).

All glassware, mortar, and pestles, stirring rods must be of laboratory standard or calibrated to an equivalent accuracy of +/- 2% as stated in the APF.

3.3.2. Non-aseptically prepared hazardous drug products

The Director of Pharmacy is responsible for providing a risk assessment to identify the varied level of containment requirements for all non-aseptically prepared products according to the occupational exposure risk for staff handling hazardous products as per the National Institute for Occupational Safety and Health *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016*, for example:

- personal protective equipment (PPE), minimum of eye protection, hair net, lab coat, gloves and N95 mask
- primary engineering controls (PECs) must be used when preparing hazardous drugs (HDs). The choice of PEC, for example powder hood, pharmaceutical isolator or biohazard safety cabinet, should be suitable for the HD and the level of risk identified during the risk assessment. For example:
    - Spironolactone and tacrolimus suspensions, must be prepared in a negative pressure high efficiency particulate air (HEPA) filtered powder containment cabinet in a negative or neutral pressure room, see *Australian Pharmaceutical Formulary Handbook* (APF)
    - Cytotoxic products must be prepared in an externally ducted PEC (cytotoxic drug safety cabinets (CDSC) or negative pressure pharmaceutical isolator) in a segregated negative pressure room, see USP<800> *Hazardous Drugs - Handling in healthcare settings* (2022)
    - Organic products, for example pre-packing aliquots of phenol, must be in a PEC which provides fume protection and is carbon filtered.

3.3.3. Reconstitution of hazardous drug products

The Director of Pharmacy is responsible for the level of containment provided for the reconstitution of oral suspensions of hazardous drugs (HDs) by pharmacy services.

Reconstitution of non-cytotoxic hazardous suspensions included on the National Institute for Occupational Safety and Health *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016*, for example mycophenolate oral suspensions, pose serious occupational exposure risks to pharmacy staff.

Oral antibiotic suspensions pose a risk of hypersensitivity reaction. Staff must don appropriate personal protective equipment (PPE) according to the risk of the HD.

Cytotoxic suspensions must be handled in accordance with Section 3.3.2 Non-aseptically prepared hazardous drug products. The Director of Pharmacy is responsible for assessing the PPE requirements. The minimum facility and PPE requirements include:

- PPE minimum of eye protection, hair net, gloves and surgical or N95 mask (depending on the level of risk identified in the risk assessment)
- reconstitution of suspensions of HDs included on the NIOSH list must be undertaken in a segregated area away from the main dispensary and should be undertaken in a negative pressure high efficiency particulate air (HEPA) filtered powder containment cabinet or equivalent
- reconstitution of oral antibiotic suspensions/ syrups must be undertaken in a segregated area away from the main dispensary and the use of a negative pressure HEPA filtered powder containment cabinet or equivalent should be considered.

As the reconstitution of oral antibiotics by nurses, midwives or medical practitioners in the patient care area occurs on an ad hoc basis and it is therefore not considered a repeated occupational exposure risk. Nurses, midwives and medical practitioners should don the

minimum PPE of eye protection, gloves and surgical mask and not reconstitute any antibiotics for which they have a known sensitivity.

3.3.4. Aseptically prepared pharmaceutical products

To minimise the risk of microbiological and particulate contamination, aseptically prepared pharmaceuticals are subject to special environmental controls, for example high efficiency particulate air (HEPA) filtered clean room and biological safety cabinets (BSCs)).

All secondary engineering controls (SECs) used to prepare pharmaceutical products intended to be sterile, must meet the specifications described in the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) and Annex 1 of the PIC/S *Guide to Good Manufacturing Practice for Medicinal Products* (PE 009).

The minimum facility and personal protective equipment (PPE) requirements for aseptic preparation of pharmaceutical products with the pharmacy service are:

- eye protection, hair net, sterile gloves, sterile N95 mask (to provide protection from sporicidal inhalation), full body protection, for example coveralls and over booties
- four HEPA filtered clean zones, Graded A, B, C and D, refer to Table 1. Comparison of PIC/S GMP PE 010 and USP <797>
- two phases of disinfectant material transfer, the first phase being a sporicidal, to reduce the risk of microbial contamination into the clean room, preferably within HEPA filtered pass through hatches. Mechanical timers should be in place to time transfer disinfection processes, where this is not possible a digital timer must be used
- preparation within an appropriate level of primary engineering control (PEC) according to the risk assessment of the product being prepared.

Older facilities that do not meet these standards may continue to aseptically prepare pharmaceuticals, where the Director of Pharmacy and Drug and Therapeutic Committee (DTC) complete a risk assessment and are satisfied that the facility is working within acceptable colony forming unit (cfu) limits.

The Chief Executive must approve the assessment of the current production facilities and provide a plan to the NSW Health Chief Pharmacist Unit, of works necessary to meet these standards (see Appendix 3 Policy Directive compliance checklist and Appendix 4 Pharmacy production facilities compliance assessment).

Products that have a high risk of allergic reactions, for example antibiotics, should be prepared in a separate cabinet, and preferably separate SEC, to all other medicines to reduce the risk of cross contamination between products and subsequent reaction by the patient during administration.

Under Section 2 Annex 1 of the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) a segregation of beta lactams from other antibiotics is required. Where facilities are unable to accommodate this level of separation, a verified decontamination process between product preparation must occur.

Section 2 Annex 1 of the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) provides information on the cleaning

requirements. Details of the appropriate decontaminant per product can be sought from the pharmaceutical manufacturer. Preparation of biological medicines for example, enzymes may be prepared with similar strategies to avoid cross-contamination.

Where sterilisation of the final product is by filtration, the Director of Pharmacy is responsible for assessing the compatibility of the filter with all ingredients used and that a protocol is in place to test the integrity of the filter prior to final release of the product.

Total parenteral nutrition must be compounded in a positive pressure environment. The nature of the formulation acts as the perfect growth media for microbial proliferation. Protection of the product from microorganisms is critical to patient safety.

3.3.5. Aseptically prepared hazardous drug products

The Australian Standards ME-060 *Controlled Environment AS2252* series provides the standards for design, installation and use of primary engineering controls (PECs) for personnel and environment protection.

Safe preparation of cytotoxic and other hazardous drugs (HDs) require handling under negative pressure in an externally exhausted cytotoxic drug safety cabinets (CDSC) or pharmaceutical isolators within a dedicated negative pressure containment secondary engineering controls (SEC) (see *AS2252-2017 Controlled environments Part 5 – Cytotoxic drug safety cabinets (CDSC): Design, construction, installation, testing and use*) separated from all other pharmaceutical preparation. Class I and Class II biological safety cabinets (BSCs) are unsuitable for handling cytotoxic products.

The minimum facility requirements for aseptic preparation of HD products with the pharmacy service are:

- personal protective equipment (PPE) minimum, eye protection, hair net, double sterile gloves, sterile N95 mask, full body protection for example coveralls and over booties plus additional disposable apron
- four high efficiency particulate air (HEPA) filtered negative pressure clean zones, Graded A, B, C and D
- two phases of disinfectant material transfer, see Section 3.3.4 Aseptically prepared pharmaceutical products
- preparation within a negatively pressured appropriate level of physical containment (PC) or CDSC according to the risk assessment of the product being prepared.

Closed system transfer devices (CSTDs) can be used for the manipulation of pharmaceutical preparations, however CSTDs must be assessed for compatibility with all ingredients being used. There are different types of CSTDs with variable compatibilities towards reactive substances, which can cause cracking of the integrity of the unit and cause leakage of hazardous substances. It is the responsibility of the Director of Pharmacy to check compatibility of substances with the manufacturer of the CSTD before their use.

3.4. Supply, transport and packaging requirements

Pharmaceutical products prepared by the pharmacy service must be supplied or dispensed in accordance with the packing, labelling, and recording requirements in NSW Health Policy

Directive *Medication Handling* (PD2022_032). Prepared pharmaceutical products can only be dispensed from a valid prescription in accordance with the same Policy Directive and labelling must include the name and contact details of the pharmacy service that prepared the pharmaceutical.

The route of administration must be clearly stated on the packaging of aseptically prepared hazardous drug (HD) products for example, cytotoxic products, in accordance with Pharmaceutical Society of Australia *Professional Practice Standards*.

All aseptically prepared pharmaceutical products must have continuous cold chain monitoring during storage and transport, including courier services, and a documented risk management process for cold chain breaches. All staff transporting aseptically prepared pharmaceutical products must be trained in cold chain management and have completed the NSW Health Vaccine Storage and Cold Chain Management online learning module.

During transport of aseptically prepared HDs, staff must don appropriate personal protective (PPE) and the product(s) are to be transported with an appropriate spill kit for example, cytotoxic spill kit. The Director of Pharmacy is responsible for assessing the requirement of PPE and providing the appropriate decontamination spill kit, including a secondary unbreakable container, during transport.

3.5. Disposal

Disposal and waste management of pharmaceutical products must be in accordance with NSW Health Policy Directive *Medication Handling* (PD2022_032). Expired, unusable or unwanted preparations, including hazardous drugs (HDs), must be destroyed in accordance with NSW Health Policy Directive *Clinical and Related Waste Management for Health Services Policy* (PD2020_049).

Any prepared pharmaceutical found to be unusable after it has been transported to a clinical area must be disposed of in that clinical area. SafeWork NSW *Cytotoxic drugs and related waste - Risk management* provides practical advice for staff on how to prevent or minimise the risks to health associated with handling cytotoxic pharmaceutical products and related waste within health care establishments.

4. INVESTIGATIONAL MEDICINAL PRODUCTS

Many clinical trials present an additional risk to patient safety through the limited knowledge of harm of unapproved medicines. The preparation of investigational medicinal products (IMPs) involves added complexity compared with handling medicines approved by a medicines' regulator, such as the Therapeutic Goods Administration (TGA).

IMPs must be prepared in accordance with the principles and detailed guidelines of the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010), Annexes of the PIC/S *Guide to Good Manufacturing Practice for Medicinal Products* (PE 009), investigator's brochure (IB) and as outlined in Section 3 Pharmaceutical Products.

It is the responsibility of the Director of Pharmacy to review:

- all documentation of the Clinical Trial Approval (CTA) or Clinical Trial Notification (CTN)
- the Office of the Gene Technology Regulator (OGTR) dealings not involving intentional release/ dealings involving intentional release (DNIR/DIR) license
- directions of the Institutional Biosafety Committee (IBC)
- Drug and Therapeutic Committee (DTC) approval and additional information provided by the sponsor/ manufacturer to assess the capacity of the pharmacy service to receipt, store, handle and/or prepare and transport each individual IMP.

