DESIGNING BIOPHARMA AND PHARMACEUTICAL CLEANROOMS

Richard Paley of Bovis Lend Lease takes a look at the key issues in the design, specification and selection of cleanrooms, considering the impact on the final build solution and comparing different classes and finishes to show the advantages or disadvantages of each.

With an overview to the key issues which need to be reviewed by a project team when developing a cleanroom for an existing or new pharmaceutical process, operation or product, this article is intended to give an insight and understanding of the complex process of cleanroom design.

The "cleanroom" has been defined by the International Organisation for Standardisation (ISO) new standard 14644 - 1 as:

> "A room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimise the introduction, generation, and retention of particles inside the room and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary."
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> Cleanroom Technology(p1) – William Whyte (2001)

This sounds simple until we introduce people, product, regulatory and pharmaceutical equipment, and operational / budget requirements into the equation, when it becomes a complex problem to which there are many contributing factors. In addition, the production throughputs and flexibility required by the cleanroom suite will also have an effect on its size and layout.

A shrinking world

Novel drug delivery systems, biopharmaceutical processing, and medical device requirements challenge our preconceptions of how products work and how we make them. It can no longer be assumed that all stages of a process will occur in the same company, country, building or cleanroom suite, or that the manufacturing equipment will originate in this industry. Pharmaceutical products are already taking technology from the micro-electronics, nano technology, and food industries.

In projects where the facility or process is copied to other locations, companies often mistakenly assume that a design, layout or specification that worked in one country, still works in another. If planned for at an early stage, the impact on design and costs can be minimised. Examples include the varying regulations for fire escape travel distances in Europe and differing building codes in Wales, Scotland and England.

Design Approach and the URS

It is vital that all relevant personnel from production, quality, logistics, and maintenance departments as well as engineering are involved in the early stages of a design. This avoids reworking of design layouts later as it develops "buy in" and ownership by the whole company, minimising costly errors because of the useful input from a wider team. The team develop the initial User Requirement Specification (URS), defining the processes, equipment, operations, capacities and environmental criteria for the cleanrooms that are to be designed.

In the URS the designers need to review the flow around the cleanrooms in order to assess the optimum layout for regulatory compliance, efficient operation and to minimise cross contamination. It is easier to simplify all the flows in new facilities, but difficult in retrofit situations where compromises may need to made due to space or cost constraints. Procedures may have to be put in place to avoid cross contamination where waste, people, raw materials and finished goods are sharing corridors.

Different types of cleanroom design require different disciplines to lead the design and layout process. In Primary pharmaceutical facilities, process is the lead discipline. The process engineering equipment and piping layouts are a key part of the manufacturing process and the cleanroom is likely to be a small offloading, vessel charging or dispensing suite. In Secondary pharmaceutical facilities the architectural or mechanical services are the lead disciplines. The architectural room layouts and air environment is the "manufacturing vessel" in which products and people are moved around. In Biopharmaceutical facilities both process and architecture are the lead disciplines, producing an integrated solution, thus process vessels / equipment and the room layouts and people flows are equally important to the process.

Cleanroom Layout

The URS for a facility will define which equipment is to be used, what options it has and what areas of the process still need to be developed, enabling the design team to accommodate equipment changes during the design process. Whether to make a piece of equipment built in or skid mounted needs to be decided early in a project as it has a significant on the layouts, programme and costs.

Built in equipment can be achieved in small cleanrooms but this requires early design freeze/ selection, which can be difficult in new process. The layout can be designed to allow move in routes for late delivery, but this is more difficult if it is located in the centre of the facility plan. If possible, locate equipment to the edges of the cleanroom footprint.

Modular, "skid mounted" or freestanding equipment may be required by a facility because one or more process steps are being developed, or the facility needs to be able to incorporate changes in process steps, which need equipment to be changed to suite a campaign or customer contract. Whenever this is the case in primary, secondary or bio-pharmaceutical cleanrooms, it is very important to think through the installation/removal route. Corridor widths may need to be increased, roof openings designed in, removable walls in the shell building or cleanroom, and access around the building to get the equipment off loaded.

Another key issue is to maximise the technical and lower classification areas around the main cleanroom suite by locating and specifying process equipment so it can be located in positions which allow maintenance from the non cleanroom area. This minimises the costly cleanroom envelope, and the maintenance procedures and costs. It may not always be easy to do and there will be limitations caused by the standard designs of some equipment. However new models are always in development. For example, Blow Fill Seal filling machine technology. Until recently the whole machine had to be inside the cleanroom, now suppliers offer machines which have 50% in a technical non-cleanroom environment and 50% in the cleanroom

The design layout should keep personnel and materials separate. If these have to be combined then procedures will have to be put in place to control them. When planning cleanrooms of the higher classifications (Class 5 and Class 7), sufficient space needs to be allowed in the layout for incorporating multiple change steps, and in the case of some Class 5 suites, and containment level 3 and 4 suites, separate exit/entrance routes to stop cross contamination of clothing. In smaller higher classification suites there can be a high proportion of the layout taken up by changing rooms and materials airlocks and transfer hatches, so it is important to cost these out in any project approval budget.

