Hi Tech Product Plant Design & Construction

Andrew Watson

Director

CBE Pty Ltd

CBE

Centre for **Biopharmaceutical** Excellence

raci ROYAL AUSTRALIAN CHEMICAL INSTITUTE

Introduction

- Life science manufacturing in Australia
- Facility Design
- Project Delivery
- Cleanrooms
- Construction and Commissioning
- Outsourcing
- Innovations
- Costing

Introduction – Andrew Watson

Chemical Engineer

1994 – Institute of Drug Technology (IDT)

1998 – Project Management Group – (PMG), Ireland

1998 – IDT

2000 – Wilkore Construction

2011 – PharmOut

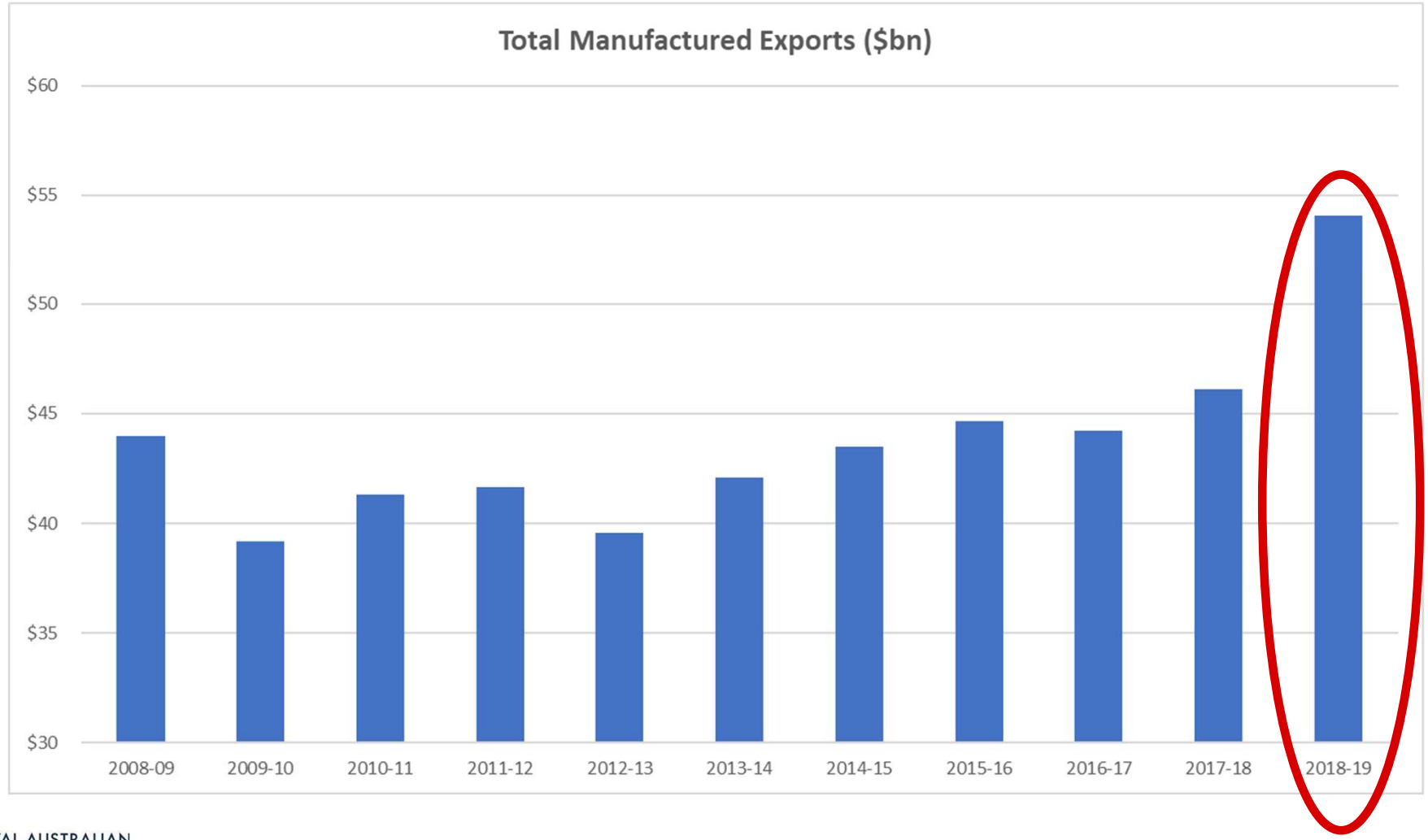
2014 – CBE Pty Ltd

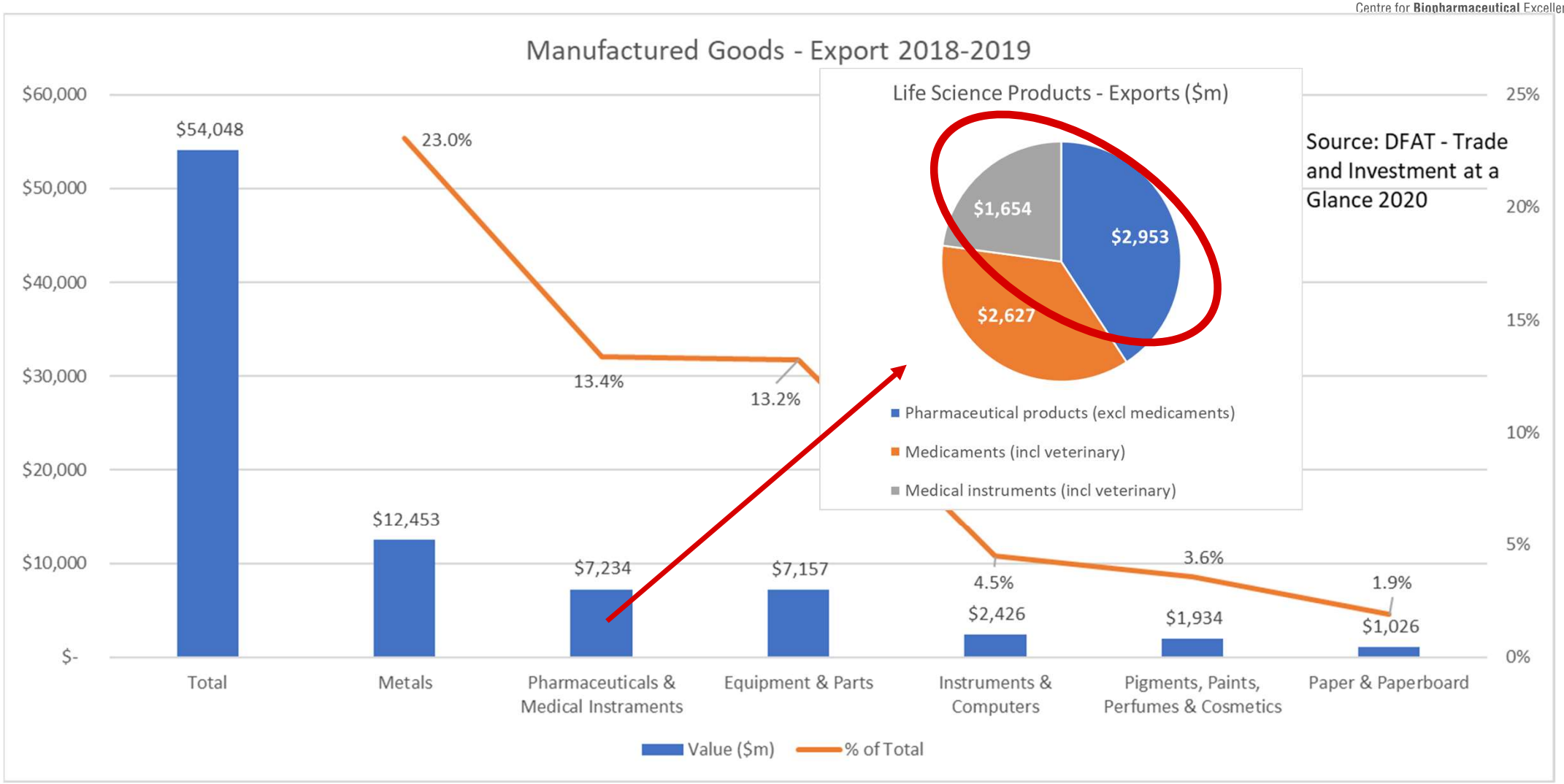
2021 – CBE Pure Solutions Pty Ltd

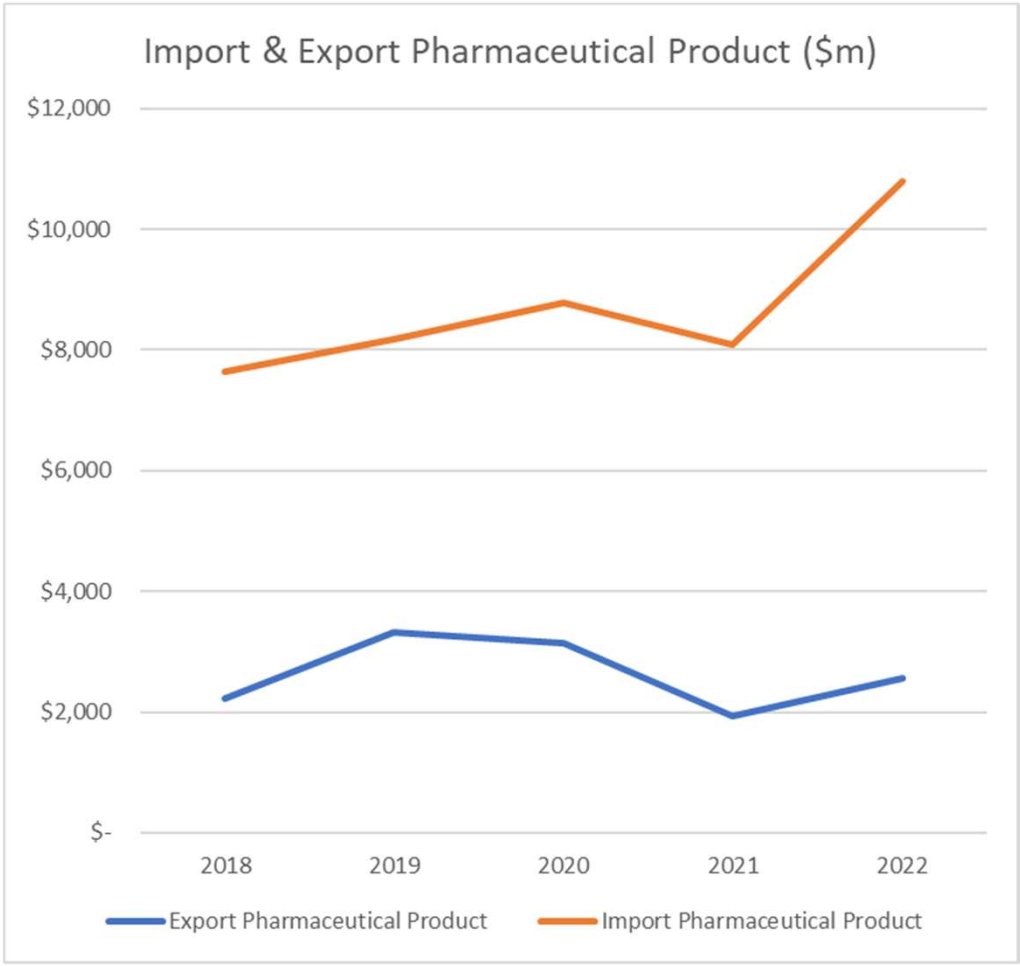
2007-2015 – International Society of Pharmaceutical Engineering (ISPE)