Where a CTA or CTN applies to multiple trial sites the responsibility and decision-making process for the clinical trial remains with the Director of Pharmacy, or delegate clinical trials pharmacist, from the principal facility in consultation with the satellite sites. A risk assessment must be completed by the Director of Pharmacy, or delegate, for each clinical trial before acceptance by the trial site.

The service responsible for the storage and handling of the product, such as the pharmacy service, must be included in the initial handling and resourcing discussions.

NSW Health has agreed to implement the National Clinical Trials Governance Framework (NCTGF) under the Australian Health Service Safety and Quality Accreditation (AHSSQA) Scheme. To embed clinical trials into routine health service provision, public health facilities will need to enter a contractual agreement with an accrediting agency to assess the *Implementation and Assessment to the National Clinical Trials Governance Framework*.

The accrediting agency will usually be the same as the one assessing the National Safety and Quality Health Service (NSQHS) Standards. Accreditation will strengthen the clinical and corporate governance arrangements for public health facilities, trial sponsors, and trial investigators that deliver clinical trials.

4.1. Legislative framework and practice standards

A pharmacy service that does not hold a Therapeutic Goods Administration (TGA) manufacturing licence, can manufacture goods under Item 1, Schedule 7 of the *Therapeutic Goods Regulation 1990* (TGR) (Cth) for first-in-human use studies on human volunteers (phase 1), and must be compliant with the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010). There is no such exemption in the TGR for a phase 2 or later study.

The *Poisons and Therapeutic Goods Regulation 2008* (NSW) applies to IMPs. If the IMP is a scheduled substance, then the usual prescribing and dispensing restrictions apply unless an exemption or authorisation by the NSW Ministry of Health can or has been issued. For example, an IMP that is a Schedule 4 substance must be prescribed by an Australian Health Practitioner Regulation Agency (AHPRA) registered practitioner. IMPs for use in clinical trials must be prescribed by the principal investigator (PI) or delegate sub-investigator(s) in accordance with the trial protocol. If the IMP is a Schedule 8 substance for use in a clinical trial, including unapproved drugs of addiction, it must be prescribed by a AHPRA registered medical practitioner.

Dispensing of IMPs in a public health facility must be by a pharmacist, or under the supervision of a pharmacist. In the absence of a pharmacist, or in an emergency scenario, for

example remote facilities or after hours if there is no pharmacist available, pre-packaged IMPs can be supplied by the PI or delegate sub-investigator(s) in accordance with the NSW Health Policy Directive *Medication Handling* (PD2022_032) and the TGA *Australian Clinical Trial Handbook*, which includes labelling requirements.

Dispensing of an IMP by a medical practitioner would be appropriate only in limited circumstances for IMPs pre-packed and stored in the medication room of the patient care area, as delegated by the Director of Pharmacy. Labelling of IMPs supplied to participants must be in accordance with the same requirements as scheduled medicines in the NSW Health Policy Directive *Medication Handling* (PD2022_032) and PIC/S *Guide to Good Manufacturing Practice for Medicinal Products* (PE 009) Annexes. For example, if the IMP is a Schedule 3, Schedule 4 or Schedule 8 substance a dispensing label is required.

Under this Policy Directive an individual patient prescription must be written by a prescriber prior to the preparation of investigational medicinal products (IMPs).

Licence LHD 005 has been issued, under the *Poisons and Therapeutic Goods Regulation 2008* (NSW), which allows a public health facility to supply scheduled medicines, other than Schedule 8 medicines, to another public health facility within NSW. Where a CTA or CTN applies to multiple trial sites this Policy Directive allows pharmacists working in the principal public health facility to prepare Schedule 2, 3 or 4 IMPs and 'unapproved' therapeutic good IMPs, other than biologicals, for supply to other public health facilities in NSW. Where the preparation of a clinical trial product is outsourced refer to Section 10 Outsourcing the preparation of pharmaceutical and advanced therapeutic products.

4.1.1. Good Clinical Practice

Regulation 12AD of the TGR (Cth) specifies that investigational medicinal products (IMPs), including pharmaceutical and advanced therapeutic products, must be handled in accordance with the International Council for Harmonisation *Guideline for Good Clinical Practice* (GCP) practice guidelines.

The GCP details the requirements for clinical trial documentation. Section 5.13 of the GCP states that the sponsor of the trial must ensure the IMPs (active and placebo) are prepared in accordance with the PIC/S *Guide to Good Manufacturing Practice for Medicinal Products* (PE 009) (in particular Annex 13), and the *Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products* outlined under Part 3.3 of the *Therapeutic Goods Act 1989* (Cth).

The TGA *Good Clinical Practice (GCP) inspection program* describes the role of sponsors, Human Research Ethics Committee (HREC), approving authorities, principle investigators (PI) and the TGA in ensuring facilities meet the GCP standards for a site inspection.

4.1.2. Batch compounding

If batch compounding of IMPs is permitted for phase 1 clinical trials under the trial protocol, this must be considered by the Drug and Therapeutics Committee (DTC) (however described) to be appropriate for compounding in a batch where:

- the quantity of a compounded product prepared in a batch is restricted to meet the need of patient access to the trial protocol, and not for convenience, with the reason documented on the risk assessment

- the microbial and error risk associated with batch preparation can be reviewed by the DTC
- assigning a beyond use date (BUD) beyond 24-hours is supported by the trial protocol, and the facility and equipment for compounding the product within the public health facility is compliant with the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010), and
- sterility testing of each batch must be performed, for example a small aliquot is inoculated in a growth media and incubated (see Table 4 Comparison of PIC/S GMP PE 010 and USP <797>).

4.1.3. Unapproved good

Any trial using an unapproved good is subject to the conditions of the CTN or CTA Schemes. An unapproved good includes medicines that are not registered or listed on the Australian Register of Therapeutic Goods (ARTG), or deviates from the ARTG entry for dose, strength, or indication. For example, a trial of fluvoxamine used for sedation, an indication not approved by the TGA, also known as off-label use, and requires a CTN or CTA.

A placebo is considered an 'unapproved' therapeutic good and a CTN or CTA must be in place before a placebo can be supplied for use in a clinical trial. This is the case even if the IMP used in a placebo-controlled trial is already included on the ARTG. Clinical trials using World Health Organisation (WHO) Risk Group 2 biological medicines (see Section 4.3 Facility and equipment requirements), can be conducted under a CTN.

The pharmacy itself does not need to be authorised by the TGA to supply 'unapproved' therapeutic good IMPs unless the substance is a Schedule 9 substance. Where a Schedule 9 substance (or a prohibited drug within the meaning of the *Drug Misuse and Trafficking Act 1985* (NSW)) is used in a clinical trial the PI must obtain an authority to possess, supply, use or manufacture the substance for the purpose of scientific research from the NSW Ministry of Health's Pharmaceutical Regulatory Unit.

The authority is required to mitigate risk of misappropriation and will specify those personnel who may have possession of the substance and the location(s) where storage and handling may occur, for example the IMP must be stored in a separate lockable safe to all other substances including Schedule 8 substances. Further advice may be sought from the Pharmaceutical Regulatory Unit on matters including transportation across state borders or outsourcing of production

4.1.4. Genetically modified organism medicinal products

Clinical Trials involving GMO medicinal products are subject to the *Gene Technology Act 2000* (Cth) and *Gene Technology Regulations 2001* (Cth) (see Section 5 Genetically modified organism medicinal products). A trial sponsor proposing to use a GMO medicinal product must apply to the Office of the Gene Technology Regulator (OGTR) for a licence which must be provided to the local Institutional Biosafety Committee (IBC) at the clinical trial site. The OGTR has published *Guidance for conducting human clinical trials involving GMOs* to help clinical trial sponsors meet the requirements under the *Gene Technology Act 2000* (Cth).

WHO Risk Group 4 biologicals (see Section 4.3 Facility and equipment requirements), such as chimeric antigen receptor (CAR) T-cell therapy, are identified as high-risk under the TGA *Australian regulatory guidelines for biologicals (ARGB)* and must meet the conditions of the CTA Scheme.

4.1.5. Clinical trial sponsors

All clinical trials must have a trial sponsor that is an Australian entity holding an Australian Business Number (ABN). If NSW Health is acting as the clinical trial sponsor, then the relevant public health facility ABN is used.

All sponsors must gain approval from a relevant Human Research and Ethics Committee (HREC) to conduct a clinical trial. The HREC accepts responsibility for the continuing review and oversight of the trial.

An overseas company cannot be the sponsor of a trial in Australia.

The trial sponsor is responsible for determining whether an exemption under the Clinical Trial Notification (CTN) Scheme is appropriate or approval under the Clinical Trial Approval (CTA) Scheme is required for the trials (such as higher risk or genetically modified organism (GMO) medicinal products).

Sponsor led clinical trials

The sponsor is responsible for the safe use of investigational medicinal products (IMPs). The public health facility is approved by the sponsor to prepare/ reconstitute IMPs according to the medicine safety data sheet (MSDS) and investigator's brochure (IB). Where required, the sponsor may assign duties for accountability over IMPs at the trial site(s) to the Director of Pharmacy or delegated pharmacy staff under the supervision of the principal investigator (PI).

Section 5.14.3 of the *Guideline for Good Clinical Practice* (GCP) states that the sponsor must provide an IB and pharmacy manual and protocols to the public health facility for handling, storage, preparation and dispensing of IMPs.

Where the preparation of a IMPs for a sponsor led trial differs from accepted PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010), PIC/S *Guide to Good Manufacturing Practice for Medicinal Products* (PE 009) Annexes provides detailed guidelines on managing the risks and challenges of preparing IMPs.

Cooperation between sponsor and trial site/ manufacturer to support GMP must be documented in a Clinical Trial Research Agreement (CTRA).

Public health facility led clinical trials

The Director of Pharmacy is responsible for approving the safe use of investigational medicinal products (IMPs). The Director of Pharmacy must ensure medicine preparation is in accordance with the PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) and the product risk assessment satisfies the *Work Health and Safety Regulation 2017* (NSW) to protect workers handling hazardous chemicals.

Regulation 12AD of the *Therapeutic Goods Regulations 1990* (Cth) (TGR) requires medicines and biologicals in a clinical trial must be handled and prepared in accordance with the *Guideline for Good Clinical Practice* (GCP). The GCP details the requirements for trial documentation.

