Investing in a controlled environment

Summary

How much do you have to pay for a house? A question that is difficult to answer – a bit like asking how much you have to invest in a clean room. This White Paper lists several reasons why.

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Introduction

Many market segments require investments in a controlled environment.
A controlled environment area can mean a clean room, a laboratory in general, a medium or high-care room in the food sector, but also a surgery room in the health care sector or a Bio Safety Lab (BSL). In specific production technology sectors, investing in a clean room is compulsory, e.g. pharmaceutics, cosmetics or medical devices.
In this white paper, we will talk about a pharmaceutics clean room as an example. Nevertheless, the content of this white paper is similar for all other controlled environment areas mentioned above.

Why is the answer on the required investment that hard?

When designing a clean room, various factors are involved and many of them have a big impact on the amount of the investment. The most important are:

- Is there an existing building or do we need to build a new one first? Is the actual shape and condition of the existing building suitable?
- The size and layout of the required clean room
- The classification level of the clean room
- The materials required to meet certain demands
- The HVAC installation required to meet the classification and other demands
- The utilities and infrastructure required

Using a new building or an existing one?

This issue is clearly very dependent on the actual situation.
If you have to design and build a new facility, it is advisable to consult an architect, preferably one who has experience in designing industrial (pharmaceutical) sites. This will allow the architect to implement certain facilities in the structure of the building, resulting in considerable savings regarding the further technical design and construction of the clean room.

If there is an existing facility, you have to study the possibility of adding a box-in-box area inside of the building. Is the height high enough and are the roof and/or the floor construction strong enough to handle the weight of clean room? You may need to consider building a mezzanine or steel support to connect and install the ceiling panels and other components, such as ducts. Depending on the technical possibilities, you can use the top floor of the mezzanine to install the AHU (Air Handling Unit) or other technical components.

The size and the layout of the required clean room

The dimensions of the clean room obviously matter, as more volume results in more ventilation air. One is often tempted to suggest a higher ceiling, but consider that this will lead to the consumption of more energy during the entire life cycle of the clean room!
Clearly, the layout has a big influence on the investment amount; consider the number of PAL and MAL facilities (Personal and Material Air Locks), for instance. Specifically in a pharmaceutical facility, the classifications of the separated areas are important.

Additional PAL and MAL areas are needed between a grade B ‘cytostatic’ and a grade C ‘packaging’ area. This situation is very often also based on the clothing regime in different clean room areas. Depending on the size of the packaging, it may be possible to install Pass-Through Cabinets (PTCs) instead of setting up large MAL areas.

The number of windows, sliding/rolling/double/single doors, specific staff registration entrance technologies and interlock-based entrance technologies will all influence the investment amount in a huge way.

The clean room and the classification

The high-tech sector has now become so well known to the general public that one may assume a certain basic familiarity with production facilities and the need to avoid dust ingress. What is less well known is the required level of decontamination and the need to also avoid chemical contamination (e.g. outgassing). This adds to increasing complexity and reliability requirements, also in the semiconductor industry. Building clean room technology, for example on the ASML Campus in Veldhoven, is quite challenging and the level of complexity is very high!

For the pharmaceutical, cosmetics, health care, medical devices and food industries, we need to engineer and install GMP-approved design and classification technology.

Not only the number of dust particles in a variety of sizes is important, but microbiological contamination needs to be controlled as well. The number of permissible germs, such as bacteria, fungi, yeasts or algae, needs to be monitored constantly. This is determined by the number of cfu’s (colony-forming units) of bacterial or fungal cells, and classified in four categories. This classification is required not only in the air, but also on surfaces. By consequence, cleaning and particularly disinfection are and will remain key themes in these sectors.

The completely semi-flush or flush installation of e.g. windows, light elements or doors, is an important discipline within a GMP environment. Cavities or open joints are forbidden – components need to be mounted without hard edges on the surface. Kit types have usually been tested for specific market sector requirements.