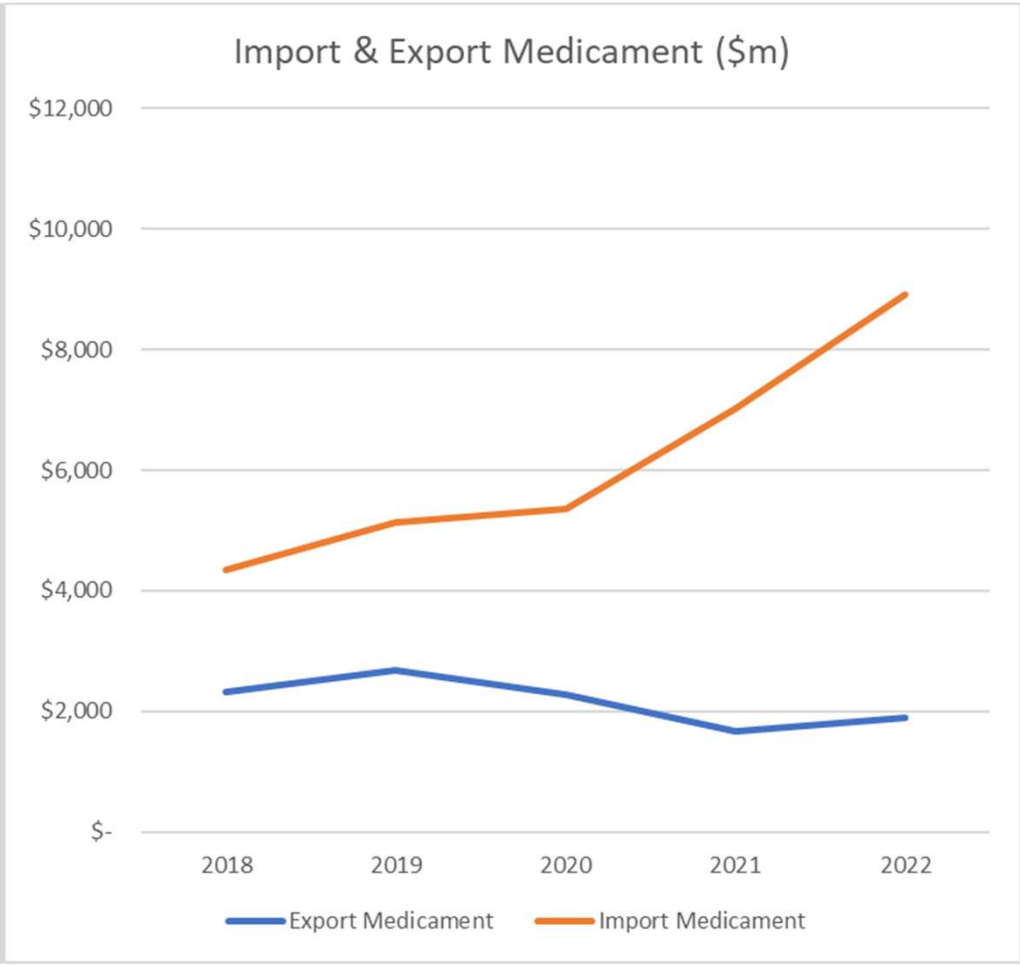
2012 – Standards Australia – ME-060 Committee Chair

2020 – NATA – Accreditation Advisory Committee (Physical Performance Testing)


Total Manufactured Exports ($bn)
$60
$55
$50
$45
$40
$35
$30
2008-09
2009-10
2010-11
2011-12
2012-13
2013-14
2014-15
2015-16
2016-17
2017-18
2018-19


Manufactured Goods - Export 2018-2019
$60,000
$50,000
$40,000
$30,000
$20,000
$10,000
$-
25%
20%
15%
10%
5%
0%
$54,048
$12,453
$7,234
$7,157
$2,426
$1,934
$1,026
23.0%
13.4%
13.2%
4.5%
3.6%
1.9%
Total
Metals
Pharmaceuticals & Medical Instraments
Equipment & Parts
Instruments & Computers
Pigments, Paints, Perfumes & Cosmetics
Paper & Paperboard
Value ($m)
% of Total
Life Science Products - Exports ($m)
$1,654
$2,953
$2,627
Pharmaceutical products (excl medicaments)
Medicaments (incl veterinary)
Medical instruments (incl veterinary)
Source: DFAT - Trade and Investment at a Glance 2020

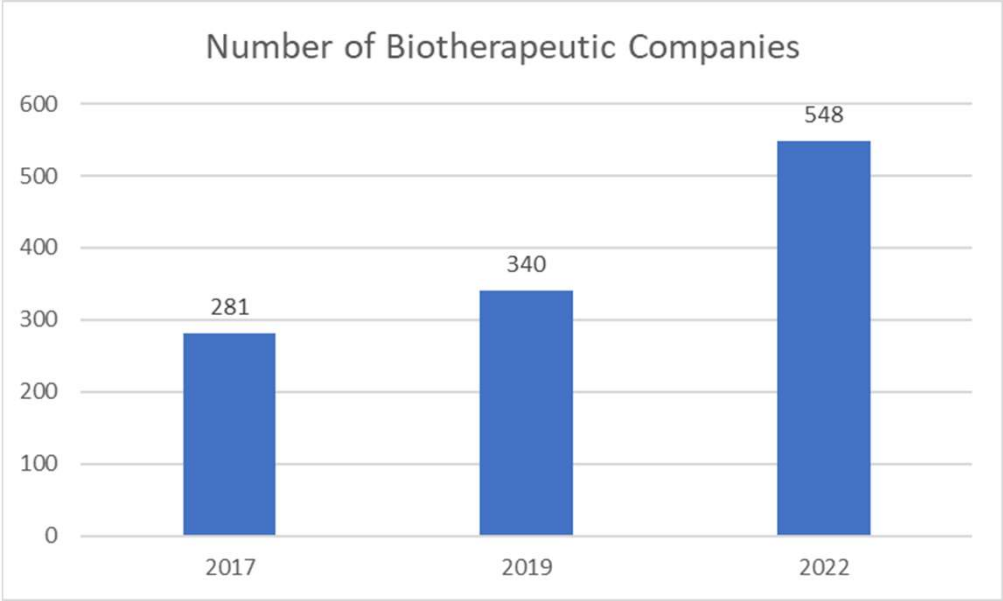




Source: www.CEICData.com | United Nations Conference on Trade and Development

Life Science Activity in Australia

- 2,654 organisations in the Life Science Ecosystem in Australia, employing 263,693
- 73% of these organisations reside in NSW and VIC
- 192 organisations listed on the ASX, 2022 market capitalisation $233bn ($170bn 2019)
- Over last 2 years, highest growth in capital raising on record



