Track 1
Session 3
Compounding facilities

Chair – Trevor Schoerie

4 July, 2016

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2 presentations

1. **Compounding Pharmacies – USP<797> and Australia** - Megan Rutherford (30 minutes)

2. **Design Considerations for TGA Licensed Pharmacies** - Ashley Isbel (60 minutes)

Compounding Pharmacies – USP<797> and Australia

Presented by Megan Rutherford

11 August, 2015

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In search of world's best practice

2015 PDA Aseptic Processing – Sterilisation Conference

- New England Compounding Centre – 64 deaths
- New regulation and oversight by FDA
- USP<797>

What is pharmaceutical compounding?

'Compounding is a practice in which a licensed pharmacist, a licensed physician, or…a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient'

Why?

- Different dosage form required
- Sensitivity or allergy to excipients and preservatives
- Discontinued or unavailable medicine

New England Compounding Centre (NECC)

May, 2012

NECC became the centre of a scandal resulting from a meningitis outbreak, linked to 64 deaths

- Recalled more than 2,000 products after distributing 17,000 vials of methylprednisolone for injection contaminated with fungi to 23 states
- NECC was only licensed to prepare individual patient prescriptions - shipped drugs to multiple states, and may have been operating outside of their legal boundaries
- Center employees are accused of using expired ingredients and failing to follow cleanliness standards, resulting in tainted steroid injections

FDA response to NECC disaster

Drug Quality and Security Act, 27 November 2013 - granted the FDA more authority to regulate and monitor the manufacturing of compounded drugs.

- Creation of Section 503B for outsourcing facilities.
- Outsourcing facilities that register under section 503B are regulated by FDA:
  - must comply with cGMP requirements
  - will be inspected
  - must meet certain other conditions, such as reporting adverse events
- Drugs compounded by an outsourcing facility can qualify for exemptions from the FDA new drug approval requirements and the requirement to label products with adequate directions for use.

Looking ahead

The future of the compounding industry

- **503B** highlights the commitment and expectation for increased quality
- Using a single Federal category is effective (versus state licensing)
- Final guidance must be reflective of
  - Medical caregivers' and patient needs
  - Depth: to assure quality and safety
  - Be flexible: to ensure evolution of best practices

Milestones expected in 2015

- Applicable GMPs for 503B industry
- Memorandum of understanding between state boards of pharmacy and FDA

Current regulation of compounding pharmacies in Australia

A license from the TGA is **not** required when a pharmacist is practicing:

- In a pharmacy which is open to the public, or on the premises of a private hospital.

OR

- Employed in public hospitals or public institutions, and medicines are manufactured for supply in public hospitals or public institutions within the same state or territory.

- Must still meet the quality standards set out in the Therapeutic Goods Act 1989
- Regulated by the Pharmacy Board of Australia

Current regulation of compounding pharmacies in Australia

Compounding pharmacies **must comply** with practice standards and guidelines including:

- Pharmaceutical Society of Australia Professional Practice Standards, Standard 10 and 11
- The Society of Hospital Pharmacists of Australia SHPA Standards of Practice
- Occupational, health and safety standards
- Australian standards for cleanrooms
- State, territory and Commonwealth legislation relevant to the practice of pharmacy and pharmacy supply of medicines
- The section *Extemporaneous dispensing* in the current edition of the *Australian Pharmaceutical Formulary and Handbook*

Future regulation of compounding pharmacies in Australia

Option A:

- Status quo

Option B:

- Enhance co-regulation and update legislation

Option C:

- Manufacturing license for specified manufacture in pharmacies

Why get a TGA license?

Flexibility

- Ability to go beyond named patient compounding
- Use own stability data to extend expiry dates

Reputation and status

- Improve commercial opportunities
- Greater perception of quality

Government funding

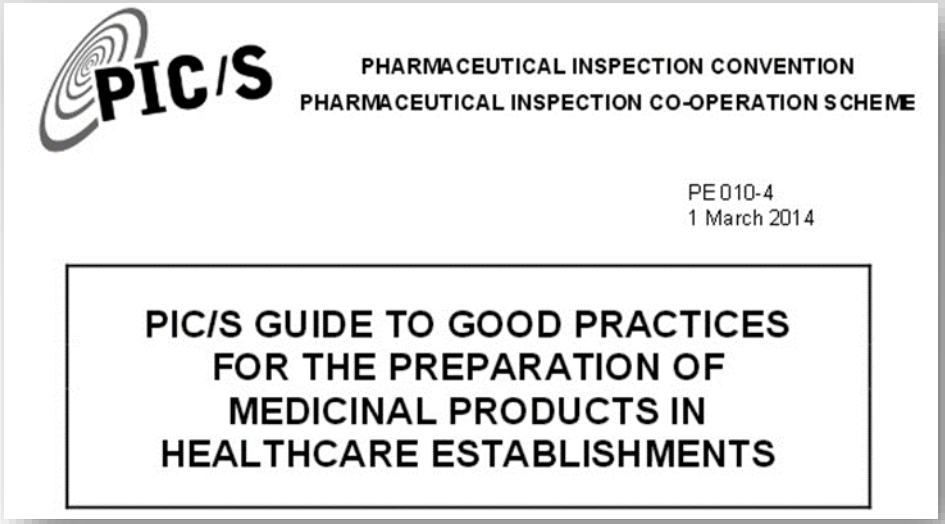
- A TGA licensed pharmacy may receive up to 50% more per script than an un-licensed pharmacy