If a pharmacy service is requested by the trial sponsor to aseptically prepare a phase 1 clinical trial IMP other than by PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) principles, the *Therapeutic Goods (Manufacturing Principles) Determination 2020* (Cth) provides the criteria that the Director of Pharmacy must address before an alternative procedure is adopted. A risk management plan must be included with the trial documentation to support the equal quality and safety of the alternative preparation approach.

The principal investigator (PI) is responsible for the safe preparation and use of IMPs which have not been compounded or aseptically prepared by the pharmacy service. The Drug and Therapeutics Committee (DTC) must approve the PI to prepare an IMP in a patient care area ready for administration to the patient.

Table 5. Additional Legislation, practice standards and policy relevant to investigational medicinal products

Type of legislation	Title	Purpose
Commonwealth legislation	*National Health and Medical Research Council Act 1992*	Improve and develop consistent national health standards and support medical and public health research and training.
NSW Legislation	-	-
NSW Health Policy Directive	*Research - Ethical & Scientific Review of Human Research in NSW Public Health Organisations* (PD2010_055)	Outlines that the supply of goods cannot commence without TGA and HREC approvals.
	Research - Authorisation to Commence Human Research in NSW Public Health Organisations (PD2010_56)	Outlines the requirements for accepting trials, ensuring there are suitable and adequate facilities and resources.
	Clinical Trial Research Agreements for use in NSW Public Health Organisations (PD2011_028)	Outlines the processes for the use of the Clinical Trial Research Agreements, for clinical trials to be conducted at sites under their control.
NSW Health Guidelines	*Research Governance in NSW Public Health Organisations* (GL2011_001)	Summarises the principles, standards, and requirements for the responsible conduct of quality research e in NSW Public Health Organisations
	Operations Manual: Research Governance Officers (GL2010_015)	Provides standard operating procedures for Research Governance Officers employed within NSW Public Health Organisations.
Enforceable Standard under *Therapeutic Goods Regulation 1990*	International Council for Harmonisation (ICH) *Guideline for Good Clinical Practice* (GCP)	Standards for the technical requirements for designing, conducting, recording, and reporting of pharmaceutical products for human use in clinical trials.

Enforceable Standards under *National Health and Medical Research Council Act 1992*	Australian Clinical Trial Handbook	Guidance on the legislative, regulatory, and good clinical practice (GCP) requirements for clinical trials using 'unapproved' therapeutic goods.
	National Statement on Ethical Conduct in Human Research 2007	Clarify the responsibilities of institutions and researchers for the ethical design, conduct and dissemination of results of human research.
	National Clinical Trials Governance Framework (NCTGF)	Accreditation for the hospital clinical trial services.
Professional Practice Standards	See Section 3 Pharmaceutical Products	
	The Society of Hospital Pharmacists of Australia *Standard of Practice in Clinical Trials for Pharmacy Services 2020*	Describes the best practice for the provision of clinical trials pharmacy services.

4.2. Procurement, receipt and storage

The trial sponsor, either external or public health facility led, is responsible for ordering and supply of stocks of all investigational medicinal products (IMPs). The Director of Pharmacy is responsible for the receipt, and storage of all IMPs in accordance with the NSW Health Policy Directive *Medication Handling* (PD2022_032), trial sponsor protocol and directions of the Institutional Biosafety Committee (IBC). Where the pharmacy service does not have the appropriate facilities to store the IMP, the sponsor is requested to provide the required storage and calibrated temperature monitoring devices.

Ordering, receipt, and storage requirements of IMPs vary depending on individual clinical trial protocols, refer to the investigator's brochure (IB), pharmacy manual and the Society of Hospital Pharmacists of Australia (SHPA) *Standards of Practice in Clinical Trials for Pharmacy Services* (2020). IMPs may be required to be stored frozen and may be shipped on dry ice. Pharmacy services must have work health and safety procedures in place for the handling and disposal of dry ice.

It is the responsibility of the Director of Pharmacy to ensure that all IMPs obtained from a non-manufacturing licensed NSW public health facility are manufactured or prepared in compliance with PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) standards prior to ordering.

Pharmaceutical IMPs cannot lawfully be sourced from a wholesaler that does not hold a licence to supply a pharmaceutical by wholesale issued by the NSW Ministry of Health or another state or territory. In some circumstances the Director of Pharmacy of a public health facility is permitted to make wholesale supply of pharmaceutical IMPs to another public health facility. Public health facilities wanting to wholesale supply a pharmaceutical IMP must be compliant with this Policy Directive and the *Poisons and Therapeutic Goods Regulation 2008* (NSW) and may seek advice from the Chief Pharmacist Unit at the NSW Ministry of Health.

4.2.1. Importation

All pharmaceutical products imported into Australia must comply with the *Therapeutic Goods Act 1989* (Cth) and the Australian Border Force (see How to Import).

Therapeutic goods may be imported into Australia prior to Therapeutic Goods Administration (TGA) notification or approval being granted, provided they are held under the direct control of the sponsor in accordance with the provisions of Schedule 5A in the *Therapeutic Goods Regulations 1990* (Cth) (TGR).

Under the Clinical Trial Notification (CTN) Scheme, investigational medicinal products (IMPs) may be imported into Australia prior to TGA notification, however the clinical trial sponsor must notify the TGA before IMPs are supplied or administered to the patient.

Under the Clinical Trial Approval (CTA) Scheme, IMPs may be imported into Australia prior to TGA approval being granted, however the sponsor must gain approval from the TGA before IMPs are supplied or administered to the patient.

Public health facility led clinical trials may require an import permit to import unapproved therapeutics whether the IMP is imported under a CTN or CTA Scheme. Where the product contains biological material of animal, plant or genetic origin refer to Section 5 Genetically modified organism medicinal products.

Schedule 4 of the *Customs (Prohibited Imports) Regulations 1956* (Cth) lists products that require a licence or permit to import. To import a prohibited substance, a licence must be obtained from the Office of Drug Control (see Importers). The licence does not authorise the importation of a specific substance. A permit to import each specific consignment of goods must be obtained from the Office of Drug Control. Examples include narcotic, psychotropic, anabolic, androgenic, precursor or medical cannabis.

4.3. Facility and equipment requirements

Facility and equipment requirements will vary for each investigational medicinal product (IMP) prepared. For specific facility and equipment requirements refer to the relevant Section of this Policy Directive.

4.4. Supply, transport and packaging requirements

Where the principal trial site facility is the holder of the Clinical Trial Approval (CTA) or Clinical Trial Notification (CTN) that applies to multiple satellite clinical trial sites, the pharmacy service at the principal trial site facility may supply prepared investigational medicinal products (IMPs) by transport to the multiple sites within NSW stipulated in that approval.

It is the responsibility of the Director of Pharmacy to ensure that all investigational medical products (IMPs) where relevant, have continuous cold temperature monitoring as per the investigator's brochure (IB), *Guideline for Good Clinical Practice* (GCP) and NSW Health Policy Directive *Medication Handling* (PD2022_032). A downloadable continuous temperature logging device is required for all stages of storage and transportation of refrigerated or frozen IMPs within the same public health facility and when transporting all IMPs, including room temperature products, to another facility, including courier transportation.

4.4.1. Re-packing

Pre-packing or re-packing of investigational medicinal products (IMPs) must only be prepared by Therapeutic Goods Administration (TGA) facilities licenced to manufacture. Pharmacists in a public health facility may re-package bulk stock at point of dispensing for an individual patient as per the investigator's brochure (IB).

The Drug and Therapeutics Committee (DTC) must approve clinical trial supply pre-packs of products entered on the Australian Register of Therapeutic Goods (ARTG) being trialled for off-label use.

Pre-packed and labelled IMPs can be prepared by the pharmacy service and supplied by the principal investigator (PI) or delegate sub-investigator through emergency departments in accordance with the NSW Health Policy Directive *Medication Handling* (PD2022_032).

Use of dose administration aids, for example Webster packs in clinical trials is not best practice as the rigorous requirements for labelling of clinical trial medicines could not be provided on a dose administration aid label.

4.5. Disposal

The *Guideline for Good Clinical Practice* (GCP) requires that trial sponsors must maintain a system for the retrieval and disposition of investigational medicinal products (IMPs) and for the documentation of this disposition. Disposal of all IMPs at the trial site must first be approved by the trial sponsor and disposed of in accordance with the NSW Health Policy Directive *Clinical and Related Waste Management for Health Services* (PD2020_049).

Accountability of used IMPs must be provided to the pharmacy service by empty boxes or photographic records according to the requirements of the clinical trial protocol.

Unused IMPs returned from a patients' home, must be sealed in clear plastic bags, by the principal investigator (PI) or clinical trials pharmacist, within their labelled secondary containers before returning to the pharmacy service for disposal. For accountability, unused IMPs, for example tablets, must be returned to the pharmacy services for disposal.

Used and partially used aseptically prepared IMPs by the pharmacy service will be destroyed by the pharmacy service. Unused or partially used aseptically prepared IMPs, for example pharmacy prepared genetically modified organism (GMO) medicinal intravenous infusions, within the public health facility must not be returned to pharmacy services and must be destroyed in the patient care area in accordance with the NSW Health Policy Directive *Clinical and Related Waste Management for Health Services* (PD2020_049).

5. GENETICALLY MODIFIED ORGANISM MEDICINAL PRODUCTS

The NSW Health *Genomics Strategy* (2017) aims to facilitate the introduction of genetically modified organism (GMO) medicinal products into public healthcare. It is the responsibility of the Director of Pharmacy to assess risks and determine procedures for handling and preparing individual GMO medicinal products by the pharmacy service.

The World Health Organisation (WHO) classifies biologicals under Risk Groups to describe the relative hazard posed by toxins or infectious product which guide the facility and equipment requirements for product preparation.

Table 2. Risk Group Definition

Risk Group (WHO)	Risk Group Definition
Risk Group 1	• No or low individual or community risk – unlikely to cause human disease, for example, faecal microbiota transplant and bacteriophage
Risk Group 2	• Moderate individual risk – can cause human disease and might be a hazard to workers • Low community risk – effective therapeutic intervention is available, for example, most GMO medicinal products and GMO bacteriophage
Risk Group 3	• High individual risk usually causes serious human disease • Low community risk - effective therapeutic intervention is available, for example, human immunodeficiency virus (HIV)
Risk Group 4	• High individual risk – usually causes serious human disease • High community risk – readily transmitted from one individual to another, and no effective therapeutic intervention available, for example, CAR T-cell products

All GMO medicinal products must be prepared in accordance with the principles and the detailed guidelines of PIC/S *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments* (PE 010) and outlined in Section 3 Pharmaceutical Products and Section 4 Investigational Medicinal Products.