Source: Australia's Life Sciences Sector Snapshot 2022 (AusBiotech)

Manufacturing Activity in Australia

- 400+ organisations with a TGA manufacturing licence
  - Includes testing organisations
  - 84 of these are Red Cross Donor and Processing Centres
- 150+ organisations with an APVMA manufacturing licence
  - Includes testing organisations
  - Many organisations have both a TGA and APVMA licence
- Hundreds of medical device manufacturers (TGA)
- Dozens of Compounding Pharmacies (Various State-Based Authorities)
- Multiple organisations manufacturing Phase 1 Clinical Trial Products (no licence required in Australia)
- Many companies on the fringes – No therapeutic claim

Reasons to (not to) Manufacture in Australia

- Highly trained and experienced workforce (Shortage of staff)
- Ability to do a lot with a limited workforce (Labour is expensive)
- Abundant land (Land and construction costs exorbitant)
- A regulator that is well regarded internationally (High entry point to industry)
- A genetically diverse population (Small population overall)
- World-renowned medical discoveries (Poor record translating to local manufacture)
- A wealthy country (Poor entrepreneurial and philanthropic culture)

Reasons to (not to) Manufacture in Australia

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Regulations & Guidelines

- Medicinal Products – PE009 Guide to the Good Manufacturing Practice of Medicinal Products – Version 15
  - Version 16 released by PIC/S - 01/02/2022
  - New Annex 1 – Manufacture of Sterile Medicinal Products
- Medical Devices – Broad range of categories of goods
  - Range of 'Essential Principles' that applies to all or some of the categories
  - Conformity Assessment
- Veterinary Products – Australian Code of Good Manufacturing Practice for Veterinary Chemical Products (2007)
- Genetically Modified Organisms (GMOs)
  - Range of Guidelines dependent on type and Physical Containment (PC) level (1 to 4)

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Government
Australian Pesticides and Veterinary Medicines Authority

Australian Government
Department of Health and Aged Care
Office of the Gene Technology Regulator

Introduction to Life Science Facility Design

Life Science Facilities need to be:

- Secure
- Controlled
- Zoned
- Laid out in a logical manner
- Safe
- Efficient

Fundamental aspect of design is to work around the flow paths of:

- Materials
- Personnel
- Waste

The movement of one should not adversely affect the other in terms of:

- Contamination and cross contamination
- Mix ups
- Breaches of health and safety

In addition, note Clause 3.5 in PE009 (Part 1)

Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Facility Design

Cleanroom Areas

PERSONNEL

Space required for:

- Changerooms
  - Before entry to manufacturing
  - Within manufacturing
- Personnel Amenities
  - Toilets
  - Lunchrooms
  - Personal storage
- Write-up areas
- Meeting rooms
- Offices

MATERIALS

Space required for:

- Setdown areas
- Sampling
- Warehousing (quarantine and released)
- Dispensing
- Manufacturing
- Packaging – Primary (Fill & Finish)
- Packaging – Secondary
- Finished Goods Storage (quarantine and released)
- Dispatch
- Rejected/Recalled/Returned Materials

Facility Design – cont…

Cleanroom Areas

AMENITIES

Space required for:

- Equipment cleaning
  - Washing
  - Drying
  - Clean equipment storage
- In process QC
- Facility cleaning repositories
- QA/QC Laboratories
- Critical services
  - Air conditioning (HVAC)
  - Water systems (Deionised, Purified, Water for Injection)
  - Compressed gases
  - Liquid Nitrogen

EXTERNAL

Space required for:

- Access of materials and personnel
- Egress of materials, personnel and waste
- External services, including:
  - Chillers
  - Cooling towers
  - Generators
  - Waste treatment (non GMO)
- Carparking
- Car and truck access and egress
- External material storage (solvents, Liq N_2)
- Incoming services
  - Sewer
  - Power
  - Data
  - Gas

Facility Design cont…

WASTE

- General waste
  - Can cause particulate waste
  - Provide microbial growth
  - Attract pests
- Hazardous waste
  - Infectious/GMO
  - Toxic
  - Flammable, corrosive
- Returns/Rejects/Recalls
- Autoclaves

Must ensure that all waste does not interact with process materials or personnel

SAFETY

- Hazardous materials
  - AS 1940
  - Segregation distances & bunding
- Biocontainment
  - AS 2243.3
  - Includes waste
- Hydrants, hose reels and fire extinguishers
- Safety showers and eyewashes

Cleanroom Areas

Facility types

Greenfield

Pros

- Build what you want
- Investment
- Growth

Cons

- Time and cost
- Capital outlay
- Planning
- Authorities
- Workforce

Brownfield

Pros

- Fast and cost effective

Cons

- Neighbours
- Change of use - planning
- Sufficient power
- Location of sewer
- Access
- Carparking
- Can be growth limiting

Institutional

Pros

- Workforce
- Minimal investment
- No planning or authorities

Cons

- Neighbours
- Shared services and space
- Planning
- Authorities
- Growth limiting

Important facility attributes

- Building integrity
  - Weatherproof, vermin proof, secure
  - Floor should be flat and integral
  - It should smell good
- Height
  - Floor to floor, or floor to roof should be at least four metres
- Neighbours
  - Avoid dirty industrial areas
  - Avoid areas under active development
  - Avoid neighbours with processes that has a high bio-load (bakeries, breweries etc)
  - Be cautious if in close proximity to residential areas
- Power
  - 100amps supply is just enough for the smallest projects
  - Suddenly realising you don't have enough power is the best way to blow out a timeline
- Sewer location
  - Drainage locations are critical
  - Try and cluster wet areas close to where the sewer leaves the site

Project delivery

Architects & Engineers – very few have real experience in this area (many claim to)

Builders and service installers:

- Very few specialists in this space
- Most focus on small projects
- Top and mid-tier builders don't like specialists
- Specialists don't like top and mid-tier builders
- Key is to have an experienced client advocate to guide you through the project – this can make up for a wealth of in-experience on the project team
- The contractors need a reputation of attention to detail. They also need to be proactive in providing solutions, not just doing as the architect instructs

RED FLAGS

Use of "clean room" not cleanroom

Constantly referring to your cleanroom as a laboratory

"GMP? Yep, we've delivered lots of Guaranteed Maximum Price projects!"