Requirements & regulations for TGA licensed pharmacies

TGA licensed compounding pharmacies would be subject to the same requirements as conventional sterile manufacturing facilities, including:

- **TGA fees and charges** – application fee, annual charges for sterile manufacture (includes 48 inspection hours).
- **Capital investment** and on going costs in order to comply with the requirements of the manufacturing license
- **Inspections**
- **Bound by PIC/S PE009** - Guide to Good Manufacturing Practice for Medicinal Products, and Annex 1 (sterile manufacture)

Useful guidance for compounding pharmacies

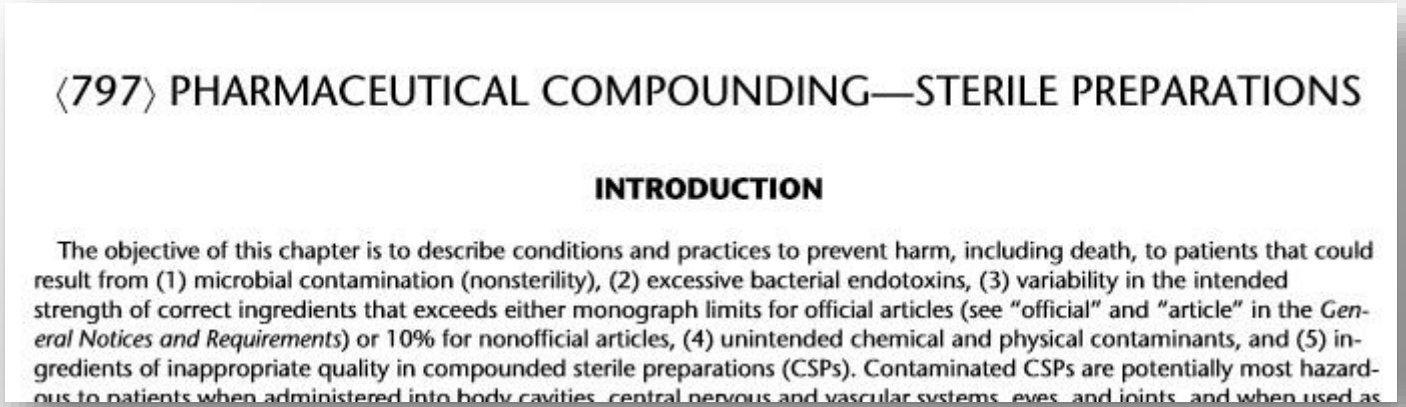


PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 010-4
1 March 2014

PIC/S GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS



⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

INTRODUCTION

The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles (see "official" and "article" in the *General Notices and Requirements*) or 10% for nonofficial articles, (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in compounded sterile preparations (CSPs). Contaminated CSPs are potentially most hazardous to patients when administered into body cavities, central nervous and vascular systems, eyes, and joints, and when used as

PE010-4, PIC/S Guide to Good Practices for Healthcare Establishments

Basic requirements for preparation of medicinal products performed by healthcare establishments for direct supply to patients, including:

- Quality Assurance System
- Personnel
- Premises and Equipment
- Documentation
- Production
- Complaints and Product Recalls
- Self Audits

Endorsed by the Society for Hospital Pharmacists of Australia

PE010-4, PIC/S Guide to Good Practices for Healthcare Establishments

Annex 1 – Guideline on the standards required for the sterile preparation of medicinal products

Supplement to the main part of the Guide

- Product type examples – cytotoxics, radiopharmaceuticals, infusions, syringes, irrigations
- Personnel
- Premises and equipment, clothing, cleaning
- Documentation
- Sterile processing
- Monitoring – classification and testing frequencies (LFCs and isolators), limits

USP<797>, Pharmaceutical Compounding: Sterile Preparations

Formerly USP<1206> Sterile Drug Products for Home Use

- Became effective 01 January, 2004
- Revised in 2008, notice of intent to revise issued December 2013
- Applies to all healthcare settings where sterile preparations are compounded (U.S.)

In Australia: it is not a GMP code but is useful guidance for pharmacies

Updates to USP<797>: What to expect

- More information to assist compounding pharmacies with ISO 14644 cleanroom classifications & cleanroom design and construction
- Recommendations on the restriction of materials that may compromise the integrity of the air
- Classification of cleaning requirements
- Clarification of environmental monitoring requirements
- Alignment with USP <1116> - relying on incident rates rather than Action/Alert Levels

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Thank you for your time.
Questions?