Grades of Cleanroom Suite

Classification of cleanrooms has until recently been a complicated by different countries having different, contradictory classification systems, which were not easy to compare. The different classes have been redefined simply defined in the new Global ISO Classification system now adopted by the FDA/MCA , and table below shows how it compares to other systems.

Classification System	Classifications					
ISO 14644-1	Class 3	Class 4	**Class 5**	**Class 6**	**Class 7**	**Class 8**
Federal Standard 209E	1	10	**100**	**1000**	**10,000**	**100,000**
EU GGMP	-	-	**A/B**	**-**	**C**	**D**

The pharmaceutical industry is now using the ISO Classes 5 – 8. A detailed assessment should be made with production, QA personnel and regulatory authorities to define which category is required before the design starts, as it will impact on the specification and operational costs of the facility.

Containment Suites

Cleanrooms may also be designed as containment suites (virus and potent product manufacture and research). An analysis of the typical product groups requires the following containment environments:

ACDP Containment level	Hazard / Biological Agent Types
	Viruses / Genetically Modified Organisms
Hazard Group 2 Cat 2	Bacillus Cereus, Bacteroides Fragillis etc
Hazard Group 3 Cat 3	Bacillus Anthracis, Brucella Abortus, Canis etc
Hazard Group 4 Cat 4	[old world], Lassa fever [new world], Eboli, Seira, Sudan, Zaire

These are only a guide, but increasingly some products are requiring a containment level Category 2 to 4, to protect the operator, and a cleanroom environment or ISO 5 to 8, to protect the product.

Types of Cleanroom Construction

There are 4 basic types of clean room construction; the advantages and disadvantages for each are summarised in the table below. If speedy construction and flexibility is of prime importance then usually types 3 and 4 will be selected. Alternatively, if economy is paramount then types 1 and 2 are best, but these come with time penalties and less flexibility in the construction phase. The type of wall construction needs to be defined early in a project as it affects the total project cost, time table, and engineering and detailing costs.

Type	Description	Advantages	Disadvantages
1	Plaster / Blockwork /paint	Low cost, different finishes can be applied	Inflexible and slow construction. Difficult to repair if damaged during construction or operation
2	Plasterboard /Studwork /paint	Low cost, different finishes can be applied, More flexible and faster to install than blockwork walls.	Quicker than blockwork, Difficult to repair if damaged during construction or operation
3	Solid core panel "monoblock"+factory applied paint finish	Speed of erection and completion of the cleanroom envelope. Simple to replace damaged areas during construction or operation	Cost is slightly higher than plasterboard or blockwork wall construction. In larger schemes this cost difference diminishes.
4	Hollow core/ 2 part panel /factory applied finish	Speed of erection and completion of the cleanroom envelope. Simple to replace damaged areas during construction or operation. One side can be removed to install services in adjacent rooms whilst other is in	Cost is higher than monoblock panel, plasterboard or blockwork wall construction. In larger schemes this cost difference diminishes. Limited number of suppliers.

		operation	

Completing the Details

The fixtures and fittings that complete the cleanroom bring with them their own variety of complex problems.

Electrical Fittings / Fixtures

Within the cleanroom there will be a range of electrical fittings, each presenting its own challenges to the final room quality and operation. Switches and lights need to be flush, warning lights need to be simple, speaker panels need to be carefully located. Interlocks and indicator lights need to be planned very early on to avoid later confusion and to minimise costs. Finally, control panels should be built into the wall if possible, minimising the number of ledges to be cleaned, and reducing the room area.

HVAC Fittings / Fixtures

Most common problem areas for the heating, ventilation and air conditioning (HVAC) fittings appear in the form of grilles, filter boxes and room gassing systems. Grilles are generally located in the ceiling and can be difficult to co-ordinate with lighting, sensors, service pipework and equipment that is also entering the cleanroom through the ceiling. Ceiling filter boxes need vertical space planning to accommodate their height, especially for class 5 and class 7 cleanrooms, and can make some buildings unsuitable for use. Low level filter boxes often take off a 0.6 x 0.6 metre space from the room and can compromise the design if introduced late in the project. Finally, room gassing systems required by some processes can have a big effect on the finishes, specification and containment of the whole facility, and must be established early on in a project. If low humidity environments are required in the cleanrooms for product reasons this can have a significant effect on the finishes specifications, and will reduce options available and increase costs.