An obsession with biocontainment

"I mean, it's just a fancy coolroom, isn't it?"

Cleanrooms

What is a cleanroom?

Definition:

Room within which the number concentration of airborne particles is controlled and classified, and which is designed, constructed and operated in a manner to control the introduction, generation and retention of particles inside the room

Note 1 to entry: The class of airborne particle concentration is specified.

Note 2 to entry: Levels of other cleanliness attributes such as chemical, viable or nanoscale concentrations in the air, and also surface cleanliness in terms of particle, nanoscale, chemical and viable concentrations might also be specified and controlled.

Note 3 to entry: Other relevant physical parameters might also be controlled as required, e.g. temperature, humidity, pressure, vibration and electrostatic.

Clause 3.1.1, ISO 14644-1:2015

NOTE:

A **cleanroom** is a room that has been **quantified** through **ISO 14644-1**.

A **clean room** is a room that has been **qualified** by someone.

Typically, your **mother**.

Types of Cleanrooms

Unidirectional

- Full ceiling coverage of air filters (HEPA or ULPA)
- Air moves at a steady and uniform velocity in airstreams that are to be considered parallel
- **Displaces** particle contamination with clean air
- In biotech generally found in separative devices

Non-unidirectional

- Partial ceiling coverage of air filters (may or may not be HEPA)
- Clean air disperses and mixes with the room air
- **Dilutes** particle contamination with clean air

Sources of Contamination

Three key sources of contamination:

- The facility
  - Shedding from the building fabric
  - Through the HVAC system (considered zero if air supply through HEPA filters)

Tiny

- The process
  - Movement of materials
  - Processing of materials
  - Equipment

Moderate (non-sterile)

Small (sterile)

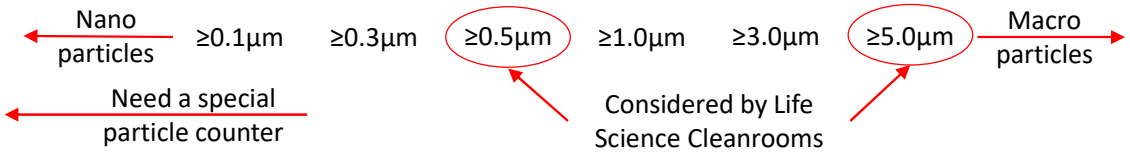
- People
  - Up to 95%

HUGE!

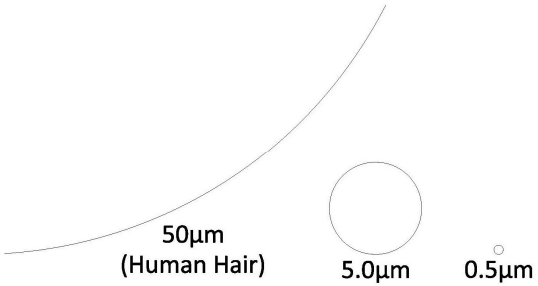
Contamination size

Total particle counts separate particles into sizes:

- Specifically, counts particles that are greater than or equal to a particular size



- Microbes always attached to particles (>~10µm). These particles are called Microbe Carrying Particles (MCPs)
- Particles less than 5µm tend to be entrained into the airstream and removed
- Particles greater than 5µm settle to the floor



Read – Particle and microbial airborne dispersion from people, W Whyte and M Hejab

European Journal of Parenteral & Pharmaceutical Sciences 2007; 12(2): 39-46

ISO 14644 Suite of Standards – Key documents

ISO 14644 – Cleanrooms and associated controlled environments

Part 1: Classification of air cleanliness (Australian Standard Version AS ISO 14644-1)

Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1 (Australian Standard Version AS ISO 14644-2)

Part 3: Test methods (Australian Standard Version AS ISO 14644-3)

Part 4: Design, construction and start-up (Soon to be AS ISO 14644-4 – Currently AS/NZS ISO 14644-4)

Part 5: Operations – (being revised) (Australian Standard Version AS/NZS ISO 14644-5)

Part 7: Separative devices (clean air hoods, gloveboxes, isolators, and mini-environments) – (being revised) (Australian Standard Version AS/NZS ISO 14644-7)

Part 16: Energy efficiency in cleanrooms and separative devices

Part 21: Airborne particle sampling techniques (Technical Report (TR), not a Standard)

AS ISO 14644-1 : 2017

Key standard, referenced in the PIC/S guidelines (Annex 1 – Sterile Products)

Details:

- How cleanrooms are classified
- How cleanrooms are tested to show they meet their designated classification

Cleanrooms are classified according to their occupancy state – ie what is the state of the room during testing.

Occupancy States

3.3.1 as-built

condition where the cleanroom or clean zone is complete with all services connected and functioning but with no equipment, furniture, materials or personnel present

3.3.2 at-rest

condition where the cleanroom or clean zone is complete with equipment installed and operating in a manner agreed upon, but with no personnel present

3.3.3 operational

agreed condition where the cleanroom or clean zone is functioning in the specified manner, with equipment operating and with the specified number of personnel present

Utilised in life science facilities

AS ISO 14644-1 : 2017

Table 1

ISO Class number (N)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
1	10[b]	d	d	d	d	e
2	100	24[b]	10[b]	d	d	e
3	1,000	237	102	35[b]	d	e
4	10,000	2,370	1,020	352	83[b]	e
5	100,000	23,700	10,200	3,520	832	d, e, f
6	1,000,000	237,000	102,000	35,200	8,320	293
7	c	c	c	352,000	83,200	2,930
8	c	c	c	3,520,000	832,000	29,300
9[g]	c	c	c	35,200,000	8,320,000	293,000

a All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10,200 particles shown at 0.3 µm include all particles equal to and greater than this size.

b These concentrations will lead to large air sample volumes for classification.

c Concentration limits are not applicable in this region of the table due to very high particle concentration.

d Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

e Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

f In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size. (See C.7.)

g This class is only applicable for the in-operation state.