In a non-GMP-classified clean room, it is your own choice to install a monitoring system. More often than not, this choice will depend in part on whether your clients require constant monitoring and reporting. In a GMP-classified clean room, on the other hand, it is mandatory to have a monitoring system for a number of parameters. In this case, it is up to the user if he wants to do this fully automatically or manually. Depending on the number of parameters that need to be monitored, the required level of investment in such a system can vary widely.

The requirements for ISO 14644-1 classification and the classification according to GMP grades A, B, C and D are outlined below.

Classification numbers Numbers (N)	Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below					
	0.1µm	0.2µm	0.3µm	0.5µm	1µm	5.0µm
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1 000	237	102	35	8	
ISO 4	10 000	2 370	1 020	352	83	
ISO 5	100 000	23 700	10 200	3 520	832	29
ISO 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO 7				352 000	83 200	2 930
ISO 8				3 520 000	832 000	29 300
ISO 9				35 200 000	8 320 000	293 000

Grade	At Rest		In Operation	
	Maximum permitted number of particles/m³ equal to or above			
	0.5µm	5µm	0.5µm	5µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	not defined	not defined

Grade	Recommended limits for microbial contamination (a)			
	air sample cfu/m³	settle plates (diam. 90 mm), cfu/4 hours(b)	contact plates (diam. 55 mm), cfu/plate	glove print 5 fingers, cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

If you look at the different classifications in the ISO 14644 or GMP guidelines, it is quite clear that the higher the level of cleanliness, the more air filtration is needed. The number of ACH (Air Changes per Hour) can range from 10 to 500. Can you imagine what kind of impact this will have not only on capex (capital expenditure or investment), but also later on opex (operational expenditure)?
The smaller the allowed tolerance in temperature or humidity, the more complex the installation has to be engineered and the higher the investment amount.

The materials required, to meet certain demands.

Whether it is the specific working process, material properties, cleaning policy or disinfection method, they all influence the kind of materials used for e.g. the interior and doors of the clean room, furniture or a PTC (Pass Through Cabinet).
Clearly all materials used in a clean room have to be smooth and unperforated, simple to clean and must never generate dust particles by themselves.

In GMP-classified cleanrooms the interior is normally made of HPL (High Pressure Laminate). In the past, this sheet material was often glued to a plasterboard substrate. Nowadays the (Volkern or Compact) HPL is installed as a modular cassette panel. The same can be said of steel cassette panels. Mostly coil coated but often also treated with specific coating materials (PVC, PET or specific food-safe coating).

The filling of such a modular panel is mostly rock wool or aluminium honeycomb. The current 'modular cassette panel construction method' provides a significantly faster and cleaner building process, simply because the panels are prefabricated and installed on location as a LEGO package.

Furniture or PTCs can be made of HPL or Stainless Steel 304 or 316.

You have to be aware of the specific cleaning or disinfection methods for a specific area, such as VHP (Vaporized Hydroxide Peroxide) processing. This way of disinfecting is very often used in GMP areas and demands thorough staff safety procedures, as well as a very good chemical resistance of materials used in the interior.

There are several types of floor finish available, such as coatings, self-levelling floors or mortar floors with an Epoxy (EP) or Polyurethane (PU) base or even a PU/cement base.
Naturally, there is also the possibility of using a PVC floor. The curved skirting that is normally required for GMP environments due to cleaning considerations can be installed for both kinds of flooring (PVC or polymer-bonded floors).
The floor may be installed in a normal way, but may also be ESD classified to avoid electronic discharges.
For microbiologic decontamination, it is even possible to install polymer-bonded floors with antimicrobial properties.

The HVAC installation required to meet the classification

The HVAC installation has to take care of filtering the air on a HEPA or ULPA level, facilitate as much air as is needed to create a number of air changes per hour (ACH), heat or cool down the temperature within a specific temperature range and possibly keep the humidity at a certain level, all within a specific tolerance.