Wall Protection Systems

There are several approaches to wall protection. Protection on the equipment reduces facility costs, but all equipment must have it to be effective and walls must still be substantial enough to withstand being hit by the equipment item. Alternatively, floor mounted rails can be used to keep the equipment totally away from the walls, enabling lighter cleanroom wall construction, but adding width to the corridors in the facility. Wall mounted rails, if located correctly, allow the equipment to contact the wall whilst only increasing the corridor widths slightly, and can be replaced when damaged.

Vision Panels / Windows

Comprehensive views into the suite can help visitors to quickly understand the process without having to enter the cleanroom at all, which brings operational benefits. Key features to consider when specifying and locating the windows and vision panels in a cleanroom suite range from the number required (more help to reduce lone worker risks but add to overall build costs) to their location (they need to be located in positions which don't compromise the mechanical and electrical building services installation, or be blocked out by process equipment). In addition, factors such as size and flush fitting need to be considered.

Doors

There are several types of door finishes / sizes and their selection depends on the process: laminate finish; encapsulated finish; metal finish; glass reinforced plastic (GRP). All require protection from collision damage from equipment, and may benefit from powered door openers or "hold open devices" to help reduce this. Early selection of doors and their fittings is particularly important as they represent a large part of the wall/ floor/ ceiling envelope costs.

Wall, Floor and Ceiling Finishes

There are a variety of wall finishes to choose from and their selection depends on the equipment to be used on them. Vinyl, epoxy paint and emulsion paint are all site applied, usually after installation work is complete, and will be selected depending on the ultimate use of the cleanroom. Panel / GRP Walls are factory applied and need additional site protection as they are installed very early in the construction programme, and have to withstand site conditions for longer.

Floor finishes are also selected depending on the equipment to be used on them and the amount of traffic that they will have to endure. Choices range from vinyl, epoxy paint, epoxy screed or stainless steel, each with its own cost implications. The key to a successfully laid floor with long term problem free life is the correct specification, correct preparation of the sub base and using the correct adhesives and primers.

A higher cost option for the ceiling would be the "walk on ceiling". This can provide an access platform during construction to install lights, grilles fittings, and can allow service side changing of filters/ lighting tubes and ultimately can be a cost effective long term option. Plasterboard plus paint finish is an economical solution and a range of finishes can be applied - emulsion paint, epoxy paint, grp coatings, or vinyl. The disadvantage is the requirement for access panels to reach HVAC dampers. Metal Tiles in grid give good access to the ceiling services for maintenance but need sealing if positive pressures are required in the cleanroom. Finally, PVC faced plasterboard tiles in grid provide another economical solution and allow ease of access to the ceiling for maintenance but these also need sealing if positive / negative pressures are required.

Ancillary Fittings

A cleanroom will require additional items fitted onto or into the walls, to make the changing rooms or the process function correctly. A general rule should be to minimise fittings in cleanrooms as they increase ledges, potential dust traps, and increase the number of things to keep clean. Pass through hatches, transfer ports and speaker panels can all benefit the operation if carefully selected whilst hands free washing facilities, hand driers, mirrors and hooks can all help to increase productivity and keep the cleanroom organised and un-cluttered.

Particle Monitoring Systems

There are two basic types of particle monitoring system and they have significantly different effects on the facility costs. The choice needs to be made early in the cleanroom design project in conjunction with QA / regulatory personnel with respect to the product requirements and the FDA / MCA's requirements for the products being made. Hand held, or manual particle counting equipment is taken into suites with a frequency to suit the manufacturing licence, collecting data on paper or electronically. This has the little effect on the cleanroom design and costs. Built in, or automatic equipment measures particles, temperature, room pressures and humidity, all sensed through a built in and validated particle monitoring system. The parameters have to be specified by the project team and have a considerable effect on the project costs. An alternative may be to have the building management system validated, but again this adds cost.

Summary

With increasing demands for bio-pharmaceutical cleanrooms as the increasing percentage of new drug discoveries are biotech based, the future of cleanroom design seems certain to follow a number of trends.

Market forces are driving shorter project delivery times, to get products to market faster and with less expense. This calls for greater flexibility in layout to accommodate easy reconfiguration and modular layouts of suites to simplify equipment relocations within a site and between sites. This in turn leads to cloning of facilities across country borders to allow dual site flexibility/security.

Finally, technology cross-overs from other industries e.g. microelectronics are changing some delivery systems and manufacturing equipment.

Bibliography

The following documents were used for information in this article:-

1.   An Introduction to Contamination Control and Cleanroom Technology – Matts Ramstorp, Wiley – VCH Verlag GmbH – ISBN 3-527-301142-9
2.   Cleanroom Design – William Whyte – Wiley (1999) – IBN-0-471-94204-9
3.   Cleanroom Technology – William Whyte (2001) – ISBN-0-471-86842-6
4.   PEAT Module 4, Facility Design, Construction and Finishes, Dr Roger Edwards, UMIST,(1997)

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