PIC/S PE009 Classification – Current Annex 1

Grade	Current Annex 1 - Classification - Maximum permitted number of particles/m³ *					
	At-rest			In operation		
	≥0.5µm	≥5.0µm	ISO** Equivalent	≥0.5µm	≥5.0µm	ISO** Equivalent
A	3,520	20	ISO 4.8	3,520	20	ISO 4.8
B	3,520	29	ISO 5	352,000	2,930	ISO 7
C	352,000	2,930	ISO 7	3,520,000	29,300	ISO 8
D	3,520,000	29,300	ISO 8	Not defined	Not defined	Not defined

* Table derived from PE009-13 Annex 1 Clause 4

**Approximate (e.g. for ISO 7 ≥5.0µm limit is 2,930 as per AS ISO 14644 Part 1)

Grade	Air sample CFU/m³	Settle plates (diameter 90mm) CFU/4 hours	Contct plates (diameter 55 mm) CFU/plate	Glove Print 5 Fingers CFU/glove
A	<1			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

PICS/PE009 Classification – New Annex 1

Grade	New Annex 1 - Classification - Maximum permitted number of particles/m³ *					
	At-rest			In operation		
	≥0.5µm	≥5.0µm	ISO Equivalent	≥0.5µm	≥5.0µm	ISO Equivalent
A	3,520	Not Specified	ISO 5	3,520	Not Specified	ISO 5
B	3,520	Not Specified	ISO 5	352,000	2,930	ISO 7
C	352,000	2,930	ISO 7	3,520,000	29,300	ISO 8
D	3,520,000	29,300	ISO 8	Not Pre-determined**	Not Pre-determined**	Not Pre-determined**

* Tables derived from new Annex 1

** The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

Grade	Air sample CFU/m³	Settle plates (diameter 90mm) CFU/4 hours	Contct plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

PICS/PE009 Monitoring – New Annex 1

Grade	New Annex 1 - Monitoring - Maximum permitted number of particles/m³ *					
	At-rest			In operation		
	≥0.5µm	≥5.0µm	ISO Equivalent	≥0.5µm	≥5.0µm	ISO Equivalent
A	3,520	29	ISO 5	3,520	29	ISO 5
B	3,520	29	ISO 5	352,000	2,930	ISO 7
C	352,000	2,930	ISO 7	3,520,000	29,300	ISO 8
D	3,520,000	29,300	ISO 8	Not Pre-determined**	Not Pre-determined**	Not Pre-determined**

* Tables derived from new Annex 1

** The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

Grade	Air sample CFU/m³	Settle plates (diameter 90mm) CFU/4 hours	Contct plates (diameter 55 mm) CFU/plate	Glove print, Including 5 fingers on both hands CFU / glove
A	No growth			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Use of Grade A, B, C & D

Grade A – (ISO 5 at rest, ISO 5 in operation)

- Filling of high risk sterile products
- Unidirectional air flow (0.36-0.54 m/s)
- Constant particle monitoring

Grade B – (ISO 5 at rest, ISO 7 in operation)

- Background environment for Grade A
- Non-unidirectional air flow
- Regular background particle monitoring

Grade C – (ISO 7 at rest, ISO 8 in operation)

- Filling of products to be terminally sterilised, or preparation of solutions to be filled in Grade A
- Non-unidirectional air flow
- Used for closed system biotech - downstream

Grade D – (ISO 8 at rest, in operation set by manufacturer)

- Preparation of solutions to be filled in Grade C, or handling of components after washing.
- Non-unidirectional air flow
- Used for closed system biotech – upstream
- Also used for non-sterile production.

Cleanroom HVAC

Fundamentally, non-unidirectional cleanrooms are supplied with sufficient clean air to maintain a specific cleanroom class or Grade in operation

- Temperature is tightly controlled
- Room pressures help to maintain cleanliness and or containment
- Humidity is important, but not always critical

For pressure control

- Supply air is fixed
- Return air or exhaust air is varied

Filtration

- HEPA filters are not essential for non-sterile / Grade D cleanrooms

Supply and return location

- Supply always at high level
- Return nearly always at low level
- Exhaust can be either
- Ensure sufficient distance between a supply and a return

Controls

- Should be simple
- Complex control systems rarely provide stable cleanrooms
- Avoid humidification

Building Management System (BMS)

- You need to know how it works

Environmental Monitoring System (EMS)

- Should be independent of the BMS

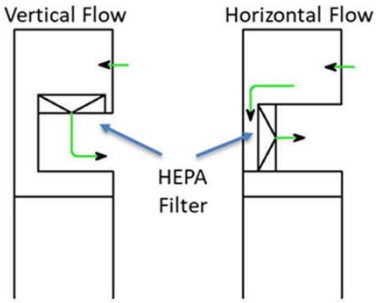
Separative Devices

From ISO 14644-7 Clause 3.17

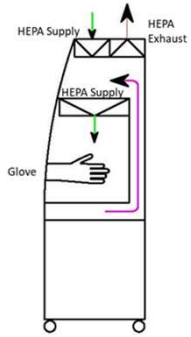
separative device

equipment utilizing constructional and dynamic means to create assured levels of separation between the inside and outside of a defined volume