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Design Considerations for TGA Licensed Pharmacies

Presented by Ashley Isbel

11th August 2015

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Focus of the session

Primarily of relevance to sterile compounding facilities, particularly those producing cytotoxic/chemotherapy drugs.

In this session

- GMP licensing of pharmacies – some background
- Key regulatory issues affecting design
- Other licensing challenges facing pharmacies
- TGA inspection concerns

GMP and Pharmacies - Background

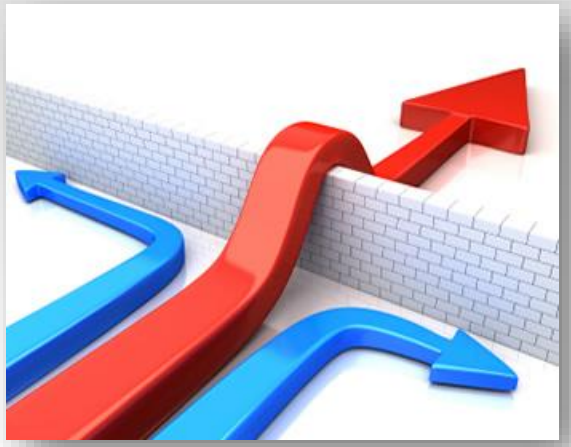
The last few years have seen an increase in focus on regulating compounding pharmacies.

- In the **US** – New England Compounding Center disaster has led to a new regulatory (currently voluntary) regime
- In **Australia**, TGA has been pushing for some time to regulate … gaining traction
  - 6CPA has provided financial incentive for chemotherapy compounders
  - Recent NSW adverse reaction incident has highlighted the lack of regulatory oversight of non-licensed compounders

GMP and Pharmacies - Background

GMP regulators in most of the world (and notably in Australia) have some challenges in regulating pharmacies

- Typically constrained to assess GMP through various finished product GMP guidances (eg. PE009-8 in Australia)
- Finished product GMP guidances are typically written with "big Pharma", or emerging trends (e.g. biologicals) in mind
- Challenging anomalies can arise between standard practice, what is practical and what the GMPs say



GMP and Pharmacies - Background

Some compounders in Australia have actively pursued licensing

- Allows added flexibility in manufacture (e.g. Batch size and product expiry)
- Creates perception of increased quality among potential clients
  - Increased marketing opportunities

Design issues in the GMPs

The move to a licensed facility needs to include a review of existing facilities and systems as early as possible in the business case development

Almost always identifies insurmountable deficiencies between existing facilities and regulatory requirements for sterile manufacturing facilities

Outcome is almost inevitably the requirement for new facilities

- Green or brownfield site
- Renovation of existing site (if ceasing/disrupting operations is acceptable)

Design issues in the GMPs

Some of the key regulations which can cause design issues:

- Materials and personnel flow – concept of personnel and material airlocks
- Separation of product types & manufacturing stages
- Room grading requirements
- Continuous particle monitoring of critical zones
- Gowning requirements (and therefore gowning facilities)
- Facility finish requirements
- Facility monitoring requirements
- Storage requirements, including segregation

Design issues in the GMPs

Material & Personnel Flow

1. The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

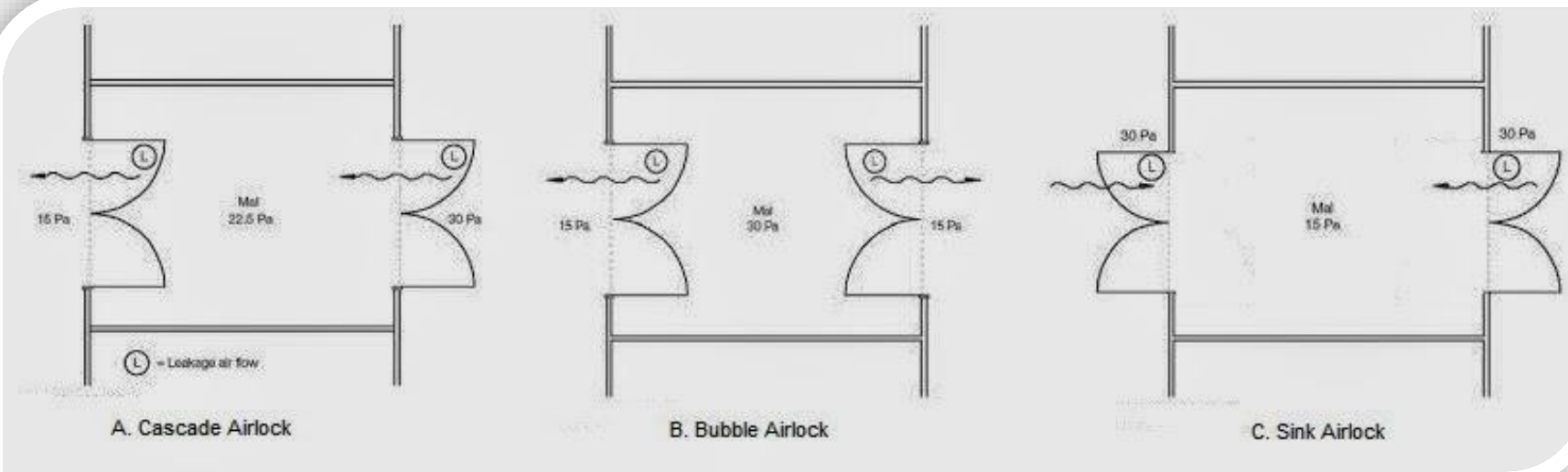
What is an airlock?