All in vivo GMO medicinal products must be handled and prepared by the pharmacy service, appropriate public health facility laboratory or outsourced to an eligible third-party provider (refer to Section 10 Outsourcing the Preparation of Pharmaceutical and Advanced Therapeutic Products) to minimise the risks of environmental contamination, product microbial contamination and medication errors. In vivo GMO medicinal products must not be dose prepared on the ward by nursing or medical staff.

The preparation of each specific GMO medicinal product must meet the requirements set out in the:

- Office of the Gene Technology Regulator (OGTR) licence
- directions of the local Institutional Biosafety Committee (IBC), and
- the investigator's brochure (IB).

GMO medicinal products entered on the Australian Register of Therapeutic Goods (ARTG) must be prepared according to the Therapeutic Goods Administration (TGA) approved product information and the sponsors protocol to meet the obligations of the OGTR licence for the individual product.

A fundamental obligation of an OGTR licence is the requirement for staff to be trained in the use of the GMO medicinal product. At a minimum, staff must review and attest their understanding of:

- the GMO medicinal product standard operating procedure (SOP)

- the local tailored SOP
- associated risk assessment and risk management plan (RARMP)
- clinical trial protocol (where appropriate), and
- the pharmacy manual.

Only staff that have completed the documented training can handle and prepare GMO medicinal products.

5.1. Legislative framework and practice standards

NSW Health restricts prescribing of genetically modified organism (GMO) medicinal product investigational medicinal products (IMPs) to the principal investigator (PI), delegated sub-investigator or specialist physicians as approved by the local Drug and Therapeutics Committee (DTC).

In vivo gene therapy is regulated under the *Therapeutic Goods Act 1989* (Cth) as a prescription medicine, rather than a biological. Any biological or pharmaceutical that involves genetic modification is subject to the *Gene Technology Act 2000* (Cth) and *Gene Technology Regulations 2001* (Cth) and must be approved for use by the Office of the Gene Technology Regulator (OGTR).

Before a public health facility can be approved by the OGTR, the Chief Executive must ensure the facility has:

- established, or have access to, an appropriately constituted Institutional Biosafety Committee (IBC), under the *Therapeutic Goods Regulation 1990* (Cth), who outline how the GMO medicinal product is to be handled at an institutional level (see OGTR Organisation accreditation requirements)
- a licence for dealings not involving an intentional release of GMO medicinal products into the environment/ dealings involving an intentional release of GMO medicinal products into the environment (DNIR/DIR), which must be endorsed by the IBC
- approval for use of GMO medicinal product obtained from the relevant DTC
- compliance with the requirements of the OGTR licence held by the sponsor of the GMO medicinal product (where appropriate). Where the OGTR licence is held by the sponsor, the public health facility does not need a separate OGTR certification.

Note: A licence application can be endorsed by the IBC of another public health facility when the submitting facility does not have its own IBC.

The OGTR may require a Therapeutic Goods Administration (TGA) manufacturing licence and Australian Register of Therapeutic Goods (ARTG) registration for a product. Although under the *Poisons and Therapeutic Goods Act 1966* (NSW) a medical practitioner may supply a Schedule 4 medicine directly to a patient, where a GMO medicinal product is in Schedule 4 of the Poisons Standard, then this must be dispensed by a pharmacist. Only under specific urgent situations, approved by the Director of Pharmacy, a Schedule 4 GMO medicinal product can be supplied to a patient by a medical practitioner or delegated trial sub-investigator when a pharmacy service is not available.

Note: In the case of the GMO medicinal product onasemnogene abeparvovec (Zolgensma®), once registered it was listed in Schedule 4.

Table 7. Additional legislation, practice standards and policy relevant to GMO medicinal products

Type of legislation	Title	Purpose
Commonwealth legislation	*Gene Technology Act 2000*	Regulatory measures to protect the health and safety of people and protect the environment by identifying and managing risks posed by gene technology.
	Gene Technology Regulations 2001	Provides instructions for regulators to issue licenses to ensure the health and safety of people and the environment are protected from the risks posed by gene technology.
	The Biologicals Regulatory Framework 2011	Amendment to the *Therapeutic Goods Act 1989* and the *Therapeutic Goods Regulations 1990* to improve the regulation of human tissues and cell-based therapies.
	Australian Regulatory Guidelines for Biologicals (ARGB) 2019	Provides instructions on the supply and use of human cell and tissue-based therapeutic goods.
NSW legislation	-	-
NSW Health Policy	-	-
Enforceable Standards under Office of the Gene and Technology Regulator (OGTR)	Australian/New Zealand Standard 2243.3:2010 *Safety in laboratories Part 3: Microbiological safety and containment*	Instructions for Physical Containment Level 2 (PC2) facility requirements for preparing medicines using risk group 2 microorganisms.
	Australian/New Zealand Standard 2252.4 *Biological safety Cabinets Classes I and II- Installation and use*	Instructions for use of Class I and II Biological Safety Cabinets (BSC) that provide protection against risk group 2 and 3 micro-organisms.
Professional Practice Standards and Guidelines	See Section 3 Pharmaceutical Products and Section 4 Investigational Medicinal Products	

5.2. Procurement, receipt and storage

The ordering of stocks of genetically modified organism (GMO) medicinal products outside of a clinical trial is the responsibility of the Director of Pharmacy. Where the GMO medicinal product is an investigational medicinal product (IMP), the clinical trial sponsor is the supplier of the GMO medicinal product.

It is the responsibility of the Director of Pharmacy in collaboration with the clinical trial principal investigator (PI) (where appropriate) to ensure an unbroken chain of custody for GMO medicinal products from receipt, through storage, preparation, and administration to the patient.

All staff handling GMO medicinal products, including all stages from the receipt, unpacking, storage, transportation, administration, and destruction, are required to don appropriate

personal protective equipment (PPE), for example disposable gloves, an isolation gown, and splash-proof surgical mask or face shield as per Office of the Gene Technology Regulator (OGTR) licence requirements, Institutional Biosafety Committee (IBC) obligations and manufacturer's recommendations.

All areas where GMO medicinal products are stored, handled, and prepared must have a GMO medicinal product decontamination spill kit appropriate for each GMO medicinal product, unless otherwise advised by the OGTR. Appendix F of the AS/NZS 2243.3-2010 *Safety in laboratories Part 3: Microbiological safety and containment* or the investigator's brochure (IB) provides information regarding the appropriate decontamination chemical for the individual GMO medicinal product

The OGTR provides the *Guidelines for the Transport, Storage and Disposal of GMO medicinal products*. Shipment packaging must be removed before storage, but the primary package must only be opened in the primary engineering control (PEC).

GMO medicinal products must be stored according to the conditions in the relevant OGTR licence in a dedicated area with access restricted to authorised pharmacy staff. The storage area must be clearly signed with 'biohazard', unless otherwise advised by the OGTR. For more information refer to the Office of the Gene Technology Regulator (OGTR) standards in the *Guidelines for Certification of PC2 Facilities/Physical Containment 2 Requirements*.

Where refrigerator or freezer storage is required, GMO medicinal products should be stored in a dedicated appliance, separate from non-biohazard medicines, unless otherwise advised by the OGTR. Most GMO medicinal products involve the use of viral vectors therefore an ultra-low temperature freezer may be required for appropriate storage.

5.2.1. Importation

Under the *Biosecurity Act 2015* (Cth), the importation of genetically modified organism (GMO) medicinal products requires a permit from the Department of Agriculture, Fisheries and Forestry.

The Biosecurity Import Conditions (BICON) system is used to determine whether a material of biological origin (human, animal, plant or microbial) intended for import into Australia needs an import permit. *The Gene Technology Act 2000* (Cth) describes permission requirements for importing GMO medicinal products including GMO bacteriophage.

Imported GMO medicinal products that do not meet the definition of toxic substances or infectious substances must display the international packing label identifier UN 3245 "Genetically Modified Organisms" prior to receipt by the pharmacy service.

5.3. Facility and equipment requirements

The AS/NZS 2243.3-2010 *Safety in laboratories Part 3: Microbiological safety and containment* classifies microorganisms according to the degree of risk, based on pathogenicity, mode of transmission and, the availability of effective preventive measures against infection and availability of effective treatment.

Physical containment (PC) levels for the preparation of genetically modified organism (GMO) medicinal products must, at a minimum, be appropriate to the risk group of the GMO medicinal product; PC1 for Risk Group 1, PC2 for Risk Group 2, etc., unless otherwise

advised by the Office of the Gene Technology Regulator (OGTR) (see Table 6 Risk Group Definition).

Preparation of a Risk Group 2 GMO medicinal product, for example, requires a minimum Class II biological safety/ biohazard cabinet, to ensure that both the operator and medicine are protected from contamination.

A Class II cytotoxic drug safety cabinet (CDSC) or Class III pharmaceutical isolator are also appropriate primary engineering controls (PEC). The PEC can be recirculating or externally exhausted. The PEC must be in a separate clean room to all other aseptically prepared products, protected by an airlock, to avoid cross contamination.

Table 8 Risk group physical containment (PC) level and biosafety level requirements identifies the minimum biosafety level requirement for each Risk Group being handled in the public health facility. Class II biological safety cabinets (BSCs) provide a degree of protection when working with biologicals of Risk Groups 2 and 3 and where the work produces a significant quantity of aerosol.

Table 3. Risk group physical containment (PC) level and biosafety level requirements

Physical containment (PC) level and biosafety level requirements	Risk Group (RG)			
	RG 1	RG 2	RG 3	RG 4
Isolation of laboratory	×	×	✓	✓
Controlled heating, ventilation and air conditioning (HVAC)	×	✓	✓	✓
HEPA-filtered air exhaust	×	×	✓	✓
Double door entry	×	×	✓	✓
Airlock	×	×	✓	✓
Class I Biological safety cabinet	×#	×	×	×
Class II Biological safety cabinet	×#	✓	✓	✓
Class II cytotoxic drug safety cabinet (CDSC)	×#	✓	✓	✓
Class III pharmaceutical isolator	×#	✓	✓	✓

#BSC may be required when preparing Risk Group 1 biologicals if large amounts of aerosol are produced.

Where the public health facility does not meet the facility requirements, preparation of GMO medicinal products must not be performed. Where an external research laboratory is used by the pharmacy service to prepare GMO medicinal products, it is the responsibility of the Director of Pharmacy to ensure pharmacy staff have access to required consumables and chemicals to support aseptic preparation of GMO medicinal products (see Section 10 Outsourcing the Preparation of Pharmaceutical and Advanced Therapeutic Products on the process for outsourcing).