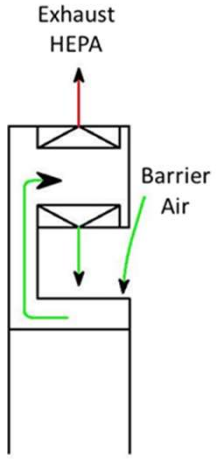
- Incorporate a range of devices that protect the product from staff, staff from the product and a combination of the two
- Devices include
  - Biological Safety Cabinets (Class II)
  - Clean workstations (“laminar flow” cabinets etc)
  - Grade A / Unidirectional Flow Hoods
  - Restricted Access Barrier Systems (RABS)
  - Isolators
- Devices do not include
  - Biological Safety Cabinets (Class I)
  - Fume cupboards
  - Powder containment booths



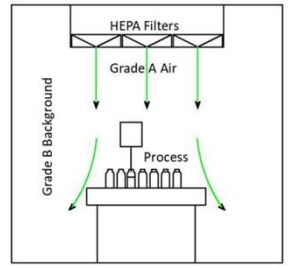
Clean Workstation



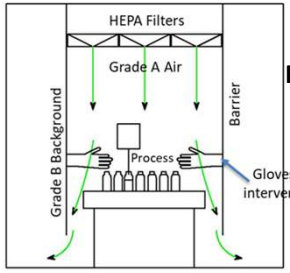
Isolator



Biological Safety Cabinet (Class II)



Grade A Hood



Restricted Barrier Access System (RABS)

Design Tips

For the cleanest cleanrooms, try to make them as simple a box as possible. Low level returns, pass thrus etc should be flush to the wall of the cleaner side

Doors – Use push plates and 'D' Handles, not latches

Flooring – Vinyl easier to repair than epoxy. Epoxy essential if using heavy equipment like forklifts

Rivets should be avoided – use concealed fixings, double sided tape instead

Smoke detectors near to useless on cleanroom ceilings (unless there is no air conditioning). Highly effective in return air ducts

Windows – Double glazing for 'cleanroom to cleanroom', single glazing for 'cleanroom to non-cleanroom'

Furniture – Grades B to D, flat stainless steel is fine. Perforated benches and open wire shelves are very difficult to clean

Only use external insulation on ductwork

Lighting – Code asks for top access lighting. Surface mounted LED is actually better, as long as it is <15mm thick

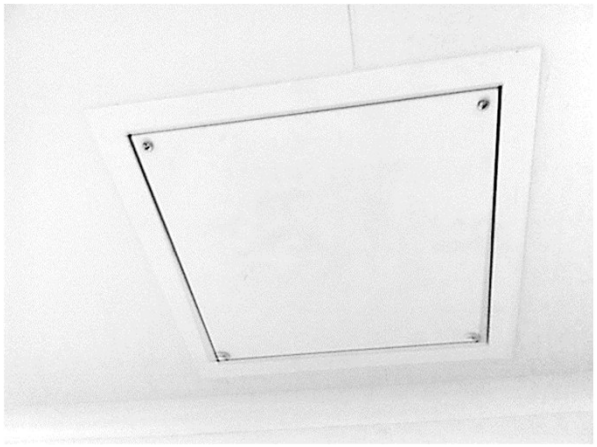
Access panels – Ceiling mounted access panels should be avoided, but if absolutely necessary must close on a rubber seal and then be over-sealed with silicone