An enclosed space between two or more adjacent areas which prevents airflow to one or more of the areas.

- Typically works through pressurization:
  - Can be a cascade arrangement (intermediate pressure, allowing airflow from critical to less critical zone)
  - A bubble (higher pressure than adjacent areas)
  - A sink (lower pressure than adjacent areas)

Design issues in the GMPs

Material & Personnel Flow

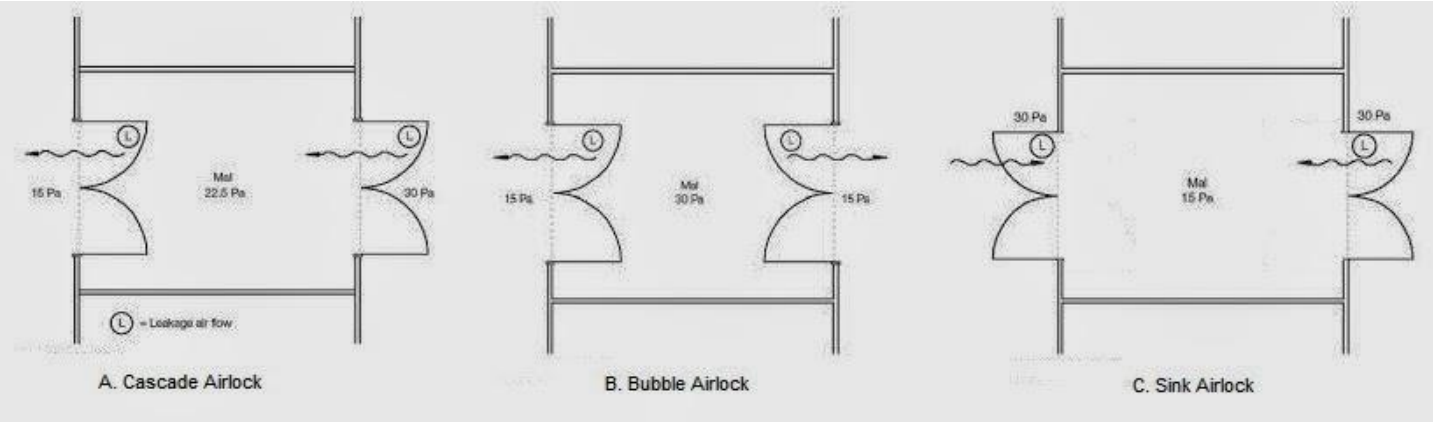


Design issues in the GMPs

Material & Personnel Flow

These **three principles** are relevant for both personnel and materials airlocks (including pass through boxes)

1. Cascade is standard arrangement
2. Bubble and sink are typically used in containment applications (including cytotoxic facilities)
3. Bubble or sink will usually depend on the capability of the HVAC system



Design issues in the GMPs

Separation of products & manufacturing stages

2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.

5.19. Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

b) providing appropriate air-locks and air extraction;

Design issues in the GMPs

Separation of products & manufacturing stages

Two key principles:

1. It is not permissible to perform discreet manufacturing stages in the same area (room) – dispensing, component preparation, solution preparation, filling and packing should all have their own dedicated areas
2. It is not usually permissible to manufacture products with a high degree of risk associated with cross-contamination in the same area, even if separated by time (e.g. cytotoxic vs non-cytotoxic, beta lactams vs anything else)

Design issues in the GMPs

Separation of manufacturing stages

Non-licensed facilities typically have a change room or two, and 1-2 manufacturing areas.

- Affect of fully separating manufacturing stages depends on which stages are used
  - **Dispensing** often not a cleanroom activity in licensed compounders
  - **Solution prep** often not performed
  - **Segregation** of storage, filling, packing still required
- More complex operations need more segregation of stages and therefore larger facilities

Design issues in the GMPs

Separation of manufacturing stages

Still some grey areas:

- Can you prepare solutions (or pack) in a UDAF cabinet or isolator background environment?
- Can you do batch preparation and packing in the same environment?