5.4. Supply, transport and packaging requirements

The Office of the Gene Technology Regulator (OGTR) provides the *Guidelines for the Transport, Storage and Disposal of GMOs*. The requirements for transport of genetically modified organism (GMO) medicinal products, unless otherwise advised by the OGTR, are:

- all GMO medicinal products transported within or between buildings must be by a staff member who has completed the appropriate local GMO spill training
- all GMO medicinal products must be accompanied by an appropriate GMO decontamination spill kit during transportation
- all GMO medicinal products must be transported in double sealed containers; the primary container, such as a vial, and a secondary sealed, unbreakable container. The type of secondary container may vary depending on the type of organism and the exposure risk level in the event of a spill or leak
- the external surface of the secondary container must be decontaminated by the pharmacy service with an appropriate GMO medicinal product deactivator prior to transport. The individual GMO medicinal product deactivator for each product should be provided in the GMO licence or the public health facility must seek advice from their Institutional Biosafety Committee (IBC)
- the outermost container of GMO medicinal product must display a biohazard label.

In NSW Health facilities, administration of GMO medicinal products must be in a single patient isolation room to provide containment if a spill were to occur, unless otherwise advised by the OGTR. Registered nurses, midwives or medical practitioners administering doses of GMO medicinal products must follow the same personal protective equipment (PPE) precautions as handling cytotoxic medicines.

5.5. Disposal

Genetically modified organism (GMO) medicinal products must be packed in plastic containers and labelled as 'biohazard' and discarded into a clinical waste or cytotoxic waste bin as agreed upon with the Institutional Biosafety Committee (IBC), Safe Work Australia or other relevant committee, in accordance with OGTR licence conditions and managed as per NSW Policy Directive *Clinical and Related Waste Management for Health Services* (PD2020_049).

Clinical waste or cytotoxic waste bins must be readily available in any area(s) used for receipt, preparation, and administration of a GMO medicinal product. Each public health facility must also consult their local work health and safety and waste management policy.

Non-disposable ancillary supplies/ equipment are to be decontaminated with an appropriate agent for each specific GMO medicinal product prior to disposal.

Destruction advice will be provided by the dealings not involving intentional release/ dealings involving intentional release (DNIR/DIR) licence, unless otherwise instructed by the local IBC, the Office of the Gene Technology Regulator (OGTR) *Guidelines for the Transport, Storage and Disposal of GMOs*, or the manufacturer/ sponsor of the specific GMO medicine.

6. CHIMERIC ANTIGEN RECEPTOR T-CELL PRODUCTS

Chimeric antigen receptor (CAR) T-cell products are currently not manufactured in public health facilities. Pharmacy services do not have the infrastructure or training to handle living cell products.

The Medical Director of the Bone Marrow Transplant and Cellular Therapy (BMT+CT) laboratory is responsible for shipping the initial apheresis material to a licensed manufacturer, for example, either a United States Food and Drug Administration (FDA) or Therapeutic Goods Administration (TGA) licenced manufacturing facility (see Section 6.4 Supply, transport and packaging requirements).

Products that are transported cryopreserved are initially processed (plasma reduced/ cryopreserved) by the public health BMT+CT Laboratory prior to shipping. The manufactured product is returned to the BMT+CT Laboratory, for storage and distribution.

Pharmacy services can prepare cytotoxic products used for pre-therapy desensitisation and lymphodepletion during therapy according to eviQ protocols (see Section 3 Pharmaceutical Products).

6.1. Legislative framework, governance and practice standards

Chimeric antigen receptor (CAR) T-cell products are regulated under the *Therapeutic Goods Act 1989* (Cth) as an 'ex vivo' Risk Group 4 biological. NSW Health facilities must be accredited by the Foundation for the Accreditation of Cellular Therapies - Joint Accreditation Committee International Society for Cell & Gene Therapy (ISCT)-Europe and EBMT (FACT-JACIE) and have a quality management system in place prior to handling CAR T-cell products.

The Bone Marrow Transplant and Cellular Therapy (BMT+CT) Network is a collaborative network, under the Agency for Clinical Innovation (ACI), that helps public health facilities obtain accreditation from the National Pathology Accreditation Advisory Council (NPAAC) and FACT-JACIE. The BMT+CT Network also provides a centralised quality management system for public health facilities to use for all BMT+CT therapies.

The Chief Executive of the public health facility in collaboration with the Medical Director of the BMT+CT Laboratory is responsible to ensure that all standard operating procedures (SOPs) and the quality management system are in place prior to providing CAR T-cell therapy.

Under a service level agreement between the ACI and the NSW Ministry of Health Specialty Service and Technology Evaluation Unit, the BMT+CT Network helps public health facilities to write all required SOPs (see Appendix 5 Bone Marrow Transplant Network NSW Immune Effector Cell (IEC) procedures and forms for CAR T-cell products and therapy), and provides the quality management systems required to handle and administer CAR T-cell products.

Public health facilities that do not implement the BMT+CT Network Quality Management Systems are outside of this service level agreement and must be approved independently by the NSW Ministry of Health Specialty Service and Technology Evaluation Unit to provide CAR T-cell therapy.

The collection of starting material and administration of CAR T-cells is under the governance of the public health facility. The governance of BMT+CT Laboratories is provided by NSW Health Pathology (except for St Vincent's Hospital, who are governed under a service level agreement with the NSW Ministry of Health Specialty Service and Technology Evaluation Unit).

The BMT+CT Laboratory Medical Director is responsible for the storage, handling, and distribution of CAR T-cell products in public health BMT+CT Laboratories. CAR-T cells must only be prescribed by the BMT+CT specialist treating physician who has completed all required training provided by the immune effector cell (IEC) manufacturer on the Therapeutic Goods Administration (TGA) Risk management plans for medicines and biologicals.

Early phase clinical trials of CAR T-cell products must be under the Clinical Trial Approval (CTA) Scheme. The CTA Scheme is mandatory for all Risk Group 4 biologicals unless sufficient safety information is available, for example an existing clinical trial or overseas regulatory body with comparable regulatory requirements has approved a clinical trial for an equivalent indication. Advice may be sought from the TGA whether the Clinical Trial Notification (CTN) route would be appropriate.

TGA licenced manufacturers of CAR T-cell products will require BMT+CT programs including clinical, collection and laboratory departments, handling CAR T-cell products must be FACT-JACIE accredited.

As a novel therapy, facilities that are already engaged in use of these therapies must be actively working toward accreditation. Facilities introducing CAR T-cell therapies must have applied for accreditation prior to proceeding with treatment.

Table 9. Additional legislation, governance and practice standards relevant to CAR T-cell products

Type of legislation	Title	Purpose
Commonwealth legislation	See Section 3 Pharmaceutical Products, Section 4 Investigational Medicinal Products and Section 5 Genetically Modified Organism Medicinal Products	
NSW legislation	-	-
NSW Health Policy	-	-
Enforceable Standards	-	-
Standards	Agency for Clinical Innovation, Blood and Marrow Transplant + Cellular Therapies Network	Maintain the centralised quality management service for the NSW blood and marrow transplant and cellular therapies programs and adapt to changes in national and international standards and work practices. See Appendix 5 Bone Marrow Transplant Network NSW Immune Effector Cell (IEC) procedures and forms for CAR T-cell products and therapy for relevant BMT+CT Network SOPs and forms.
	Australian/New Zealand Standard 2252.3-2011 *Controlled environments Biological safety Cabinets Classes III - Design*	Provides the minimum performance criteria for safety cabinets for work with micro-organisms and required test procedures with respect to the worker, environment, product prevention and cross contamination.
	Australian Standard AS 1807.2021 *Biological and Cytotoxic Drug Safety Cabinets, Clean Workstations, and Pharmaceutical Isolators – Methods of Test*	The testing methods required for filter integrity to meet NATA accreditation.

	ISO 15189:2012 *Medical Laboratories–Requirements for Quality and Competence*	Standard requirements for a quality management system for apheresis units and BMT+CT Laboratories to meet the joint NATA/RCPA accreditation
	National Pathology Accreditation Advisory Council (NPAAC)	Ensures the quality of Australian pathology services and is responsible for the development and maintenance of pathology practices for the collection and processing of mononuclear cells (MNCs) as the starting material for CAR T-cell manufacture.
	Foundation for the accreditation of cellular therapy The Joint Accreditation Committee ISCT-Europe & EBMT (FACT-JACIE)	Clinical, collection and laboratory standards and accreditation for haematopoietic progenitor cells and cellular therapies.
	cGMP Australian Code of Good Manufacturing Practice for human blood and blood components, human issues and human cellular therapy products	Compliance for all phase 2 and above clinical trials CAR T-cell manufacturing and the qualification process of apheresis units and BMT+CT Laboratories.

6.2. Procurement, receipt and storage

The Medical Director of the Bone Marrow Transplant and Cellular Therapy (BMT+CT) Laboratory is responsible for ordering chimeric antigen receptor (CAR) T-cell products directly from the manufacturer. For standard of care this is through individual pharmaceutical manufacturer online portals.

All staff handling CAR T-cell products must have completed specialised training provided by the manufacturer of each individual CAR T-cell product. Staff must have previous BMT+CT training in the processing, storage, and distribution of haemopoietic progenitor cell (HPC) products prior to receiving training for CAR T-cell products.

Upon receipt from the manufacturer to the BMT+CT Laboratory, products must be checked for chain of custody/ identity, transport conditions, product integrity and evidence of meeting the manufacturing release criteria, for example certificate of analysis or product report (see Appendix 5 Bone Marrow Transplant Network NSW Immune Effector Cell (IEC) procedures and forms for CAR T-cell products and therapy). The BMT+CT Laboratory Medical Director is responsible for the storage of CAR T-cell products cryopreserved in tanks of liquid nitrogen and stored at minus 150°C in the pathology liquid nitrogen inventory.

A specialised spill kit is not required for storage or transport of CAR T-cell products. There is no risk to the environment beyond usual blood derived products for CAR T-cell product which are not viable outside of the human body or under culture conditions and have no replication competent viral vector present.

6.3. Facility and equipment requirements

Chimeric antigen receptor (CAR) T-cell products are not currently manufactured in public health facilities. CAR T-cell products are provided to public health facilities in ready to use packaging and are not prepared or diluted by NSW Health staff prior to administration.

Investigational medicinal products (IMPs) may provide an exception, where specific products may be dispensed at the bedside by specialist trained Bone Marrow Transplant and Cellular Therapy (BMT+CT) scientist or registered nurse immediately prior to administration. Staff must check the approved product information for allowable manipulation and administration procedures. CAR T-cell products are not prepared for use by pharmacy services.