Depending on a number of specifications, the AHU will also mix fresh air with the return air from the clean room. All the requirements and the permissible tolerance for the air quality inside the clean room are usually specified in the URS.

In a number of cases, air may be extracted from the clean room. Very often, this is heated air from ovens or other heat sources, but it can also be air contaminated with e.g. solvents or a high concentration of dust particles. This contaminated air should be transported outside and replaced with fresh air, as mentioned above.

The duct design and the number and type of grids in the ceiling will determine the airflow within the clean room area. Air return ducts may be placed near the ceiling or near the floor.

In many cases, galvanised steel ducts are used to transport air away from the clean room. It is important to mention that there are different types of ducts, each with their own price level. The Netherlands follows the ISO classification, which is based on factors such as airtightness:

Class	Leak factor	Max. Test pressure
A	0,027	500 Pa
B	0,009	1000 Pa
C	0,003	1000 Pa
D	0,001	2000 Pa

In terms of cleanliness, there are three classes (LR-L/LR-M/LR-H) based on the ISO 8502-3 classification:

Cleanliness class		ISO 8502-3
LR-L	High	Dust quantity rating 5 and above
LR-M	Medium	Dust quantity rating 3 and 4
LR-H	Low	Dust quantity rating 1 and 2

In modular cassette panels, internal ducts may be used to achieve a transport capacity of up to 500 m3/hour. It is also possible to install steel ducts inside the clean room and cover them with panels made of material similar to that used for the clean room interior.

Furthermore, a raised floor may be installed to create a return plenum. Raised flooring systems are available in a variety of grades and finishes, depending on the weight load. While this is the most expensive type of floor available, it comes with highly specific advantages.

The air handling unit

In order to achieve certain conditions in the clean room, you will require an air-handling unit (AHU) with a specific air transport capacity in addition to cooling and heating units (as well as steam humidifiers, if required). There are various types of AHU design and they are available in both sanitary and non-sanitary versions and versions for both indoor and outdoor use.

For larger AHU units, you have a choice of various control options: the operating system can either be based on a single central point measurement or the AHU can be controlled on the basis of parameters in multiple areas, i.e. set up for each area separately. As you can imagine, this has resulted in dramatic price variations in air handling technology.

The required capacity is again calculated on the basis of a number of parameters, including air volume in m3, pressure, and cooling/heating capacity in KW. Depending on your requirements, you may also need a condenser (humidifier) to ensure a specific, stable humidity level inside the clean room.

For smaller clean rooms with limited air volume requirements, a close-control unit will suffice. These often come fully equipped with a cooling unit, a condenser and a central control module.

The utilities and other infrastructure required

The average clean room will have a number of utilities installed, such as electricity (230 V), data traffic and pressurised air.
Naturally, matters become much more interesting (but also more expensive) if you have specific needs, each with their own quality requirements:

- Process water: normal (hot?), purified or WFI (Water For Injection) quality?
- Pressurised air: CDA (Clean Dry Air) or XCDA (Extreme Clean Dry Air) quality?
- Additional 380 V power source required in addition to the 230 V mains power?
- Specific gasses required (oxygen, nitrogen, helium, acetylene etc.)?

And what about possible VHP decontamination units? Will the decontamination units be integrated into the construction, with a VHP generator and a specially designed control unit installed?

Do you need cranes and or lifting equipment? Normal-sized cranes do not fit inside clean rooms, as a result of which specific controlled-environment crane technology must often be considered as early as the design stage.

There is an increasing need for specifically appointed areas with a higher ISO 14644 rating, e.g. RVS booths with a specially modified interior for certain activities. There may also be a requirement for LAF (Laminar Air Flow) cabinets or special storage facilities for chemicals.