Lack of compliance with the letter of the code is not always addressed in inspections!

Design issues in the GMPs

Separation of product types

Can be a significant challenge – most compounders want to be able to perform a broad range of manufacture

- Non-sterile and sterile manufacture should be separated
- Cytotoxics and most sensitizing agents should be manufactured in a dedicated area
- Beta lactams are expected to be manufactured in a dedicated facility
- Each of these expectations adds size, complexity and cost to a facility

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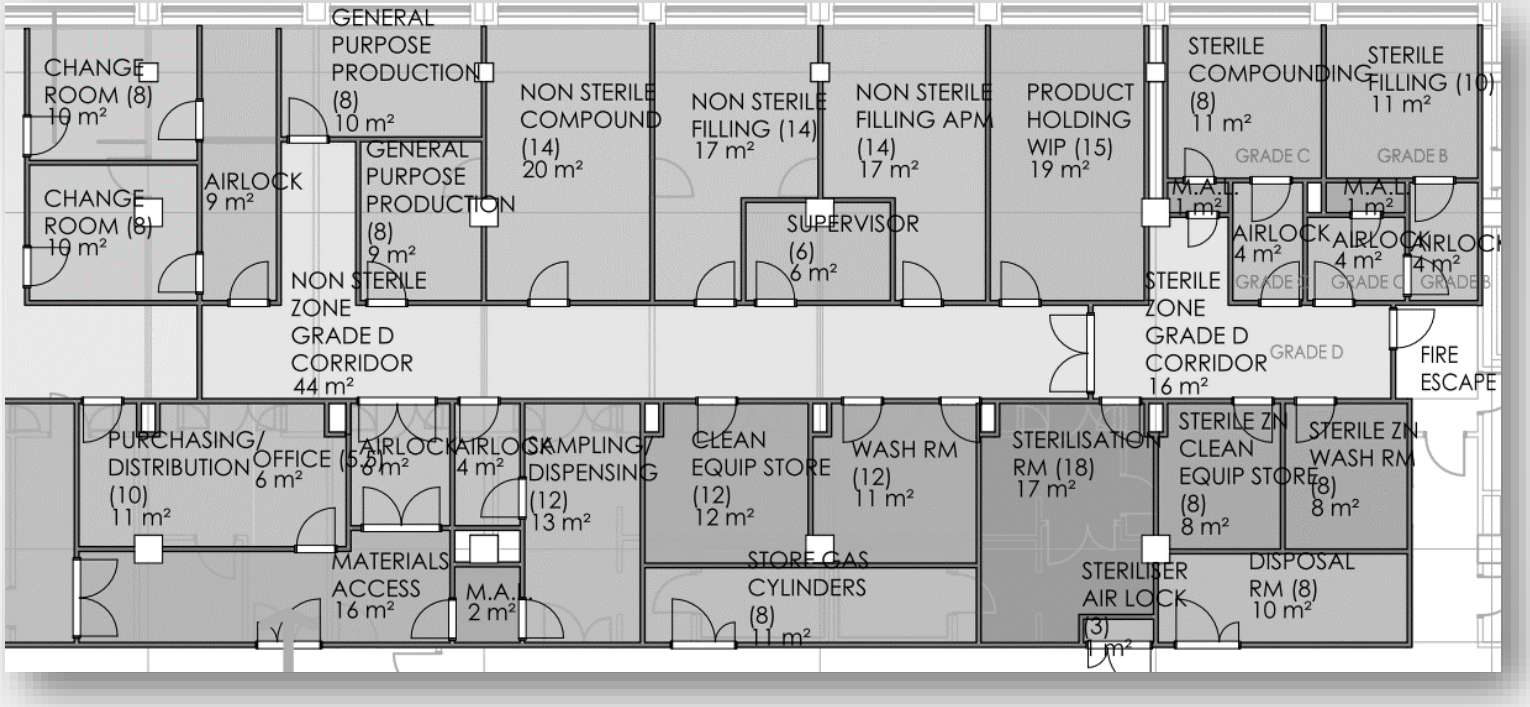
Design issues in the GMPs