Public health facilities performing apheresis must be accredited by the joint National Association of Testing Authorities and Royal College of Pathologists of Australia (NATA/RCPA) Accreditation Program.

6.4. Supply, transport and packaging requirements

Once lymphodepletion has been completed, the chimeric antigen receptor (CAR) T-cell product can be supplied for the patient from the liquid nitrogen inventory stored in the Bone Marrow Transplant and Cellular Therapy (BMT+CT) Laboratory.

The Medical Director of the BMT+CT is responsible for ensuring all CAR T-cell products meet strict release criteria prior to issue for administration (see Appendix 5 Bone Marrow Transplant Network NSW Immune Effector Cell (IEC) procedures and forms for CAR T-cell products and therapy for receipt and manufacturer checklists). Key criteria the BMT+CT Medical Director must check includes donor eligibility (including non-reactive infectious disease markers), product quality (sterility, or cell dose), appropriate cold chain storage, product identity and integrity, and appropriate cryopreservative content.

An exceptional release process is required if a CAR T-cell product does not meet specification, for example endotoxin level. Under delegation of the Drug and Therapeutics Committee (DTC), the Medical Director of the BMT+CT Laboratory, in collaboration with the treating specialist physician, can determine on a case-by-case basis, to evaluate the risk versus need for urgent medical treatment and accept responsibility to release the product for use by the patient. The patient must provide informed consent.

To maintain an unbroken chain of custody, it is the responsibility of the specialist trained BMT+CT scientists to transport the CAR T-cell product to the patient area using specialist dry shippers, where the product is thawed at the bedside in a 39°C water-bath (see Appendix 5 Bone Marrow Transplant Network NSW Immune Effector Cell (IEC) procedures and forms for CAR T-cell products and therapy).

The manufacturer will provide information regarding the appropriate decontamination chemical for the CAR T-cell product.

6.5. Administration

Chimeric antigen receptor (CAR) T-cells must be handled and administered only by staff who have received risk management training from the manufacturer of the CAR T-cell product. For standard of care CAR T-cell therapy staff must be trained in local and/or Bone Marrow Transplant and Cellular Therapy (BMT+CT) Network standard operating procedures (SOPs)

and have had experience in handling/ infusing blood products and haemopoietic progenitor cell (HPC) products.

Supervised training by the specialist trained BMT+CT scientists is required prior to infusion of CAR T-cells.

For investigational medicinal products (IMPs) staff must be trained in the clinical trial protocol and relevant *Guideline for Good Clinical Practice* (GCP).

A range of delivery systems, for example infusion pumps, bolus injections, or gravity devices, may be used to administer CAR T-cell products. The manufacturer's instructions for the delivery system must the followed.

6.6. Disposal

Chimeric antigen receptor (CAR) T-cell product waste is managed as clinical waste as per the NSW Policy Directive *Clinical and Related Waste Management for Health Services* (PD2020_049). Each public health facility must also consult their local work health and safety, and waste management policy.

7. ANTIGEN SPECIFIC CELL PRODUCTS

Antigen specific cells target a specific infection such as a virus or fungus, or abnormal patient cells such as tumour cells. There are also many antigen-specific cells in development that have other targets, including some that have multiple targets. These products can be used prophylactically or to treat disease. There are two types of products:

- individualised, which are derived from a specific donor that has been matched to the patient through human leukocyte antigen (HLA)-matching, or
- off-the-shelf, which are selected from partially HLA-matched donors in highly characterised antigen specific cell banks.

Regardless of the type of product or target, all antigen-specific cells are regulated under the *Therapeutic Goods Act 1989* (Cth) as an 'ex vivo' biological. Investigational antigen specific cells are accessed through the Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) Schemes (see Section 4 Investigational Medicinal Products), or through the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS).

The Chief Executive of the public health facility in collaboration with the Medical Director of the Bone Marrow Transplant and Cellular Therapy (BMT+CT) Laboratory is responsible to ensure that all standard operating procedures (SOPs) and the quality management system are in place prior to providing antigen specific cell products.

Prior to handling investigational antigen specific cells, staff must be trained in the clinical trial protocol and relevant *Guideline for Good Clinical Practice* (GCP). The trial sponsor is responsible for providing all relevant protocols. The facility must have a TGA manufacturing licence to manufacture all clinical trials phase 2 and above.

The Medical Director of the BMT+CT Laboratory must provide the following to the BMT+CT Network to enable the public health facility to access the quality system's procedures and forms:

- notify the Agency of Clinical Innovation (ACI) of the trial, local investigator, and its regulatory approval
- TGA manufacturing licence or TGA Good Manufacturing Practice (GMP) certification of the manufacturer as a supplier
- written confirmation from the sponsor that the BMT+CT Network procedures and forms appropriate and applicable for specific the clinical trial.

Antigen specific cell products are receipted, stored, supplied, transported, and disposed as described for chimeric antigen receptor (CAR) T-cells (see Section 6 Chimeric Antigen Receptor T-cell Products).

The Medical Director of the BMT+CT Laboratory must risk assess each new product for storage with other haemopoietic progenitor cell (HPC) and CAR T-cells. These may use other cell types for example, CAR NK-cells.

8. BACTERIOPHAGE PRODUCTS

As a result of the growing threat of antibiotic-resistant bacterial strains, there is interest in bacteriophage therapy as a potential alternative. Once a bacterial infection has been isolated and identified, bacteriophage therapy may be requested from the Westmead Bacteriophage Therapy Team who have identified and produced a library of bacteriophage in their medical laboratory.

The route of administration of bacteriophage products may vary to facilitate direct contact with the pathogenic bacterium, for example inhaled bacteriophage therapy for respiratory tract infections, increasing the work health and safety risk of airborne particulate.

Genetically modified organism (GMO) bacteriophage therapy must be handled according to GMO standards (see Section 5 Genetically Modified Organism Medicinal Products).

8.1. Legislative framework and practice standards

Genetically modified organism (GMO) bacteriophage are regulated under the *Gene Technology Act 2000* (Cth) and *Gene Technology Regulations 2001* (Cth). While bacteriophage products are not regulated under the *Therapeutic Goods Act 1989* (Cth), they are managed by the Therapeutic Goods Administration (TGA) as 'unapproved' therapeutic goods through the Special Access Scheme (SAS) under Category A or Category B.

The regulation of bacteriophage and GMO bacteriophage therapies is under review by the TGA in consultation with the NSW Ministry of Health's Office for Health and Medical Research (OHMR).

To ensure quality and safety of bacteriophage therapy in public facilities bacteriophage are handled as World Health Organisation (WHO) Risk Group 1 biological and genetically modified organism (GMO) bacteriophage as WHO Risk Group 2 biological, unless otherwise advised by the Office of the Gene Technology Regulator (OGTR).

The Drug and Therapeutic Committee (DTC) is responsible for the governance of bacteriophage therapy at the public health facility and must provide determination on the containment level required for the preparation dependent upon the bacterial strains used to

propagate the bacteriophage. A bacteriophage therapy specialist and specialist infectious diseases physician must be members of the approving DTC. Where the approving DTC does not have a bacteriophage therapy specialist member, a bacteriophage therapy specialist from another public health facility can be consulted.

Each GMO bacteriophage product requires an individual OGTR licence. Non-GMO bacteriophage do not require a OGTR licence. All bacteriophages must be prepared according to Good Manufacturing Practice (GMP) processes as per investigational medicinal products (IMPs).

Bacteriophage products must only be prescribed by a specialist infectious diseases physician and use must be monitored for appropriateness under antimicrobial stewardship programs.

Table 10. Additional legislation, practice standards and policy relevant to bacteriophage products

Type of legislation	Title	Purpose
Commonwealth legislation	See Section 3 Pharmaceutical Products, Section 4 Investigational Medicinal Products and Section 5 Genetically Modified Organism Medicinal Products	
NSW legislation	-	-
NSW Health Policy Directive	-	-
Enforceable Standards	-	-
Professional Practice Standards and Guidelines	See Section 3 Pharmaceutical Products	

8.2. Procurement, receipt and storage

Bacteriophage products are unapproved therapeutic goods. For the purpose of this Policy Directive bacteriophage are classified as pharmaceutical products and must be ordered and stored by the pharmacy service according to NSW Health Policy Directive *Medication Handling* (PD2022_032) and Section 3 Pharmaceutical Products.

Bacteriophage products are managed under the Special Access Scheme (SAS).

8.3. Facility and equipment requirements

Bacteriophage products are diluted by the pharmacy service, ready for administration, in a negative pressure primary engineering control (PEC) under clean room conditions in accordance with the principles and the guidelines of PIC/S *Guide to Good Manufacturing Practice for Medicinal Products* (PE 009), Section 3 Pharmaceutical Products and Section 4 Investigational medicinal products.

Class I and Class II biological safety cabinets are required when handling microorganisms of World Health Organisation (WHO) Risk Groups 2 and 3 and WHO Risk Group 1 where the work produces a significant quantity of aerosol (see Table 6 Risk Group Definition).

GMO medicinal product bacteriophage therapy must be handled according to genetically modified organism (GMO) medicinal product standards (see Section 5 Genetically Modified Organism Medicinal Products).

8.4. Supply, transport and packaging requirements

Bacteriophage products must be supplied and transported as if it is a Schedule 4 medicine in accordance with NSW Health Policy Directive *Medication Handling* (PD2022_032).

Registered nurses and medical practitioners may prepare doses of bacteriophage products ready for administration in the patient care area, following the same strict aseptic techniques and handling precautions in accordance with medium risk products (see Section 2.1 Occupational exposure risk to staff).

Local policy and procedure must be followed when administering nebulised bacteriophage therapy including placing the patient in a separate individual room.

8.5. Disposal

Bacteriophage waste must be managed under clinical waste in the NSW Policy Directive *Clinical and Related Waste Management for Health Services* (PD2020_049). Each public health facility must consult their local work health and safety, and waste management policy.

9. RECORD AND INCIDENT MANAGEMENT

NSW Health Policy Directive *Medication Handling* (PD2022_032) mandates the requirements for records management and retention periods for the following records when preparing pharmaceutical products:

- dispensing, prescriptions, Special Access Scheme (SAS) approvals, and drug registers
- procurement, prescribing, administration and supply of pharmaceutical products in patient care areas.

The *Australian Pharmaceutical Formulary Handbook* (APF) and the Society of Hospital Pharmacists of Australia (SHPA) *Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments* (2010) outline the type of records that must be available for the preparation of pharmaceutical products and advanced therapeutic products, for example risk assessments, master formulation records, quality assurance and quality control documentation, staff training and validation relevant to the scope of practice, and dispensing records.