Ceiling arrangements – HVAC should take priority over lighting position

Silicone versus Polyurethane

- Use Polyurethane for adherent strength
- Use Silicone for external finishes

Common facility issues

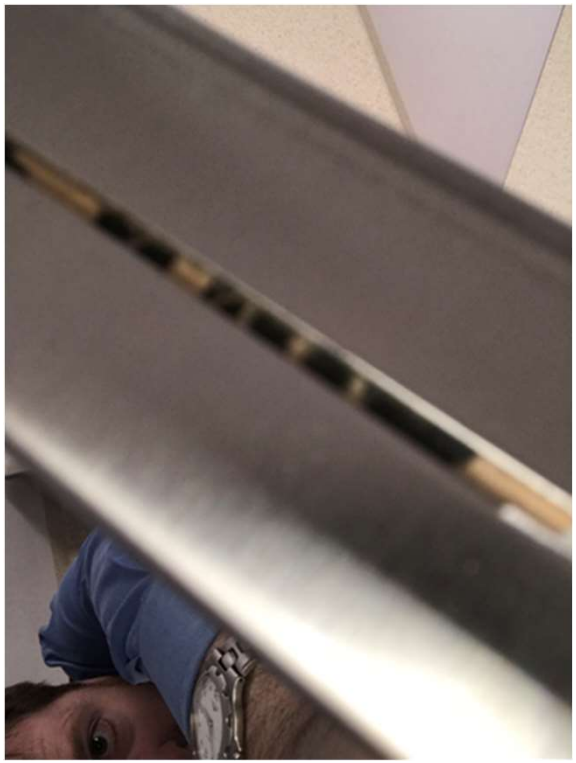


Unsealed access hatch in a cleanroom

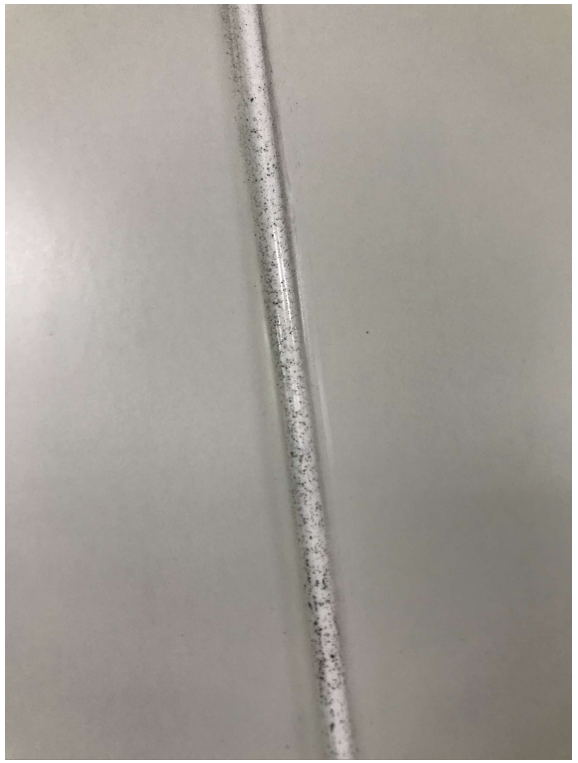
Brass fittings in a cleanroom

Gap under facility perimeter door

More common facility issues



Unfinished top of cleanroom door



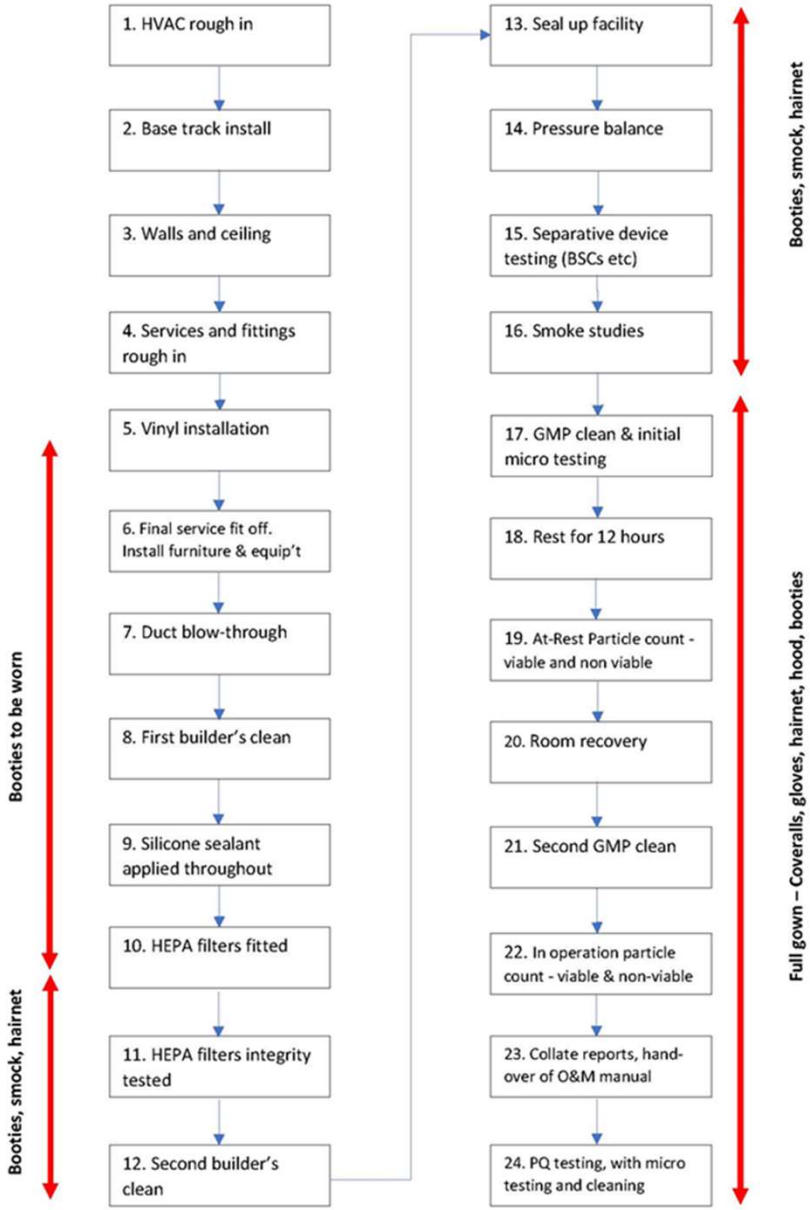
Silicone sealant applied in dirty environment

Construction

Important things to expect from your builder:

- A program – regularly updated
- A detailed budget – regularly updated
- A clean build protocol*
- A clear agreement on the cleanroom details to be applied – consider prototype room
- A clean and tidy site
- A commissioning plan
- A single point of contact
- A comprehensive manual on the day of handover

*Rarely implemented



New build construction & commissioning sequence

Commissioning & Qualification

Commissioning

- Allow several days for pressure balancing
- Temperature, pressure and humidity compliance should be over a 24-hour period
- Sequence is important
- At-rest particle counts should be performed by the contractor
- Testing company should be accredited by NATA to perform the work

Qualification

- Consider who to perform the work – needs experience
- In operation particle counts should be performed by the client
- Sterile cleanrooms take a long time to qualify – 3 to 6 months
- Water systems take even longer – 6 to 12 months
- Production can commence after sufficient data is obtained

Innovations in facility design

Modular / Transportable Facilities

- Overseas units:
  - Great for an international standard
  - Expensive
  - Potential issues with Building Code
- Local units:
  - Expensive, but not as expensive
  - Limited players in the market

Shared/Multi-user Facilities

- Great opportunity for start-ups going through clinical trials
- Significant regulatory hurdles
  - Who is in control?
- Possibly the way of the future with smaller scale operations

Outsourcing

Even the largest facilities outsource to a degree

Common options:

- Fill and finish
- Microbiological testing
- Chemical testing
- Sterility and bioburden testing
- Production staff
- Product development
- API manufacture
- Pharmaceutical qualification and validation services

What should it cost?

Greenfield Government Projects

- Up to $20,000/m²
- Excludes land purchase

Cleanrooms

- For sterile / biotech $10-15,000/m²
- For non-sterile $4-7,000/m²
- Includes:
  - Cleanroom building fabric
  - HVAC
  - Electrical & Hydraulic
  - Flooring
  - Furniture
- Excludes equipment & critical services

Other costs

- Fill and finish $500k to $50m
- Water system
  - Small purified water - $100k
  - Small WFI - $500k - $1m
- EMS
  - Non – Sterile - $50k to $200k
  - Sterile - $100k to $400k
- Pharmaceutical Quality System
  - Partially outsourced - $50k to $100k
  - Fully outsourced - $150k to $500k
- Qualification & Validation
  - 10 to 20% of cost
- Quality Manager
  - $150k+

Thanks

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