Separation of product types

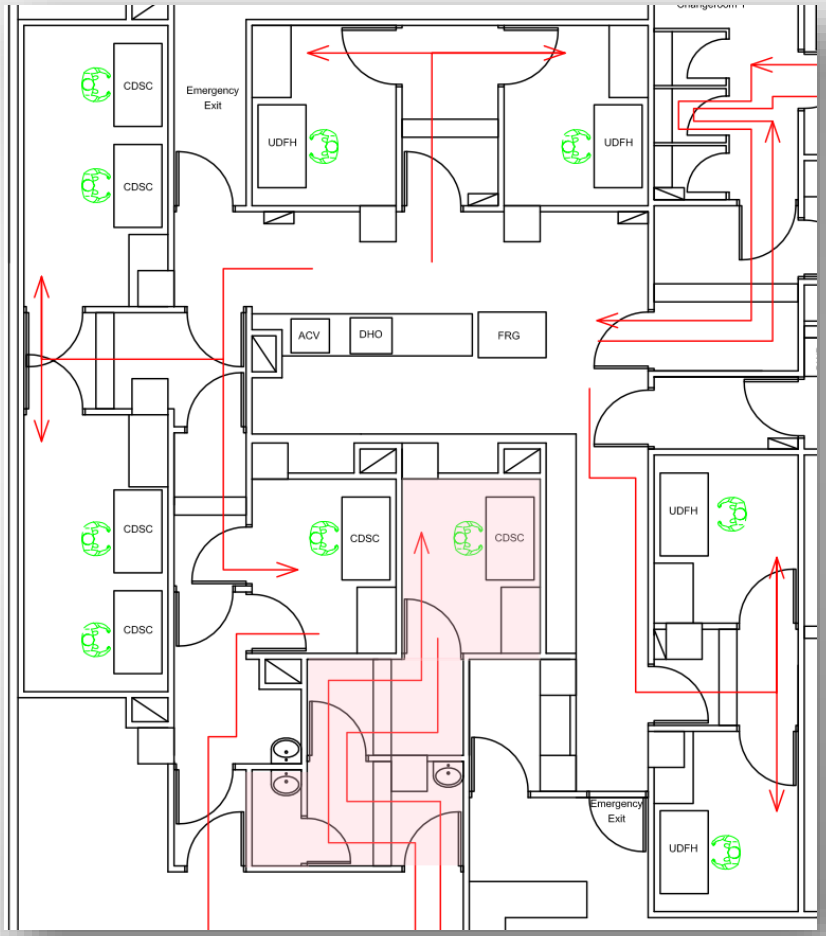


Facilities can quickly grow in size …

- This facility does not do ‘everything’

Design issues in the GMPs

Separation of product types



Shaded area is isolated AB suite

Design issues in the GMPs

Cleanroom Grading

Regulatory **requirement** for certain operations to take place in defined environments

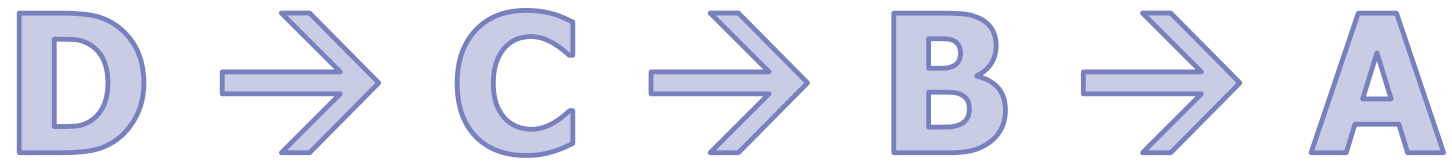
Grade	Examples of operations for terminally sterilised products (see para. 28-30)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see para. 31-35)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

Design issues in the GMPs

Cleanroom Grading

Regulatory **expectation*** that personnel and materials entering any grade, must have passed through all lower grades in sequence



*WHO has the only guidance to refer to this (TRS 961, Annex 6, 11.7)

Design issues in the GMPs

Continuous Particle Monitoring

9. For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

10. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

Design issues in the GMPs

Continuous Particle Monitoring

Rarely (never?) seen in unlicensed facilities

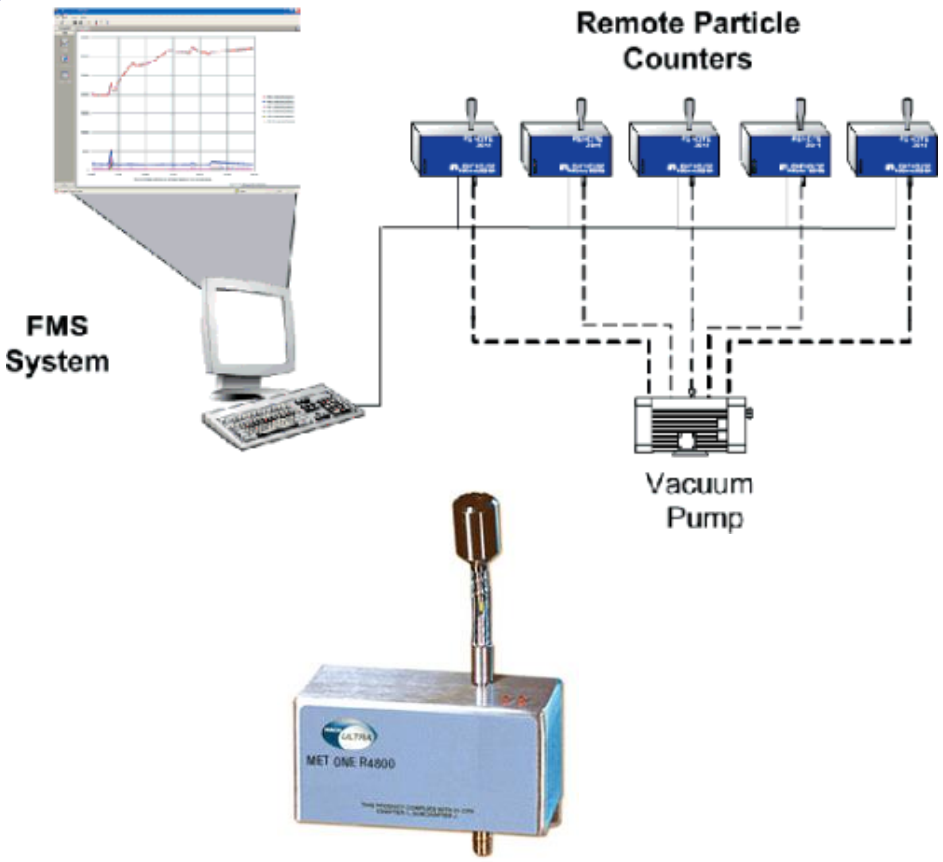
- Manifold or sequential testing no longer acceptable