Retention periods of records in public health facilities can be found in the NSW State Records *GDA-17-General Retention and Disposal Authority Public health services: patient/client records* and *GDA-21-General Retention and Disposal Authority Public health services: administrative records*, under the *State Records Act 1998* (NSW).

Records management for investigational medical products (IMPs) must comply with the *Poisons and Therapeutic Goods Regulation 2008* (NSW), the *Australian Clinical Trial Handbook*, and the trial sponsor requirements.

Table 11. Record type and retention period

Record type	Retention period
Dispensing and compounding documents	Minimum of 10 years after action completed, then destroy
Quality assurance and control documents	Minimum of 6 years after last action, then destroy
Staff validation documents	Minimum of 3 years after completion of the program, then destroy
Clinical trial documents	TGA requires records to be retained by the sponsor for 15 years following the completion of a clinical trial

9.1. Recalls and incident reporting

NSW Health Policy Directive *Medication Handling* (PD2022_032) mandates the process for medication recalls, the system for recall actions and incident reporting. Recalls and incident reporting for investigational medical products (IMPs) must be managed through the trial protocol.

In the event that an incident occurs while preparing pharmaceutical or advanced therapeutic products a needle stick injury must be managed under the NSW Health Guideline *Work Health and Safety - Blood and Body Substances Occupational Exposure Prevention* (GL2018_013) and incidents must be reported in accordance with NSW Health Policy Directive *Incident Management* (PD2020_047).

10. OUTSOURCING THE PREPARATION OF PHARMACEUTICAL AND ADVANCED THERAPEUTIC PRODUCTS

A patient's own pharmaceutical preparation initiated prior to admission, for example compounded topical cream, must be brought into the public health facility and is not the responsibility of the public health facility to prepare. As a result of long stay patients, this Policy Directive provides an exemption to Justice Health and provides an authority to the Drug and Therapeutic Committee (DTC) to approve the preparation of non-aseptically compounded extemporaneous preparations for products that were initiated prior to admission.

Where a pharmaceutical product is initiated in a public health facility that does not have the facilities to prepare onsite, products can be sourced from a third-party supplier:

- non-aseptically prepared compounded products can be sourced from a community compounding pharmacy
- aseptically prepared products intended to be sterile must only be sourced from a Therapeutic Goods Administration (TGA) manufacturing licenced facility
- all preparations must have continuous environmental monitoring by both public health facility and third-party supplier, during transport and storage, and a documented risk management process for cold chain breaches for products intended to be stored below 8°C.

When investigational medicinal products (IMPs) or advanced therapeutic products cannot be prepared on site in a public health facility, an arrangement for supply can be made from a third-party supplier. For example, genetically modified organism (GMO) medicinal product preparation requires physical containment level 2 (PC2) facilities which may need to be outsourced to a medical or research laboratory under approval of the DTC.

In addition, approval by a Human Research and Ethics Committee (HREC) is required if the GMO medicinal product is an IMP. Prior to outsourcing the Director of Pharmacy must be able to confirm that the products are prepared either:

- at a Therapeutic Goods Administration (TGA) licenced manufacturing facility
- a Good Manufacturing Practice (GMP) certified facility overseas, or
- under a technical service level agreement between the Director of Pharmacy in the requesting public health facility and the Director of Pharmacy in the public health facility preparing the product, and the product is prepared in accordance with:
    - a formulation specified by the requesting public health facility, and
        - the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (PE 010)
        - Guideline for Good Clinical Practice (GCP) principles, or
        - Society of Hospital Pharmacists of Australia (SHPA) Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments (2010).

If sourcing investigational medicinal products (IMPs) or advanced therapeutic products from outside of Australia, it is the responsibility of the Director of Pharmacy to ensure the products are prepared by a manufacturer that has obtained a TGA GMP certification following a successful onsite inspection by the TGA. NSW Health Policy Directive *NSW Health Procurement* (PD2022_020) provides information on purchasing procedures and contracts with providers.

11. OBTAINING A LICENCE TO MANUFACTURE

There are no Commonwealth or state restrictions on NSW public health facilities obtaining a Therapeutic Goods Administration (TGA) licence to manufacture a therapeutic good. Facilities wishing to apply for a TGA manufacturing licence, must meet all the following criteria and gain approval from the Chief Executive to fund the process. For costs associated with applying for a TGA manufacturing licence refer to TGA *Fees and charges*.

See the TGA *Australian manufacturing licences and overseas GMP certification* for guidance for Australian manufacturers of therapeutic goods to apply for a manufacturing licence and the *responsibilities of manufacturers of medicines and biologicals*.

12. REFERENCES

- Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel https://www.edcan.org.au/sites/default/files/Alexander_et_al-2014-Internal_Medicine_Journal.pdf
- Australian Injectable Drugs Handbook. The Society of Hospital Pharmacists of Australia. Online resource
- Australian Pharmaceutical Formulary Handbook 25. 2021. Pharmaceutical Society of Australia. Canberra
- Australasian Health Facility Guidelines. https://healthfacilityguidelines.com.au/
- Clinical Oncology Society of Australia (COSA) Guidelines for the safe prescribing, dispensing and administration of systemic cancer therapy https://www.cosa.org.au/media/1093/cosa_guidelines_safeprescribingchemo2008.pdf
- Clinical Oncology Society of Australia (COSA) Position Statement: Safe handling of monoclonal antibodies in healthcare settings https://www.cosa.org.au/media/173517/cosa-cpg-handling-mabs-position-statement_-november-2013_final.pdf
- Medical Board of Australia. List of specialties, fields of specialty practice and related specialist titles. 2018
- National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016 https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf
- NSW Government SafeWork Guide on Cytotoxic Drugs and Related Waste – Risk Management 2017 https://www.safework.nsw.gov.au/__data/assets/pdf_file/0005/287042/SW08559-Cytotoxic-drugs-and-related-risk-management-guide.pdf
- NSW Health Information Bulletins, Guidelines and Policy Directives:
  - Approval Process of Medicines and Their Use (PD2022_056)
  - Clinical and Related Waste Management for Health Services (PD2020_049)
  - High-Risk Medicines Management (PD2020_045)
  - Vaccine Storage and Cold Chain Management (PD2020_028)
  - Work Health and Safety: Better Practice Procedures (PD2018_013)
- Office of the Gene Technology Regulator under the Gene Technology Act (2000) for clinical trials in humans involving GMO medicinal products – Guidance for clinical trial sponsors. https://www.ogtr.gov.au/
- Pharmacy Board of Australia:
  - Guidelines on compounding of medicines 2015 https://www.pharmacyboard.gov.au/codes-guidelines.aspx

  - Joint statement on compounded medicines 2017 https://www.pharmacyboard.gov.au/codes-guidelines.aspx
- Pharmacy Council of New South Wales:
  - Fact sheet: Raw materials used in compounding, and
  - Frequently Asked Questions for the Fact sheet: Raw materials used in compounding https://www.pharmacycouncil.nsw.gov.au/list-compounding-resources
- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme:
  - PIC/S Guide to Good Practices for the Preparation of Medicinal Medicines in Healthcare Establishments PE 010-4 (2014) https://picscheme.org/docview/3443
  - PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annexes PE 009-16 (2022) https://picscheme.org/docview/4590
  - PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part II PE 009-8 (2009) https://picscheme.org/docview/4589
- Society of Hospital Pharmacists of Australia:
  - Guidelines for Medicines Prepared in Australian Hospital Pharmacy Departments (2010)
  - Standard of Practice in Oncology and Hematology for Pharmacy Services (2020)
  - Standards of Practice for the Safe Handling of Cytotoxic Drugs in Pharmacy Departments (2005)
  - Standards for the Transportation of Cytotoxic Drugs from Pharmacy Departments (2007)
  - Standards of Practice for Clinical Trials for Pharmacy Services (2020)
- Therapeutic Goods Administration:
  - Australian clinical trial handbook. Guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods https://www.tga.gov.au/resource/australian-clinical-trial-handbook
  - Compounded medicines and good manufacturing practice (GMP) Guide to the interpretation of the PIC/S Guide to GMP for compounded medicinal medicines https://www.tga.gov.au/sites/default/files/compounded-medicines-and-good-manufacturing-practice-gmp.pdf
  - Manufacturing therapeutic goods https://www.tga.gov.au/manufacturing-therapeutic-goods
  - Special Access Scheme (SAS) Guidance for health practitioners accessing unapproved therapeutic goods https://www.tga.gov.au/sites/default/files/2023-

02/special-access-scheme-sas-guidance-health-practitioners-accessing-unapproved-therapeutic-goods.pdf

- The Australian Code of Good Manufacturing Practice for Blood and Blood Components, Human Tissues and Human Cellular Therapy Medicines at: https://www.tga.gov.au/publication/australian-code-good-manufacturing-practice-human-blood-and-blood-components-human-tissues-and-human-cellular-therapy-medicines

- United States Pharmacopeia Pharmaceutical Compounding Standards:
  - <795> *Pharmaceutical Compounding – Nonsterile Preparations*

    https://www.usp.org/compounding
  - <797> *Pharmaceutical Compounding – Sterile Preparations*

    https://www.usp.org/compounding
  - <800> *Hazardous Drugs – Handling in Healthcare Settings*

    https://www.usp.org/compounding

13. APPENDICES

1. Appendix 1: Checklist of requirements prior to approving the preparation of a product in a public health facility
2. Appendix 2: Production Risk Assessment
3. Appendix 3: Policy Directive compliance checklist
4. Appendix 4: Pharmacy production facilities compliance assessment
5. Appendix 5: Bone Marrow Transplant Network NSW Immune Effector Cell (IEC) procedures and forms for CAR T-cell products and therapy