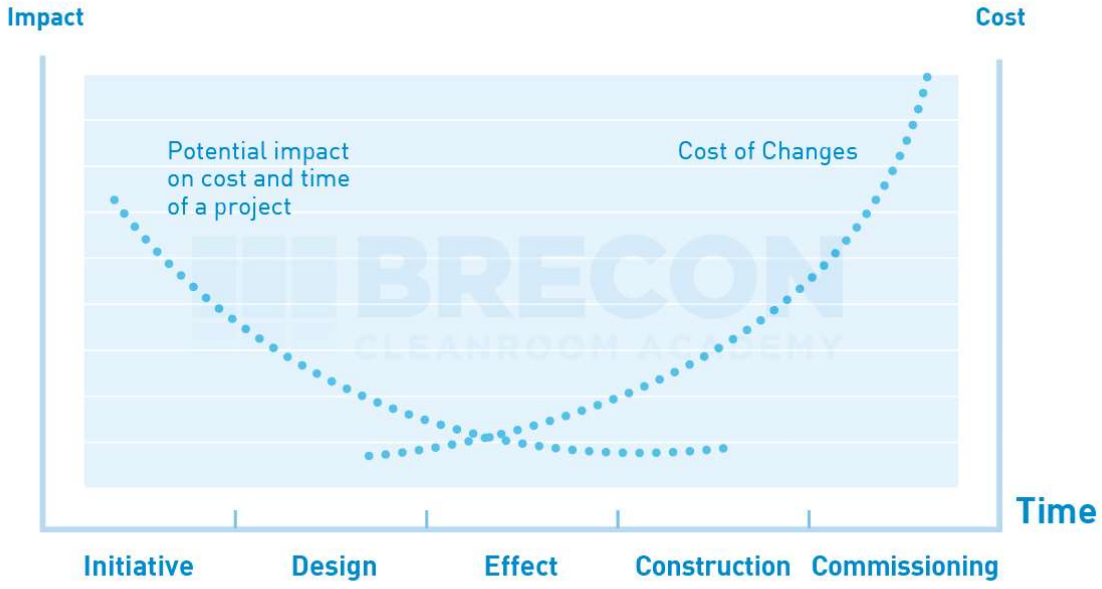
Engineering, commissioning and classification are also required!

Don't forget that design and engineering costs have to be taken into consideration. Pharmaceutical clean rooms in particular demand a design qualification approach. In addition, it is necessary to carry out an impact assessment for each construction and installation component in order to define the commissioning plan.
GMP clean rooms also require an enhanced review to be carried out at the end of the design stage in order to be absolutely sure that the final design covers all the demands mentioned in the URS (User Requirements Specification). These are but a few of the cost factors that are often neglected in the early stages!

Conclusion

Based on the above-mentioned variations and questions, it is quite logical to conclude that it is not possible to estimate an average price.
We have constructed large, relatively straightforward ISO 14644 class 7 and 8 clean rooms for approximately €1,500/m^2 all in. For pharmaceutical sites or hospital pharmacies, however, average prices can run as high as €6,000/m^2!

If you are planning to build a controlled environment, it is wise to contact a serious partner as early as possible. We recommend talking to turnkey suppliers such as PP4CE that provide a single point of contact for all the possibilities and specialties mentioned above, ensuring clear and straightforward communication.



Remember that there are clear advantages to spending time and energy on the preparatory stages. Changing your basic design while it is still on paper will cost you nearly nothing; changes when the construction process has already started will cost a lot of energy, trouble and money!

Origin

PP4CE (Professional Partners for Controlled Environments) is a strategic alliance between a number of specialist companies in the design, construction and maintenance of cleanrooms and laboratories in a wide range of market segments. PP4CE is also active in Medium and High Care areas within the food industry.

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Geerd is initiator of the PP4CE alliance and General Manager of Brecon International B.V. and responsible Sales and Marketing Manager of the Brecon Group as a whole. As such, he is strategically involved in the PP4CE alliance.
For more information, please visit http://www.pp4ce.com