Significant capital and operating costs

- Typically requires fixed system (small facilities may be able to manage with portable counters)

Design issues in the GMPs

Continuous Particle Monitoring



Design issues in the GMPs

Gowning

43. The description of clothing required for each grade is given below:

- Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
- Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.
- Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

44. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.

Design issues in the GMPs

Gowning

Significant design (and cultural) challenge

- Typically requires multiple changing areas

At least 3 changing stages to enter Grade B	At least 2 changing stages to enter Grade C

- May require gender specific changing areas
- Operators may need to get used to changing completely out of street clothes
- Design needs to facilitate storage and disposal of garments

Design issues in the GMPs

Facility finishes

GMPs are full of specific requirements for general and sterile manufacturing facilities, some of which are not common in unlicensed facilities:

- Smooth, impervious, unbroken surface finishes
- Minimal ledges, shelves, cupboards
- Sealed environment, including ceilings
- Absence of utilities pipework and ductwork inside facilities
- No sinks/drains in Grade A/B – minimal use in C/D
- Equipment and furnishings selected on basis of suitability for GMP environment
- Materials selected on basis of suitability for cleaning (both accessibility and resistance to chemicals)

Design issues in the GMPs

Facility monitoring

For new facilities, manually read instruments for facility monitoring no longer acceptable.

- Integrated BMS and/or EMS/FMS systems report continuously on GMP critical data

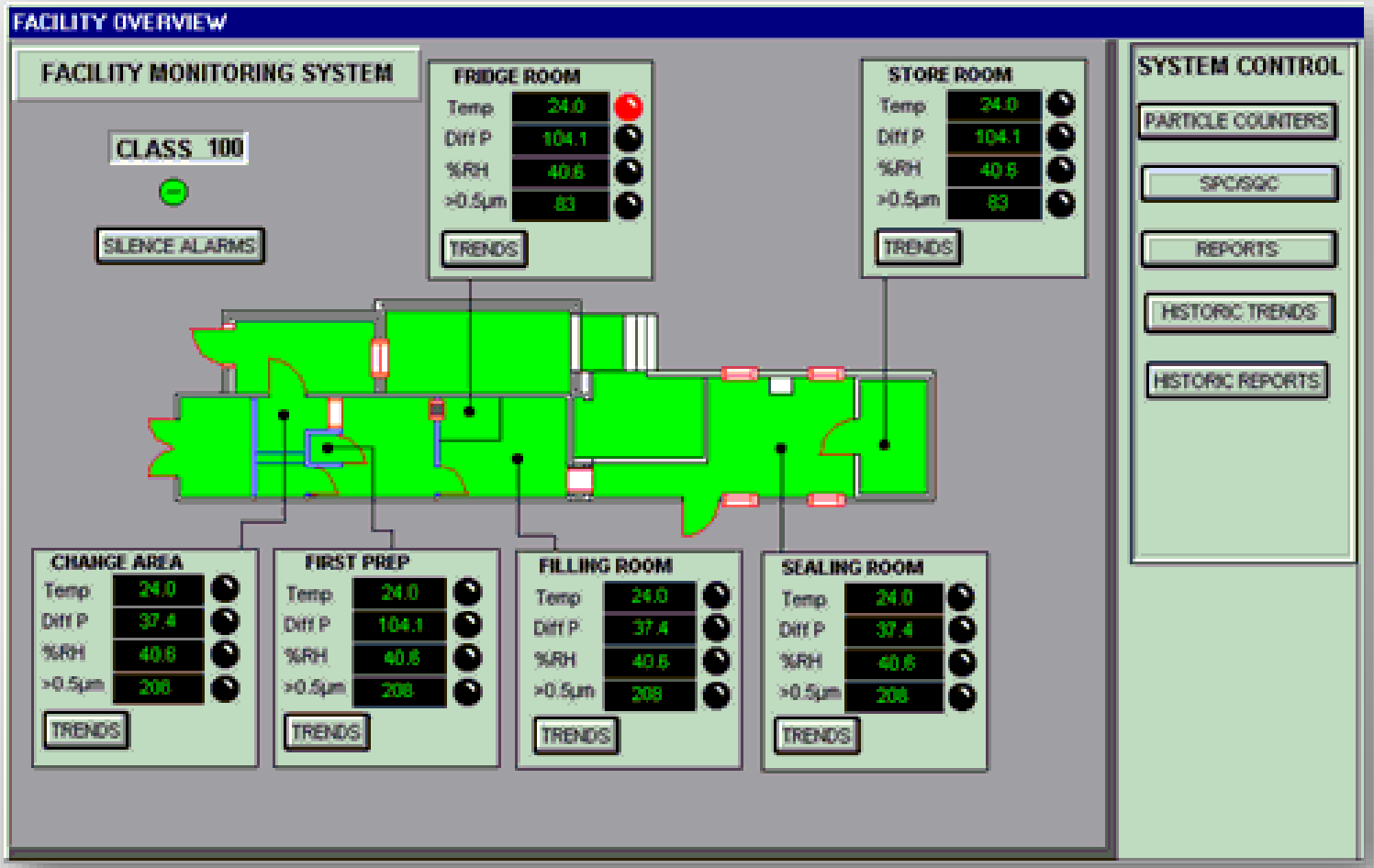
Temperatures (room and TSS devices)	Humidities	Particle counts	Differential pressures