13.1. Appendix 1: Checklist of requirements prior to approving the preparation of a product in a public health facility

- ☐ Identify the relevant medical specialist or principal investigator
- ☐ Complete Risk Assessment (see Appendix 2 Production Risk Assessment)
- ☐ Public health facility Drug and Therapeutic Committee (DTC) approval (where relevant, for example bacteriophage)
- ☐ Human Research Ethics Committee (HREC) approval (where relevant, for example IMPs)
- ☐ Develop Master Formulation Record (MFR) and Batch Record
- ☐ Standard Operating Procedures (SOP):
    - Handling SOP
    - Preparation SOP – including specific facility and equipment requirements
    - Cold chain and storage SOP
    - Transport SOP – including specialised courier service/spill kit requirements
- ☐ Staff training (where appropriate) and training log
- ☐ Identify if the therapeutic good is listed on the Australian Register of Therapeutic Goods (ARTG)
- ☐ Where the therapeutic good is not listed on the ARTG, an application and approval may be required for access:
    - Therapeutic Goods Administration (TGA) Special Access Scheme (SAS) or Section 19A
    - Compassionate supply by the manufacturer
    - Life Saving Drug Program (LSDP)
    - Importation requirements
        - Biosecurity Import Conditions system (BICON) permit
        - Clinical Trial Approval (CTA) or Clinical Trial Notification (CTN)
- ☐ Legal medication order or prescription
    - eMeds or National Inpatient Medication Chart (NIMC)
- ☐ Prepare product as per MFR
- ☐ Package for transportation
    - Label, for example biohazard or cytotoxic

- Secondary container for hazardous drugs (HDs) and genetically modified organism (GMO) medicinal products
- Protect from light. Refrigerate. Frozen. Ultra-cold freezer.
- Decontamination Spill kit (if required)
- Specialised transport between sites

☐ Supply to the principal investigator or trained clinician or trained nurse

13.2. Appendix 2: Production Risk Assessment

Product: _____

Route of administration:_____

Clinical indication: _____

Date of risk assessment: _____

Section 1. Reason for Pharmacy Service Production

☐ Nil ARTG listed/ registered product

☐ Nil ARTG listed/ registered suitable alternative because:

_____

☐ ARTG listed/ registered product unsuitable because:

_____

_____

☐ Nil unapproved product available through SAS or S19A

☐ SAS or S19A unapproved product unsuitable because:

_____

_____

☐ Clinical trial Name of trial_____

☐ HREC approval number_____

☐ DTC approval

If GMO: ☐ IBC approval number_____

☐ OGTR approval number_____

Is it possible to use an existing published pharmacopoeia formula?

☐ Yes: Reference_____

☐ No: Reputable formulation reference(s) used: _____

_____

_____

Section 2. Application of beyond use date

Minimum BUD applied of _____ hours/days according to ☐ PIC/S PE010 ☐ APF

☐ International clinical trial - USP

☐ Stability study: Reference_____

☐ Extended BUD required ☐ Approved by DTC for _____ hours/days

Reason_____

_____

☐ Prescriber informed of differences between ARTG listed/registered medicines and compounded medicines and confirmed to proceed

Section 3. Patient information (where appropriate)

☐ Paediatric Weight_____ Age _____years/months/days ☐ Adult

Gender at birth ☐ Male ☐ Female ☐ Pregnant/breast feeding

Patient previously treated with this medication ☐ Yes ☐ No

☐ Allergies or adverse drug reactions

Comment on allergen and allergic response_____

_____

Potential drug-drug or drug-disease interactions ☐ Yes ☐ No

Comment_____

_____

Section 4. Preparation in anticipation of an order (where appropriate)

☐ A delay in treatment is detrimental to the outcome for the patient

☐ DTC approval

☐ Sterility testing available

Section 5. Occupational health and safety exposure risk score for aseptic preparation of pharmaceuticals and advanced therapeutic products as per Section 2.1 Occupational exposure risk to staff

☐ Low risk (1 to 2)

☐ Medium risk (3 to 4)

☐ High risk (≥5)

Section 6. Production category and facility requirements

☐ Non-aseptically prepared	☐ Segregated area	☐ Powder containment PEC
☐ Non-aseptically prepared HD	☐ Segregated area	☐ Negative pressure PEC
	☐ Segregated room	
☐ Aseptically prepared	☐ PIC/S PE010 compliant	☐ Positive pressure PEC

☐ Non-aseptic to aseptic PEC in Grade D/C

☐ Aseptically prepared HD ☐ PIC/S PE010 compliant ☐ Negative pressure PEC

☐ Negative pressure cleanroom

☐ Aseptically prepared biohazard ☐ PIC/S PE010 compliant ☐ Negative pressure PEC

☐ Segregated negative pressure cleanroom

☐ Other

Section 7: Skill and process documentation completed

☐ Competent staff validated in processes required for specific product preparation

☐ Appropriate SOPs in place and in date

☐ Master Formulation Record

Section 8. Decision

☐ Prepare by the pharmacy service on-site

☐ Outsource: obtain from a TGA licenced manufacturing facility:

☐ Outsource: obtain IMP from a public health facility that is not TGA licenced to manufacture:

☐ Outsource: import IMP from a GMP certified facility overseas:

☐ Outsource: obtain from a medical laboratory or equivalent:

	Name and designation	Signature
Risk Assessment form completed by		
Pharmacist who made the decision to prepare		

13.3. Appendix 3: Policy Directive compliance checklist

Public health facility:	**Date of Assessment:**

Requirement	Compliant
Pharmacy production facilities compliant to PIC/S standards, including NATA accreditation	❑
Pharmacy equipment calibrated and compliant to standards in this Policy Directive	❑
The Director of Pharmacy has an appropriately qualified responsible pharmacist and/or clinical trials pharmacist to delegate tasks (within their scope of practise), or access to an appropriately qualified pharmacist	❑
Standard operating procedures for handling hazardous drugs in pharmacy and in patient care areas	❑
Spill kits available in each area where hazardous drugs are handled, stored, prepared and during transportation	❑
Spill kit training provided to staff involved in handling, storage, preparation and transportation of hazardous drugs	❑
Nurse training and accreditation for the reconstitution, dilution and preparation of medium-risk medicines and products in the patient care area	❑
Standard operating procedures in place for the management of clinical trials	❑
Continuous environmental monitoring available by the public health facility and third-party providers, during transport and storage, and a documented risk management process for cold chain breaches for products intended to be stored below 8°C	❑
Appropriate staffing levels to conduct all compounding and preparation tasks safely and effectively	❑
Pharmacy standard operating procedures completed, in each area of production, to ensure reproducibility	❑
Pharmacy production staff training package available and competencies and validations completed	❑
A production risk assessment available for all the compounding or aseptically prepared pharmaceutical or advanced therapeutic product by the pharmacy service	❑
A master formulation record for all compounded and aseptically prepared pharmaceutical and advanced therapeutic products	❑
Safety data sheets available in the production area for all raw materials, chemicals, pharmaceuticals and advanced therapeutics handled	❑
Staff risk assessment for all staff entering a cleanroom environment, including contractors and maintenance staff	❑
Compliance to material transfer and rotational cleaning procedures	❑
Quality management system in place complaint with PIC/S to support the application of appropriate beyond use dates	❑

Review of contracts and service level agreements for outsourcing of prepared pharmaceutical and advanced therapeutic products to ensure facilities providing the service have a TGA manufacturing licence	❑
Where appropriate, have access to an Institutional Biosafety Committee (IBC)	❑

	Name and designation	Signature	Date
Completed by			
Chief Executive approval			

13.4. Appendix 4: Pharmacy production facilities compliance assessment

Public health facility:	**Date of Assessment:**

Requirement	N/A Do not prepare these products	Not commenced	Partial compliance	Full compliance
Non-sterile compounding in a designated clean area away from the main pharmacy dispensary and parts of the pharmacy where there is a considerable amount of traffic (e.g., aisles, entrance and exit doors, etc.)	❑	❑	❑	❑
	Plan:			
All glassware, mortar, and pestles, stirring rods etc must be of laboratory standard or calibrated to an equivalent accuracy of +/- 2% as stated in the APF	❑	❑	❑	❑
	Plan:			
A negative pressure high efficiency particulate air (HEPA) filtered powder containment hood or equivalent to use when compounding non-sterile hazardous preparations	❑	❑	❑	❑
	Plan:			
Four HEPA filtered clean zones for aseptic preparation of products as per PIC/S PE010 and appropriate level of primary engineering control (PEC) for products prepared	❑	❑	❑	❑
	Plan:			
Four negative pressure HEPA filtered clean zones for cytotoxic preparation of products as per PIC/S PE010 and appropriate level of PEC for products prepared	❑	❑	❑	❑
	Plan:			

Separation of products to avoid cross contamination, for example separate PECs for antibiotics and monoclonal antibodies	❑	❑	❑	❑
	Plan:			
Sinks not be adjacent to a Grade B cleanroom	❑	❑	❑	❑
	Plan:			
For aseptically prepared products, have access to pathology to identify microorganisms and provide sterility testing when needed	❑	❑	❑	❑
	Plan:			

	Name and designation	Signature	Date
Completed by			
DTC review completed by			
Chief Executive approval			

13.5. Appendix 5: Bone Marrow Transplant Network NSW Immune Effector Cell (IEC) procedures and forms for CAR T-cell products and therapy

Activity	Standard Operating Procedure	Form
Training	QS-BMT-S5 Training and Assessment	QS-IEC-F15 IEC Infusion Competency QS-IEC-F30 Clinical IEC Training Record QS-BMT-F31 Laboratory IEC Training Record QS-IEC-F32 Nursing care of IEC patient assessment form
Ordering	• Procedures and Training by IEC Manufacturer • Train the trainer by IEC Quality Manager/ BMT/CT Program	Platform reviewed for security and confidentiality
Donor work-up	• DO-IEC-S1 IEC Donor Work-up • DO-BMT-S1 Donor Infectious Disease Testing • DO-BMT-S4 Donor Screening	• DO-BMT-F7 BMT+CT Donor Questionnaire • DO-IEC-F1 IEC Donor Work-up Checklist
Collection	• QS-IEC-S1 Preparation for IEC Harvest • CO-BMT-S7 Collection by Optia – CMNC Program • CO-BMT-S14 Collection by Optia – MNC Program	• CO-XXX-F4 (XXX= hospital specific) HPC/MNC Pre-apheresis Checklist • CO-BMT-F12 Collection Procedures Sheet (SMR060.832)
Processing	PR-IEC-S40 Auto MNC, Apheresis Processing	PR-XXX-F40/42 (XXX= hospital specific) MNC, Apheresis Processing worksheet
Receipt	PR-BMT-S1 Product Receipt	RE-IEC-F3 Product Receipt from Manufacturer Checklist
Distribution	PR-BMT-S9 Product Distribution	PR-IEC-F3 Manufactured IEC Product Distribution Checklist.
Lymphodepletion	TX-IEC-S4 Work-up for CAR T-cell Treatment Note: Guidance on the lymphodepletion and administration is provided by eviQ - Cancer Institute	
Infusion	TX-XXX-S13/15 (XXX = hospital specific) IEC Product Infusion	SMR060.831 Blood and Marrow Transplant Cellular Therapies Product Infusion form (Produce code NH700433)