Can also do door opening events and other equipment status

- EMS/FMS is difficult and more expensive to retrofit. Should be included in original design of new facilities

Design issues in the GMPs

Facility monitoring



Design issues in the GMPs

Storage and segregation

There are specific requirements for storage and segregation of materials during different phases of the product life cycle

3.18. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.23. Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

5.41. Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.61. Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.

Design issues in the GMPs

Facility monitoring

Dedicated zone for all material types (unless warehousing is automated)

The zones for rejected, recalled and returned materials need to be physically separated from the zones for quarantine and release

Access to rejected materials must be restricted

Access to printed materials must be restricted and secure

Other issues in the GMPs for pharmacies

Some of the key regulations which can cause challenges for successful inspections:

- Appropriate, effective and implemented Quality Management Systems (QMS)
- Understanding and implementation of Quality Risk Management (QRM)
- Appropriate personnel and segregation of responsibilities
- Effective validation program
- Materials traceability
- Third party agreements

Other issues in the GMPs for pharmacies

QMS

The gap between the QMS at an unlicensed pharmacy and what is expected in GMP can be significant

- Training
- Product Quality Review
- QC and batch release processes
- Change management
- Deviation management (inc. complaints and recall)
- Documentation, including batch records and spec's
- Self inspection

The gap is often in the implementation more than the system

Other issues in the GMPs for pharmacies

Quality Risk Management

"A quality risk management approach should be applied throughout the lifecycle of a medicinal product"

Other issues in the GMPs for pharmacies

Quality Risk Management

The QRM process must be systematic with defined policies and procedures

Must operate across the lifecycle

Principles and methodologies should be clear

Criteria and decisions from assessments should be documented

Other issues in the GMPs for pharmacies

Personnel

2.1. The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2. The manufacturer must have an organisation chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

2.3. Key Personnel includes the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the authorised person(s) designated for the purpose. Normally key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.5., 2.6. and 2.7.

Other issues in the GMPs for pharmacies

Personnel

It is typically not possible to meet the requirements of section 2 of the GMP with pharmacists and pharmacy staff alone.

GMP specialists, particularly in quality, are highly advisable when making the transition to a licensed facility

There will be changes in responsibilities

There will be cultural change required

Other issues in the GMPs for pharmacies

Validation

Validation is rarely performed to any significant extent in unlicensed facilities. Consider the requirements for:

- Facilities and HVAC
- Computer systems
- Process equipment
- Processes, including sterilization and sanitation
- Analytical methods
- Transport
- Packaging

Other issues in the GMPs for pharmacies

Third Party Agreements

The license holder is responsible for GMP compliance in all aspects of the product lifecycle. GMP agreements are essential:

- Raw material/product suppliers
- Component suppliers
- Maintenance and calibration contractors
- Transport companies
- Contract laboratories
- Any other third party providing GMP services/goods

Observed TGA Inspection Concerns for Pharmacies

- Media fill methodology
- Multi-use vial validation
- Material transfer and sanitization of starting materials
- Parallel manufacture and cross-contamination control
- Operator training, especially around aseptic work
- Environmental monitoring
- Validation in general

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Thank you for your time.
Questions?

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